

Equity Research
Pharmaceuticals/Major

Pharmaceutical Industry Pulse

News Events, Reasonable Fundamentals,
Should Drive Strong Finish To 2014

October 2014

Steve Scala, R.Ph., CFA
617.946.3923
steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA
617.946.3857
kathy.miner@cowen.com

Jean Perreault
617.946.3967
jean.perreault@cowen.com



Please see addendum of this report for important disclosures.

This page left blank intentionally.

Steve Scala, R.Ph., CFA

617.946.3923

steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA

617.946.3857

kathy.miner@cowen.com

Jean Perreault

617.946.3967

jean.perreault@cowen.com

News Events, Reasonable Fundamentals, Should Drive Strong Finish To 2014

The Cowen Insight

Further P&L improvement in Q4, over 100 news events between now and YE, and the prospect of growth in 2015 should drive a strong finish to the year for pharma stocks. A still above historical average P/E premium to the S&P 500 on 2014-15 EPS estimates is a consideration, but we believe stocks with above-average growth and/or new product excitement can still outperform.

Post A Lackluster Q3, P&L Improvement In Q4, Growth In 2015

We forecast that Q3 will be the weakest of 2014, with EPS declining 8% on a 2% erosion in revenue. Q4 should be better, with EPS declining 6% on a 2% decline in sales. Growth is expected to return in 2015, with EPS increasing 6% on flat revenue. Sales and EPS growth through 2020 is still forecast at 4% and 7%, respectively, supported by positive unit growth WW, favorable pricing in the U.S., and pipelines capable of contributing meaningfully to revenues.

Cowen 20th Annual Pricing Survey Suggests Positive U.S. Outlook

During Q3, Cowen issued the results of its 20th Annual Drug Pricing Survey and, as in past years, it continues to suggest a solid outlook in the U.S. Aggregate brand drug acquisition cost per unit is expected to increase by 3-5% annually over the next three years, albeit this is below last year's 6-8% forecast. Thirty-eight percent of respondents attribute a substantial portion of the anticipated increase to higher-priced, newer therapies.

100+ New Events On Tap For Pharma Through YE

Leading the news event list is BMY's Opdivo data at CMSTO and '017 and '057 interim looks; MRK's hep C data at AASLD; approval/rollout for ABBV's hep C regimen; Roche's MARIANNE trial results in 1st line mBC; closing of the ABBV/Shire transaction; potential for another PFE bid for AZN; and AZN and SNY analyst meetings in November. Plentiful news flow should retain interest in drug stocks.

Valuations At Least Partially Reflect Improving Fundamental Outlook

Drug stocks currently sell at 17-19x our 2014-15 EPS forecasts, representing 10-11% premiums to the S&P 500. This compares to a 3.6% discount to the S&P 500 over the past 25 years. While the sector has sold at even higher premiums over the past 25 years, it appears the improving fundamental outlook is at least partially reflected in current multiples.

Focus On Stocks With Most Robust Prospects And Greatest Upside

We currently recommend four stocks: ABBV, BMY, LLY and RHHBY. We think each has a good new product outlook that should drive either superior growth or average growth with above average visibility, while simultaneously offering opportunity for upside. Most other pharms in our universe have good prospects, but do not represent compelling buys at this point.

Table Of Contents

News Events, Reasonable Fundamentals, Should Drive Strong Finish To 2014

Positive Factors	7
Neutral Factors...	13
Negative Factors.....	17
Appendix: Tables Of Industry Fundamentals	28

Company Discussions

AbbVie	33
AstraZeneca.....	85
Bristol-Myers Squibb.....	151
Eli Lilly	217
GlaxoSmithKline	278
Merck	355
Novartis.....	416
Pfizer.....	504
Roche	583
Sanofi	660

PHARMACEUTICAL STOCK HIGHLIGHTS

	Company	Symbol	Rating	09/29/14		Dividend Yield	EPS		P/E		Operating FCF		MKT Cap/FCF		F13-20 EPS CGR	F14-20 EPS CGR	Analytical Summary
				Price	2014E		2014E	2015E	2014	2015	2014	2015	2014	2015			
Growth Ideas	Roche	RHHBY	1	\$37	3.0%	\$1.93	\$2.01	19.1x	18.4x	SFr. 11,868	SFr. 13,819	17.1x	14.7x	6%	7%	- Visible L-T growth prospects; biologics offer lower risk profile - Recent launches/pipeline has some significant opportunities	
	AbbVie	ABBV	1	59	2.9%	3.12	3.75	18.8	15.6	\$5,251	\$7,364	17.7	12.7	8%	9%	- Visible EPS growth through 2020, Shire acq. accretive albeit some risks - Humira growth likely; pipeline assets promising: ABT-199, hep C	
	Novartis	NVS	2	94	2.9%	5.15	5.80	18.2	16.1	\$11,721	\$12,960	19.6	17.8	10%	11%	- Good long-term growth but Gleevec generics the next obstacle - Business mix changes viewed positively	
Value Ideas	Merck	MRK	2	59	3.0%	3.50	3.50	17.0	17.0	\$11,329	\$11,267	15.1	15.2	4%	5%	- 2014-20E EPS growth below average; pembrolizumab looks very promising - Zetia/Vytorin franchise, anacetrapib, odanacatib are risks	
	Sanofi	SNY	2	56	3.4%	3.30	3.52	16.9	15.8	€ 8,562	€ 8,690	17.4	17.1	7%	7%	- 2014-20E EPS growth solid, but visibility limited - Pipeline has several moderate potential candidates	
	Pfizer	PFE	2	30	3.5%	2.20	2.30	13.5	12.9	\$17,115	\$18,198	11.1	10.4	7%	8%	- Good L-T growth; dividend increasing, improved new product dynamics - Looks at best fairly valued on SoTP basis; AZN likely to be revisited	
Event Driven Ideas	GlaxoSmithKline	GSK	2	46	5.7%	3.02	3.12	15.3	14.9	£3,179	£4,698	35.1	23.8	3%	6%	- Advair pressure a risk to LT growth - Business mix changes unappealing	
	Bristol-Myers Squibb	BMY	1	52	2.8%	1.80	1.80	28.7	28.7	\$2,906	\$2,676	29.6	32.1	7%	8%	- Good growth prospects - Nivolumab and other IO assets promising; clinical results are key to stock	
	Eli Lilly	LLY	1	65	3.0%	2.80	3.35	23.3	19.5	\$3,200	\$3,569	22.8	20.4	4%	12%	- Top-tier EPS growth prospects through 2020 - Pipeline visibility increasing	
	AstraZeneca	AZN	2	72	3.9%	4.40	4.10	16.4	17.5	\$4,943	\$4,943	18.3	18.3	0%	2%	- Dividend yield attractive; pipeline visibility improving - PFE likely to re-emerge late 2014	

Ratings: 1 Outperform; 2 Market Perform; 3 Underperform

Source: Cowen and Company , Company Data; ThomsonReuters

GLOBAL PHARMACEUTICAL INDUSTRY VALUATION PERSPECTIVE

Ticker	Primary Analyst	Rating*	09/29/14 Price	Mkt. Cap (\$MM)	Div	Yield	2013	EPS 2014E	2015E	P/E Ratios				2013-16 CAGR	2013-20 CAGR	2014-20 CAGR	Total Return/PE			
										2013	2014	Absolute	Relative							
										2013	2014	2015	2014	2015						
LARGE CAP - US																				
AbbVie	ABBV	Scala	1	\$59	\$93,238	\$1.68	2.9%	\$3.13	\$3.12	\$3.75	18.7	18.8	15.6	103%	111%	98%	+12%	+8%	+9%	0.63
Bristol-Myers Squibb	BMY	Scala	1	52	85,946	1.44	2.8%	1.82	1.80	1.80	28.4	28.7	28.7	157%	171%	180%	+1%	+7%	+8%	0.38
Eli Lilly	LLY	Scala	1	65	72,893	1.96	3.0%	4.15	2.80	3.35	15.7	23.3	19.5	87%	139%	123%	+0%	+4%	+12%	0.64
Johnson & Johnson	JNJ	Jennings	1	107	302,194	2.80	2.6%	5.52	5.80	6.35	19.3	18.4	16.8	106%	109%	105%	+8%			
Merck	MRK	Scala	2	59	171,664	1.76	3.0%	3.49	3.50	3.50	17.0	17.0	17.0	94%	101%	107%	+3%	+4%	+5%	0.47
Pfizer	PFE	Scala	2	30	189,243	1.04	3.5%	2.22	2.20	2.30	13.4	13.5	12.9	74%	80%	81%	+3%	+7%	+8%	0.85
LARGE CAP - EUROPE																				
AstraZeneca	AZN	Scala	2	\$72	\$90,626	\$2.80	3.9%	\$5.05	\$4.40	\$4.10	14.2	16.4	17.5	79%	97%	110%	(5%)	(0%)	+2%	(a) 0.37
GlaxoSmithKline	GSK	Scala	2	46	111,663	2.65	5.8%	3.52	3.02	3.12	13.2	15.3	14.9	73%	91%	93%	(3%)	+3%	+6%	(a) 0.75
Novartis	NVS	Scala	2	94	230,078	2.76	2.9%	5.00	5.15	5.80	18.7	18.2	16.1	103%	108%	101%	+9%	+10%	+11%	(a) 0.75
Roche	RHHBY	Scala	1	37	202,903	1.10	3.0%	1.87	1.93	2.01	19.7	19.1	18.4	109%	113%	115%	+4%	+6%	+7%	(a) 0.50
Sanofi	SNY	Scala	2	56	148,671	1.91	3.4%	3.20	3.30	3.52	17.4	16.9	15.8	96%	100%	99%	+4%	+7%	+7%	(a) 0.62
MID CAP																				
Actavis	ACT	Cacciato	1	\$244	\$64,283	\$0.00		\$8.55	\$14.90	\$16.60	28.6	16.4	14.7	158%	97%	92%	+29%			
Alkermes	ALKS	Cacciato	1	44	6,320	0.00		1.19	0.30	0.30	NM	NM	145.8	NM	NM	NM	NM	NM		
Allergan	AGN	Cacciato	1	180	53,128	0.20	0.1%	4.77	5.75	8.40	37.7	31.3	21.4	208%	186%	134%	+28%			
Endo Pharmaceuticals	ENDP	Cacciato	2	70	10,638	0.00		3.90	2.34	2.80	17.8	29.7	24.8	98%	176%	156%	(8%)			
Jazz Pharmaceuticals	JAZZ	Cacciato	1	162	9,693	0.00		6.31	8.20	10.86	25.7	19.8	14.9	142%	117%	94%	+32%			
Mylan Labs	MYL	Cacciato	1	46	16,967	0.00		2.89	3.35	4.10	15.8	13.7	11.2	87%	81%	70%	+17%			
Shire	SHPG	Cacciato	1	261	51,152	0.62	0.2%	7.66	9.53	10.59	34.0	27.4	24.6	188%	162%	155%	+15%			
Teva	TEVA	Cacciato	1	54	51,149	1.21	2.3%	5.01	5.00	5.35	10.7	10.7	10.0	59%	64%	63%	+5%			
SMALL CAP/EMERGING																				
Cubist Pharmaceuticals	CBST	Cacciato	1	\$66	\$5,014	\$0.00		\$1.45	\$1.88	\$3.60	45.9	35.4	18.5	253%	210%	116%	+55%			
Eleven Biotherapeutics	EBIO	Cacciato	1	12	188	0.00		(1.55)	(1.60)	(1.65)	NM	NM	NM	NM	NM	NM	NM			
Impax Laboratories	IPXL	Cacciato	2	24	1,706	0.00		1.50	0.70	1.00	16.2	34.8	24.3	89%	206%	153%	(1%)			
Kythera Biopharm.	KYTH	Cacciato	1	34	754	0.00		(2.71)	(3.40)	(1.20)	NM	NM	NM	NM	NM	NM	NM			
Revance	RVNC	Cacciato	1	21	490	0.00		(2.95)	(3.10)	(3.45)	NM	NM	NM	NM	NM	NM	NM			
Supernus Pharmaceuticals	SUPN	Cacciato	1	9	375	0.00		(2.90)	(0.71)	0.60	NM	NM	14.7	NM	NM	NM	NM			
Theravance, Inc.	THRX	Cacciato	1	18	2,027	0.25		(1.67)	0.08	0.56	NM	NM	NM	NM	NM	NM	NM			
Versartis	VSAR	Cacciato	1	20	468	0.00		(41.10)	(2.65)	(2.25)	NM	NM	NM	NM	NM	NM	(59%)			
US BIG CAP DRUG AVERAGE								3.0%			18.8	19.9	18.4	103%	118%	116%				
EU/UK BIG CAP DRUG AVERAGE								3.8%			16.6	17.2	16.5	92%	102%	104%				
TOTAL BIG CAP DRUG COMPANY AVERAGE								3.3%			17.8	18.7	17.6	98%	111%	110%				
MID/SMALL-CAP AVERAGE								1.0%			24.7	24.3	33.0	136%	144%	208%				
S&P 500 OPER (operating)	.spx-ut			\$1,978		\$37.35	1.9%	\$109.05	\$117.40	\$124.25	18.1	16.8	15.9				+8%	+8%	+8%	0.55

*Rating: 1 = Outperform; 2 = Market Perform; 3 = Underperform

(a) ADR earnings

LEGEND

Total Return = [2014-20 EPS Growth + Yield]

Calendar 2014 P/E

Source: Cowen and Company Estimates; ThomsonReuters

News Events, Reasonable Fundamentals, Should Drive Strong Finish To 2014

Key Factors Influencing Big-Cap Drug Stock Performance

Positive Factors	Neutral Factors	Negative Factors
<ul style="list-style-type: none"> - Industry Pipelines - U.S. Drug Pricing - New Products/News Flow - Sales and EPS Growth Outlook 	<ul style="list-style-type: none"> - U.S. Prescription Demand - FDA - Valuation - Stock Price Performance 	<ul style="list-style-type: none"> - Patent Expirations - Drug Reimbursement/Health Care Reform - Foreign Currency Exposure

Source: Cowen and Company

Positive Factors

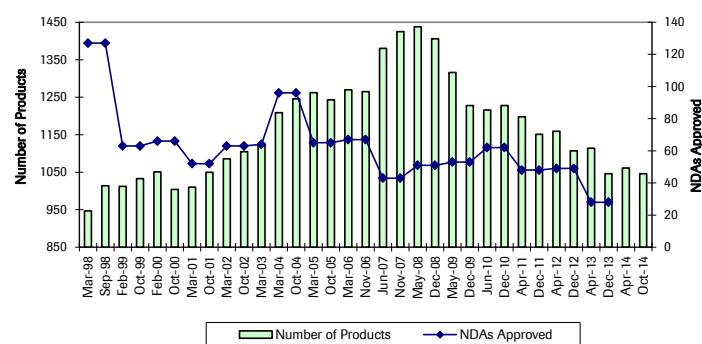
TOTAL PIPELINE PRODUCTS

2012	2013	2014
1,108	1,046	1,046

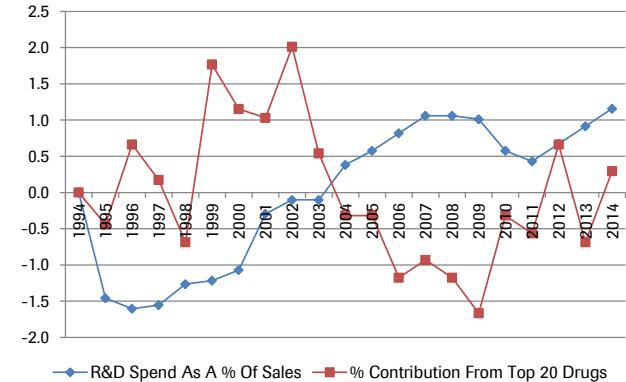
AVERAGE PIPELINE SCORE

2012	2013	2014
82	80	83

TOTAL NUMBER OF PIPELINE PRODUCTS



R&D SPEND EFFICIENCY HISTORY



Source: Cowen and Company

NEW DRUG ACTIVITY RANKED ALPHABETICALLY BY COMPANY

Company	PC	I	II	III	NDA	Total # of Pipeline Products	Score*
AbbVie	0	15	20	10	3	48	145
Actavis	2	3	1	2	4	12	39
Alkermes	3	0	2	4	0	9	25
Allergan	2	0	10	5	2	19	62
Aradigm	1	1	1	1	0	4	10
Astellas	0	18	9	15	6	48	153
AstraZeneca	2	31	25	26	3	87	258
Bayer Schering Pharma	0	17	11	10	0	38	107
Bristol-Myers Squibb	0	22	14	10	4	50	146
Chugai	0	2	4	3	0	9	28
Cubist Pharmaceuticals	0	1	0	3	1	5	19
Daiichi Sankyo	0	14	8	6	2	30	86
Dainippon Sumitomo	0	5	6	4	5	20	69
Eisai	0	0	8	7	5	20	77
Eleven Biotherapeutics	2	0	1	0	0	3	5
Eli Lilly	0	23	22	12	1	58	165
Endo Pharmaceuticals	0	0	1	1	0	2	7
GlaxoSmithKline	0	29	38	16	5	88	261
Johnson & Johnson	0	0	3	9	8	20	85
Kythera	0	0	0	1	0	1	4
Merck	0	0	10	15	3	28	56
Mitsubishi Tanabe	0	7	15	8	2	32	101
Nektar Therapeutics	6	1	1	6	2	16	45
Novartis	0	6	27	24	11	68	244
Novo Nordisk	0	9	3	5	4	21	67
Pfizer	0	36	19	12	6	73	207
Pozen	0	2	0	1	1	4	13
Revance	0	1	1	1	0	3	9
Roche	0	28	27	13	6	74	219
Salix	0	0	2	4	1	7	27
Sanofi	0	22	15	12	5	54	162
SkyePharma	0	2	1	0	1	4	12
Sucampo	0	2	1	2	0	5	15
Supernus	1	0	2	0	0	3	7
Takeda	0	18	8	13	8	47	152
Teva	1	1	6	7	9	24	94
Theravance	0	1	7	0	1	9	28
Transition Therapeutics	0	1	1	0	0	2	5
Versartis	0	0	1	0	0	1	3
Total	20	318	331	268	109	1046	
Average	1	8	9	7	3	28	83

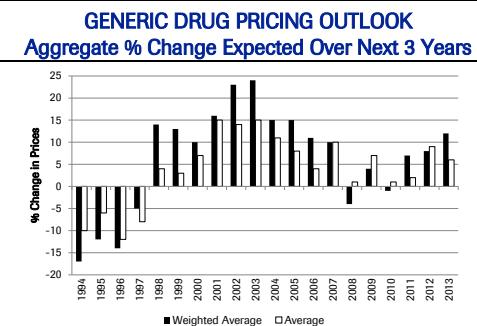
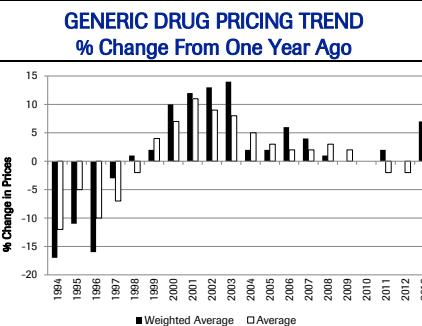
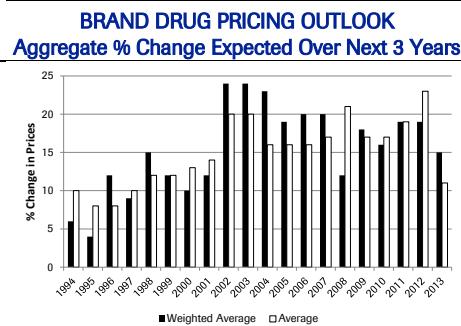
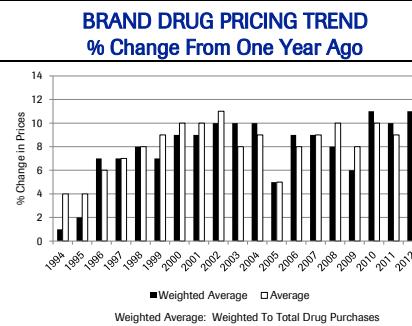
*Score: 5 points given to each product with NDA filed; 4 points to each in Phase III; 3 points to each in Phase II; 2 points to each in Phase I; and 1 point to each in preclinical development

Source: Cowen and Company

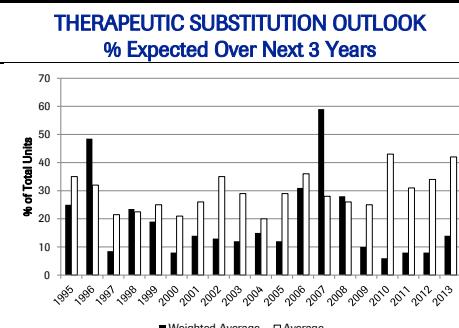
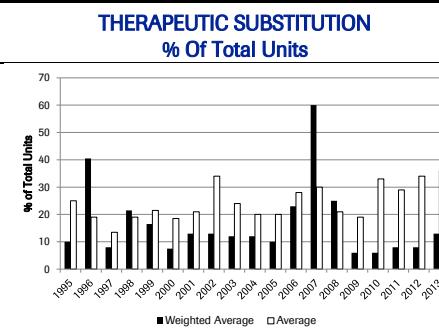
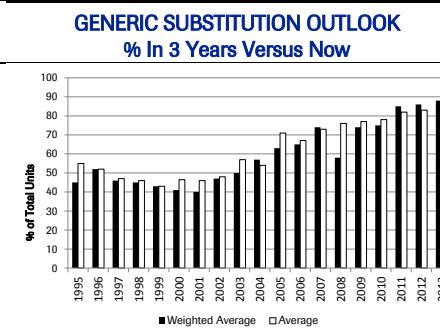
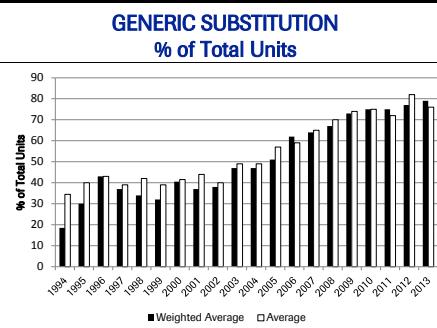
Survey Suggests Pricing Flexibility/Unit Growth In The U.S.

- Brand drug prices expected to increase 3-5% annually over the next 3 years.
- Aggregate generic drug acquisition cost per unit is expected to increase 2-4% annually.
- Generic and therapeutic substitution forecast to increase over the next 3 years.
- View of government/political considerations shifting.

Cowen and Company 20th Annual Managed Care Drug Pricing/Purchasing Trends Survey



Source: Cowen and Company, Epcrates



Source: Cowen and Company, Epcrates

New Products/News Flow – Our forecast of \$20.3B in 2019 new product sales for top drug candidates is 3.4% of estimated industry revenue in that year, versus 3.4% in 1995 and 3.3% in 1997.

Top New Drugs Of 1995 Based on 2000 Sales Potential

No.	Drug	Company	2000P Sales (\$MM)	2000A Sales (\$MM)
20	Temodar	SGP	\$75	\$121
19	Normiflo	WYE	90	35
18	Fareston	SGP	125	NA
17	Omnicef	PFE	125	0
16	Plavix	BMY	150	889
15	Geodon	PFE	150	0
14	Vaqta	MRK	150	125
13	Integriulin	SGP	175	172
12	Duract	WYE	175	0
11	Evista	LLY	200	522
10	Tritec/Pylorid	GSK	235	15
9	Cordonone IV	WYE	250	203
8	Maxipime	BMY	250	146
7	Trovan	PFE	300	0
6	Avapro	BMY	300	361
5	Lipitor	PFE	500	5,031
4	Rezulin	PFE	550	102
3	Zyprexa	LLY	1,000	2,350
2	Crixivan	MRK	1,100	530
1	Epivir	GSK	2,000	470
			\$7,900	\$11,072

Top New Drugs Of 1997 Based on 2002 Sales Potential

No.	Drug	Company	2002P Sales (\$MM)	2002A Sales (\$MM)
20	Temodar	SGP	\$125	\$278
19	Tikosyn	PFE	125	20
18	Amerge	GSK	190	143
17	Integriulin	SGP	300	304
16	Aggrastat	MRK	350	115
15	Detrol	PNU	425	757
14	Geodon	PFE	450	222
13	Relpax	PFE	450	0
12	Celexa	FRX	500	1,452
11	Plavix	BMY	500	1,890
10	Propecia	MRK	500	213
9	Maxalt	MRK	750	295
8	Rapamune	WYE	750	130
7	Raxar	GSK	835	0
6	Trovan	PFE	1,250	0
5	Evista	LLY	1,500	822
4	Vioxx	MRK	1,500	2,530
3	Agenerase	GSK	1,540	70
2	Singulair	MRK	1,800	1,505
1	Viagra	PFE	5,000	1,735
			\$18,840	\$12,481

Industry Sales	\$330,000
% of Industry Sales	3.4%

Industry Sales	\$376,000
% of Industry Sales	3.3%

Source: Cowen and Company

Top New Drugs Of 2014 Based on 2019 Sales Potential

No.	Drug	Company	2019P Sales (\$MM)
20	Necitumumab	LLY	\$500
19	Elagolix	ABBV	500
18	Lixilan	SNY	515
17	Ocrelizumab	ROCHE	535
16	RG7446	ROCHE	535
15	Firazyr	ABBV	540
14	MnB (PF-5212366)	PFE	550
13	Cinryze	ABBV	550
12	CXA0201	CBST	700
11	Eleprase	ABBV	720
10	Lialda	ABBV	740
9	Alirocumab (SAR236553)	SNY	775
8	Anacetrapib	MRK	900
7	Daratumumab	JNJ	900
6	LCZ696	NVS	1,000
5	HCV combinations	ABBV	1,200
4	ABT-199	ABBV	1,500
3	Palbociclib (PF-332991)	PFE	2,000
2	V-503	MRK	2,100
1	Opdivo	BMY	3,500
			\$20,260

Industry Sales	\$604,000
% of Industry Sales	3.4%

Source: Cowen and Company

DATES TO WATCH

FDA MEETINGS

Date	Committee	Topic
October 16, 2014	Psychopharmacologic Drugs/Drug Safety and Risk Management	Chantix adverse events (PFE)
October 20, 2014	Dermatologic and Ophthalmic Drugs Advisory Committee	Secukinumab (NVS; psoriasis)
October 30-31, 2014	Public Meeting	Abuse-deterrent opioid medications

SCIENTIFIC MEETINGS

Date	Meeting	Location
October 6-11, 2014	World Congress On Pain	Buenos Aires
October 8-12, 2014	European Academy of Dermatology and Venereology	Amsterdam
October 11-15, 2014	American Society of Anesthesiologists	New Orleans
October 12-14, 2014	American Neurological Association	Baltimore
October 17-22, 2014	American College of Gastroenterology	Philadelphia
October 18-21, 2014	American Academy of Ophthalmology	Chicago
October 18-22, 2014	European College of Neuropsychopharmacology	Berlin
October 18-22, 2014	American Society for Reproductive Medicine	Honolulu
October 18-22, 2014	American Society of Human Genetics	San Diego
October 22-25, 2014	World Stroke Congress	Istanbul
October 25-30, 2014	American College of Chest Physicians	Austin
October 27-30, 2014	American College of Emergency Physicians	Chicago
October 30 - November 1, 2014	Multidisciplinary Symposium in Thoracic Oncology	Chicago
November 6-11, 2014	American College of Allergy, Asthma & Immunology	Atlanta
November 7-11, 2014	The Liver Meeting/Amer. Association for the Study of Liver Diseases	Boston
November 11-16, 2014	American Society of Nephrology	Philadelphia
November 13-16, 2014	Society for Melanoma Research	Zurich
November 13-18, 2014	American College of Rheumatology	Boston
November 15-19, 2014	American Heart Association	Chicago
November 15-19, 2014	Society For Neuroscience	Washington, D.C.
December 5-9, 2014	American Epilepsy Society	Seattle
December 6-9, 2014	American Society of Hematology	San Francisco
December 6-10, 2014	American Society of Cell Biology	Philadelphia
December 9-13, 2014	San Antonio Breast Cancer Symposium	San Antonio

PDUFA DATES

Date	Drug	Target
November 23, 2014	Esbriet (Roche, ITMN)	IPF
November 30, 2014	Daclatasvir (BMY)	Hepatitis C
Jan-15	Secukinumab (NVS)	Psoriasis
January 3, 2015	Olaparib (AZN)	Ovarian cancer
February 14, 2015	Meningococcal B vaccine (PFE)	Meningitis
Early 2015	Duopa (ABBV)	Parkinson's disease

Source: Cowen and Company

NDAs APPROVED

2011	2012	2013	2014#
48	49	28	24

#Through August

FDA – Thus far in 2014, approvals were granted to 24 NDAs, 264 ANDAs and 7 biologics. The FDA has averaged 62 NDA approvals annually over the past 24 years, excluding 1996-98, which were years following passage of PDUFA legislation.

MONTHLY FDA APPROVALS

	Total New Drugs (NDAs)	+ Total Generic Drugs (ANDAs)	Total Biologicals (BLAs)	= Total Applications Approved
2013				
January	4	26	0	30
February	2	39	1	42
March	4	48	0	52
April	0	36	0	36
May	4	31	0	35
June	1	29	0	30
July	1	41	1	43
August	1	27	0	28
September	1	26	0	27
October	4	20	1	25
November	4	33	1	38
December	2	28	0	30
Totals	28	384	4	416
2014				
January	2	34	0	36
February	2	33	2	37
March	2	35	0	37
April	2	40	3	45
May	2	21	1	24
June	3	42	0	45
July	5	17	0	22
August	6	42	1	49
Totals	24	264	7	295

FDA APPROVAL ACTIVITY

	Total Applications Approved	=	Total New Drugs (NDAs)	+	Total Generic Drugs** (ANDAs)	+	Total Biologicals (BLAs)
1990	229		64		80		85
1991	327		63		188		76
1992	387		91		229		67
1993	370		70		249		51
1994*	304		62		219		23
1995	396		88		268		40
1996	390		146		220		24
1997	358		104		209		45
1998	333		127		183		23
1999	212		63		128		21
2000	215		66		137		12
2001	229		52		161		16
2002	279		63		201		15
2003	321		64		244		13
2004	422		96		320		6
2005	403		65		329		9
2006	341		67		265		9
2007	490		43		440		7
2008	484		51		424		9
2009	474		53		412		9
2010	493		62		417		14
2011	500		48		439		13
2012	524		49		467		8
2013	416		28		384		4
2014#	295		24		264		7

*NDA User Fee Program implemented in October '93.

**Approvals for multiple dosage strengths of the same compound are counted as a single approval.

#Through August

Source: www.drugs@FDA.gov

Neutral Factors

U.S. Prescription Demand – Prescription demand grew 1% during 2013. Prescription demand rose (3%) – +5% YTD during 2014.

Y/Y CHANGES IN NEW PRESCRIPTIONS DISPENSED* 2001-2013

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
ACE Inhibitors	+3%	+10%	-4%	+2%	+7%	+7%	-1%	+6%	+6%	+1%	+1%	+1%	+6%
Antiarthritics	-3%	-0%	-1%	+7%	+20%	+2%	+2%	+5%	+3%	+5%	+5%	+4%	+2%
Antibiotics (Macrolides)	+2%	+4%	+9%	-9%	+14%	+4%	+8%	+8%	-1%	+8%	-4%	+11%	-22%
Anticonvulsants	+12%	+11%	+8%	+8%	+7%	+14%	+7%	+9%	-1%	+0%	+7%	+5%	+9%
Antidepressants	+10%	+9%	+3%	+2%	+2%	+7%	+1%	+5%	+10%	-1%	+4%	+3%	+6%
Antihistamines	+11%	+9%	-25%	-10%	+1%	+5%	+4%	-24%	+12%	+2%	-17%	+6%	+1%
Antipsychotics	+19%	+16%	+11%	+8%	+6%	+7%	+5%	+10%	+4%	-1%	+2%	+0%	+3%
ARBs	+15%	+23%	+12%	+11%	+5%	+10%	+2%	+0%	-1%	+3%	+16%	+5%	+8%
BPH	-11%	-12%	-12%	-9%	-4%	+3%	-3%	+3%	+22%	-17%	-0%	-0%	+4%
Calcium Channel Blockers	-3%	-2%	-4%	-0%	+3%	+5%	+6%	+2%	+27%	-13%	+4%	+4%	+5%
Cephalosporins	-4%	-1%	+0%	-5%	+7%	+1%	-1%	-2%	+2%	+1%	-2%	+3%	-6%
Cholesterol Reducers	+14%	+7%	+5%	+13%	+4%	+13%	+3%	+16%	+8%	+2%	+23%	-7%	+1%
Coxibs	+7%	+2%	-2%	-6%	-72%	-2%	-1%	-5%	-10%	-4%	-5%	-3%	-1%
Diabetes	+8%	+8%	+2%	+5%	+14%	+12%	-2%	+4%	+5%	+1%	+2%	+2%	+5%
Fungicides	+5%	+2%	-3%	-1%	+5%	+5%	+1%	+8%	+10%	+0%	+5%	-1%	+2%
Migraine	+2%	+6%	-2%	+4%	-1%	+3%	+1%	+20%	-8%	-6%	+0%	+0%	+11%
Quinolones, Systemic	+13%	+3%	+4%	-1%	+13%	+7%	+5%	-0%	-9%	-2%	-2%	+6%	-4%
Ulcer	+8%	+8%	+4%	-2%	+2%	+11%	+2%	+5%	+7%	-4%	+6%	+2%	+4%
Total	+4%	+4%	+2%	+1%	+6%	+5%	+3%	+4%	+4%	+1%	+3%	+2%	+1%
Y/Y % Change													

Source: IMS America

Y/Y CHANGES IN NEW PRESCRIPTIONS DISPENSED* 2014 YTD

	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14
ACE Inhibitors	+11%	+16%	+14%	+13%	+12%	+12%	+3%	+1%
Antiarthritics	+2%	+6%	+8%	+9%	+10%	+11%	+9%	-3%
Antibiotics (Macrolides)	-23%	-20%	-9%	+5%	-1%	+1%	+1%	+2%
Anticonvulsants	+5%	+6%	+5%	+7%	+7%	+9%	+10%	+6%
Antidepressants	+6%	+6%	+4%	+5%	+6%	+9%	+7%	+7%
Antihistamines	-1%	+0%	+7%	+9%	+7%	+13%	+11%	+8%
Antipsychotics	-1%	+1%	+1%	+2%	+1%	+3%	+6%	+3%
ARBs	+5%	+8%	+8%	+10%	+9%	+11%	+14%	+15%
BPH	+1%	+2%	+5%	+3%	+3%	+3%	-0%	-4%
Calcium Channel Blockers	+3%	+6%	+7%	+8%	+8%	+10%	+7%	+6%
Cephalosporins	-10%	-8%	-5%	+1%	-0%	+3%	+1%	+0%
Cholesterol Reducers	+1%	+5%	+6%	+8%	+7%	+10%	+6%	+5%
Coxibs	-10%	-8%	-7%	-5%	-6%	-5%	-1%	-2%
Diabetes	+6%	+9%	+11%	+15%	+19%	+21%	+10%	+9%
Fungicides	-9%	-6%	-5%	-3%	-4%	-3%	+7%	+5%
Migraine	-0%	+1%	+3%	+4%	+3%	+6%	+9%	+1%
Quinolones, Systemic	-7%	-3%	-1%	+3%	+1%	+2%	+1%	+3%
Ulcer	+0%	+0%	+1%	+4%	+6%	+6%	+5%	+5%
Total	-3%	+0%	+2%	+4%	+4%	+5%	+5%	+4%
Y/Y % Change								

*Percentages adjusted for differing number of days per month

Source: IMS America

Industry Sales Growth		
2013	2014E	2015E
-2%	-3%	0%
Industry EPS Growth		
2013	2014E	2015E
-4%	-5%	6%
Brand Drug Pricing Trend		
2012*	2013E*	2014E#
11-12%	7-8%	8-9%

*Reported #Projected

Sales and EPS Growth Outlook – Big-cap EPS are forecast to decrease 5% on a 3% sales decline in 2014. EPS are forecast to increase 5-7% on flat sales growth in 2015. Sales and EPS growth during 2013-20 is forecast to compound at 3% and 5%, well below the 9% top- and bottom-line growth delivered during 1990-2013, but the outlook strengthens in 2014-20, when we forecast 4% revenue growth and 7% EPS growth. The group appears poised to deliver sustainable growth.

DRUG UNIVERSE SALES AND EPS MOMENTUM MONITOR

	C2013				C2014E				C2015E												'13-16 CY CGR			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3E	Q4E	Q1E	Q2E	Q3E	Q4E	'13A	'14E	'15E	'16P	'17P	'18P	'19P	'20P	'13-16 CY CGR	'13-20 CY CGR	'14-20 CY CGR	
Large-Cap Companies																								
ABBV	Sales	--	--	--	5%	5%	3%	4%	--	--	--	--	4%	4%	--	9%	6%	1%	3%	2%	16%	8%	9%	
	EPS	--	--	--	5%	0%	-5%	-2%	14%	18%	20%	29%	-4%	-1%	20%	17%	11%	1%	3%	2%	12%	7%	9%	
AZN	Sales	-13%	-6%	-6%	-6%	0%	4%	3%	-4%	-4%	-6%	-2%	4%	-8%	1%	-2%	2%	-8%	4%	7%	0%	2%	2%	
	EPS	-25%	-24%	-29%	-28%	-17%	8%	-12%	-29%	-16%	-32%	2%	33%	-26%	-13%	-7%	6%	-14%	9%	10%	11%	-5%	0%	2%
BMY	Sales	-27%	-9%	9%	6%	NM	NM	NM	NM	-1%	-9%	-6%	-9%	-7%	NM	-6%	2%	7%	8%	8%	12%	-3%	3%	5%
	EPS	-35%	-8%	12%	8%	8%	9%	-13%	-8%	16%	-7%	8%	-14%	-9%	-1%	0%	3%	8%	10%	14%	16%	0%	7%	8%
LLY	Sales	0%	6%	6%	-2%	-16%	-17%	-16%	-10%	1%	9%	8%	8%	2%	-15%	7%	5%	5%	-2%	3%	6%	-2%	1%	4%
	EPS	24%	40%	40%	-13%	-39%	-41%	-31%	-12%	3%	23%	18%	36%	22%	-33%	20%	25%	15%	5%	4%	4%	0%	4%	12%
GSK	Sales	-4%	0%	-2%	0%	-10%	-13%	-6%	-5%	2%	6%	10%	7%	-15%	-8%	6%	6%	3%	6%	7%	7%	1%	4%	6%
	EPS	3%	4%	14%	-4%	-20%	-24%	-8%	-7%	-5%	1%	12%	3%	4%	-14%	3%	4%	0%	10%	9%	8%	-3%	3%	6%
MRK	Sales	-9%	-11%	-4%	-4%	-4%	-1%	-5%	-5%	NM	NM	NM	NM	-7%	-4%	-9%	-1%	-1%	2%	3%	4%	-4%	-1%	0%
	EPS	-14%	-20%	-3%	5%	3%	1%	-5%	2%	-9%	-1%	2%	7%	-9%	0%	0%	9%	-1%	8%	7%	8%	3%	4%	5%
NVS	Sales	1%	0%	3%	1%	1%	2%	2%	1%	1%	1%	-2%	-1%	1%	2%	0%	0%	4%	3%	6%	8%	0%	3%	4%
	EPS	2%	-6%	-7%	-7%	1%	4%	8%	-1%	0%	-2%	23%	32%	-5%	3%	13%	10%	9%	8%	11%	13%	9%	9%	11%
PFE	Sales	NM	NM	NM	NM	-9%	-2%	-4%	-6%	0%	-5%	-2%	-2%	NM	-5%	-2%	0%	4%	3%	0%	7%	-2%	1%	2%
	EPS	-11%	-9%	10%	19%	10%	4%	-8%	-10%	2%	-1%	9%	9%	1%	-1%	5%	7%	8%	9%	5%	15%	3%	7%	8%
ROCHE	Sales	5%	3%	3%	1%	-1%	-2%	-2%	0%	1%	1%	2%	2%	3%	-1%	1%	3%	3%	4%	4%	3%	1%	2%	3%
	EPS	10%		1%		0%		7%		4%		4%	6%	6%	3%	4%	6%	8%	8%	7%	6%	4%	6%	7%
SNY	Sales	-5%	-10%	-7%	-1%	-3%	1%	5%	4%	4%	5%	5%	4%	-6%	2%	5%	1%	4%	4%	4%	5%	2%	4%	4%
	EPS	-34%	-24%	-19%	17%	-2%	5%	5%	4%	9%	4%	6%	7%	-18%	3%	7%	2%	8%	8%	9%	9%	4%	7%	7%
Big Cap Average																								
Sales		-6%	-4%	0%	0%	-4%	-2%	-2%	-2%	0%	0%	1%	1%	-2%	-3%	0%	3%	3%	3%	5%	6%	1%	3%	4%
EPS		-11%	-4%	2%	0%	-6%	-3%	-8%	-6%	2%	1%	11%	15%	-4%	-5%	6%	9%	5%	8%	8%	9%	3%	5%	7%

Notes:

(1) From operations; may differ slightly from company models due to rounding. Average growth statistics are arithmetic averages, not market cap weighted.

Source: Cowen and Company

RELATIVE P/E

2012*	2013*	2014E**	2015E***
-7%	0%	11%	11%

*12-month forward estimates

**Current year estimates

***Forward estimates

Valuation – Drug stocks sell at an 11% premium to the S&P 500 on both our 2014 and 2015 EPS estimates, respectively. This compares to the average 3.6% discount over the last 25 years on our 12-month forward EPS estimates.

VALUATION COMPARISON ANALYSIS

(EPS estimates from beginning of year indicated)

	1989 Abs. Rel.	1990 Abs. Rel.	1991 Abs. Rel.	1992 Abs. Rel.	1993 Abs. Rel.	1994 Abs. Rel.	1995 Abs. Rel.	1996 Abs. Rel.	1997 Abs. Rel.	1998 Abs. Rel.	1999 Abs. Rel.	2000 Abs. Rel.	2001 Abs. Rel.	2002 Abs. Rel.
ABBV	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --
AZN*	NM NM	21.6 118.5%	28.2 127.9%	27.6 99.4%	28.4 99.9%	16.9 71.9%	25.3 85.6%							
BMY	14.0 122.0%	15.8 121.0%	15.8 110.0%	18.3 99.0%	13.9 84.0%	12.8 81.0%	12.2 94.0%	15.5 95.0%	17.8 103.0%	26.6 123.0%	33.0 129.0%	29.9 117.0%	21.2 90.1%	19.8 67.0%
GSK	12.9 112.0%	15.2 117.0%	14.6 102.0%	23.8 129.0%	18.3 111.0%	14.9 94.0%	14.4 111.0%	15.2 94.0%	16.5 96.0%	35.5 164.0%	38.6 151.0%	28.5 117.6%	23.6 100.3%	16.3 55.2%
LLY	14.3 125.0%	15.9 122.0%	14.8 104.0%	16.3 89.0%	11.5 70.0%	12.6 79.0%	14.3 110.0%	19.6 121.0%	23.0 133.0%	29.2 135.0%	38.3 150.0%	24.9 97.6%	28.6 121.6%	24.9 84.3%
MRK	16.1 140.0%	15.8 122.0%	15.7 110.0%	25.4 138.0%	17.4 106.0%	14.3 91.0%	14.4 111.0%	20.5 126.0%	21.3 123.0%	25.0 116.0%	29.8 116.0%	23.3 91.3%	18.8 79.9%	18.0 60.9%
NVS*	NM NM	29.2 160.2%	25.7 116.6%	28.6 103.0%	21.9 77.0%	26.4 112.2%	19.0 64.3%							
PFE	9.8 86.0%	14.7 113.0%	14.3 100.0%	25.6 139.0%	18.8 115.0%	15.1 96.0%	15.5 120.0%	21.4 132.0%	23.4 135.0%	38.4 177.0%	51.0 199.0%	30.9 121.1%	30.4 129.3%	19.9 67.3%
RHHBY**	NM NM	21.0 71.1%												
SNY**	NM NM	24.3 82.1%												
Average	13.8 120.5%	14.7 112.8%	14.2 99.1%	18.9 102.5%	14.5 88.1%	13.0 82.3%	14.2 104.4%	18.4 111.3%	21.8 124.1%	29.8 137.1%	35.3 135.3%	26.8 103.1%	23.7 100.8%	20.9 70.9%
S&P	11.5	14.5	14.6	21.6	20.9	17.3	14.5	16.3	18.2	22.1	27.8	28.4	23.5	29.6
Big Cap Drug Growth Expected Over Next 3-4 Years														
S&P 500 Growth Expected Over Next 3-4 Years		16%	16%	16%	13%	7%	7%	10%	12-14%	13-15%	13-15%	13-15%	12-14%	8-10%

Source: Cowen and Company; Thomson Financial

VALUATION COMPARISON ANALYSIS

(EPS estimates from beginning of year indicated)

	2003 Abs. Rel.	2004 Abs. Rel.	2005 Abs. Rel.	2006 Abs. Rel.	2007 Abs. Rel.	2008 Abs. Rel.	2009 Abs. Rel.	2010 Abs. Rel.	2011 Abs. Rel.	2012 Abs. Rel.	2013 Abs. Rel.	Avg. 1989-13 Abs. Rel.	2014 Abs. Rel.	2015 Abs. Rel.	
ABBV	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	-- --	6.3 54.3%	6.3 54.3%	18.8 111.3%	15.6 98.0%
AZN*	19.7 103.1%	22.9 112.6%	12.5 69.8%	12.6 77.2%	13.1 81.0%	8.7 48.9%	6.3 34.5%	8.4 42.8%	6.8 45.3%	7.3 58.9%	7.8 67.2%	16.1 79.1%	16.4 97.1%	17.5 110.2%	
BMY	13.8 72.2%	19.6 96.4%	18.2 101.6%	19.4 118.8%	18.2 112.6%	15.4 86.6%	11.6 63.6%	11.7 59.4%	11.6 77.3%	18.0 145.2%	18.4 158.6%	17.7 101.1%	28.7 170.5%	28.7 180.5%	
GSK	15.2 79.5%	15.5 76.2%	16.3 91.0%	16.4 100.4%	14.2 87.8%	17.0 95.6%	9.4 51.5%	10.9 55.3%	10.9 72.6%	11.4 91.9%	11.3 97.4%	17.5 98.1%	15.3 91.0%	14.9 93.3%	
LLY	24.6 128.7%	25.4 124.9%	18.1 101.1%	18.5 113.3%	14.8 91.5%	13.1 73.6%	9.2 50.4%	7.9 40.1%	8.1 54.0%	13.5 108.9%	13.3 114.7%	18.2 101.7%	23.3 138.5%	19.5 122.5%	
MRK	18.4 96.3%	15.1 74.3%	12.7 70.9%	14.4 88.2%	14.1 87.2%	17.4 97.8%	9.3 51.0%	10.6 53.9%	9.5 63.3%	9.9 79.8%	11.4 98.3%	16.7 95.7%	17.0 100.8%	17.0 106.6%	
NVS*	18.6 97.3%	19.5 95.9%	19.1 106.6%	17.5 107.2%	20.9 129.3%	14.8 83.2%	11.0 60.3%	10.5 53.6%	10.8 72.0%	10.4 83.9%	12.3 106.0%	18.6 95.8%	18.2 107.8%	16.1 101.3%	
PFE	17.7 92.6%	16.7 82.1%	13.2 73.7%	12.2 74.7%	12.2 75.4%	9.7 54.5%	8.1 44.4%	7.9 40.2%	7.9 52.6%	10.2 82.3%	10.9 94.0%	18.2 99.9%	13.5 80.3%	12.9 81.3%	
RHHBY**	18.0 94.2%	19.0 93.5%	33.0 184.3%	27.0 165.3%	19.0 117.5%	16.0 89.9%	10.1 55.4%	12.7 64.5%	9.8 65.3%	12.3 99.2%	13.0 112.1%	17.6 101.0%	19.1 113.4%	18.4 115.3%	
SNY**	20.4 107.0%	15.6 76.7%	15.6 87.1%	13.4 82.1%	11.9 73.6%	8.4 47.2%	8.3 45.5%	8.8 45.1%	7.4 49.3%	10.2 82.3%	11.4 98.3%	13.0 73.0%	16.9 100.3%	15.8 99.4%	
Average	18.6 96.8%	18.8 94.0%	15.7 98.5%	15.6 103.0%	14.9 95.1%	13.4 75.3%	9.3 50.7%	9.9 50.6%	9.2 61.3%	11.5 92.5%	11.6 100.1%	17.1 96.4%	18.7 111.1%	17.6 110.9%	
S&P	19.1	20.3	17.9	16.3	16.2	17.8	18.2	19.6	15.0	12.4	11.6	18.6	16.8	15.9	
Big Cap Drug Growth Expected Over Next 3-4 Years	5-7%	4-6%	3-5%	1-3%	3-5%	0(-2%)	1-3%	5%	5%	7%	7%	11%	5%	5%	
S&P 500 Growth Expected Over Next 3-4 Years	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	7%	8%	8%	

Source: Cowen and Company; Thomson Financial

U.S. Presidential election years bolded.

DRUG STOCK PERFORMANCE

2011	2012	2013	2014*
12%	10%	29%	9%

*Through 9/29/2014

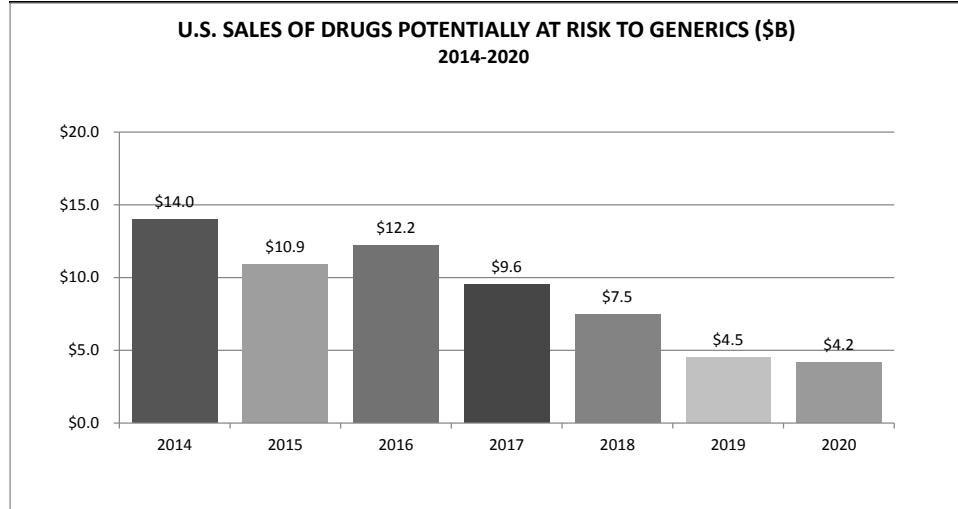
STOCK PERFORMANCE 2004 – September 29, 2014

Source: Cowen and Company

Negative Factors

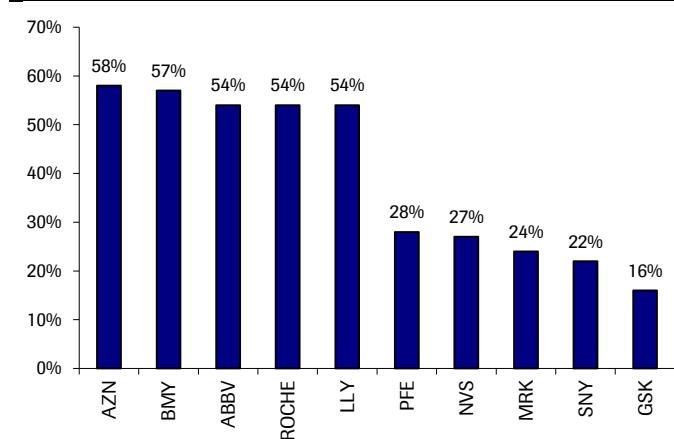
Patent Expirations – Many important products lose patent protection through 2020, clipping the industry's sales growth and margin prospects. 2014 appears to be the most challenging in terms of dollars at risk, with sales totaling \$14.0B, although this is well below 2012's \$21.2B. Patent expirations are a company-specific issue; timing and impact are known with relative certainty, and they are therefore reflected in our revenue and EPS estimates. The graphs below depict total industry dollars at risk to patent expirations and the percentage of sales and EPS vulnerable by company to these expirations.

2014 U.S. SALES OF DRUGS POTENTIALLY AT RISK TO GENERICS (\$B)



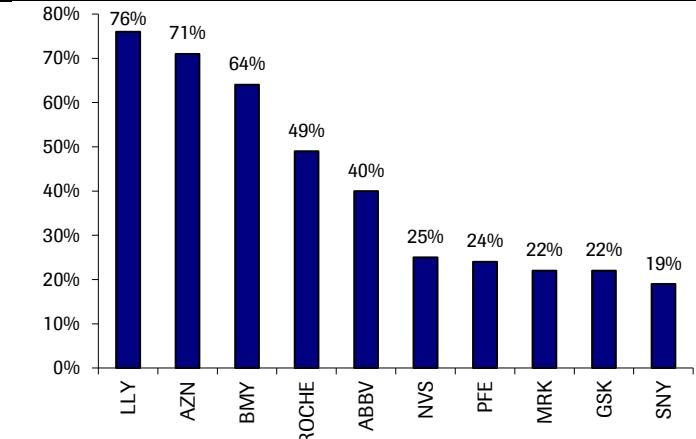
Source: Cowen and Company

% SALES VULNERABLE TO PATENT EXPIRATIONS THROUGH 2020



Source: Cowen and Company

% EPS VULNERABLE TO PATENT EXPIRATIONS THROUGH 2020



PATENT EXPIRATION VULNERABILITY THROUGH 2020

Company	Drug	Territory	Patent Exp. Date	U.S. Sales		Estimated U.S. Sales (\$MM)*	Non-U.S. Sales As % Of Total Sales	Estimated Non-U.S. Sales (\$MM)*	% Total Sales	% Total EPS	
				Estimated WW Sales (\$MM)	Total Sales					EPS (#)	EPS
ABBV	Androgel	U.S.	2015	\$860	100%	\$860			3%	\$0.10	3%
	Humira	U.S.	Dec-16	13,755	51%	6,949			24%	0.81	18%
	Kaletra	U.S.	2016	700	26%	181			1%	0.02	0%
	Humira	E.U.	Apr-18	15,700			49%	7,769	27%	0.91	18%
AZN	Nexium	E.U.	2014	\$3,872			53%	\$2,058	8%	\$0.41	9%
	Synagis/Numax	E.U.	Aug-15	1,015			22%	223	1%	0.04	1%
	Synagis/Numax	U.S.	Oct-15	1,015	78%	792			3%	0.16	4%
	Nexium	U.S.	Oct-15	3,275	47%	1,535			6%	0.31	7%
	Crestor	U.S.	Jan-16	5,240	53%	2,786			11%	0.56	13%
	Iressa	U.S.	Apr-16	710	0%				0%	0.00	0%
	Iressa	E.U.	Apr-16	710			100%	710	3%	0.14	3%
	Rhinocort	U.S.	Oct-17	80	31%	25			0%	0.00	0%
	Crestor	E.U.	2017	5,075			47%	2,377	10%	0.48	13%
	Seroquel XR	U.S.	2017	1,070	60%	637			3%	0.13	3%
	Seroquel XR	E.U.	2017	1,070			40%	433	2%	0.09	2%
	Symbicort	E.U.	2018	3,160			59%	1,876	8%	0.38	9%
	Brilinta	U.S.	Dec-19	1,050	30%	314			1%	0.06	1%
	Brilinta	E.U.	Dec-19	1,050			70%	736	3%	0.15	3%
	Pulmicort Respules	U.S.	2019	750	25%	187			1%	0.04	1%
BMY	Abilify	E.U.	2014	\$2,289			32%	\$730	5%	\$0.11	6%
	Abilify	U.S.	Apr-15	1,895	68%	1,291			9%	0.19	11%
	Baraclude	U.S.	2015	1,510	23%	344			2%	0.05	3%
	Baraclude	E.U.	Oct-16	1,385			77%	1,070	7%	0.16	9%
	Erbium	U.S.	Jan-17	690	96%	660			4%	0.10	5%
	Reyataz	U.S.	Jun-17	1,250	46%	580			4%	0.09	4%
	Orencia	E.U.	2017	2,020			37%	744	5%	0.11	6%
	Ixempra	U.S.	May-17	40	100%	40			0%	0.01	0%
	Reyataz	E.U.	Mar-19	500			54%	268	1%	0.00	0%
	Orencia	U.S.	2019	2,360	63%	1,491			8%	0.22	9%
	Sprycel	E.U.	Apr-20	2,290			56%	1,276	6%	0.19	7%
	Sprycel	U.S.	Jun-20	2,290	44%	1,014			5%	0.15	5%
LLY	Cymbalta	E.U.	Aug-14	\$5,085			72%	\$3,665	19%	\$0.85	31%
	Evista	U.S.	Mar-14	1,050	51%	535			3%	0.12	4%
	Aliimta	E.U.	Dec-15	2,865			55%	1,573	8%	0.37	11%
	Yentreve	U.S.	2015	20	0%	0			0%	0.00	0%
	Aliimta	U.S.	Jan-17	2,850	45%	1,285			6%	0.32	7%
	Strattera	U.S.	2017	720	63%	457			2%	0.11	2%
	Cialis	U.S.	2017	2,510	47%	1,175			5%	0.29	6%
	Cialis	E.U.	2017	2,510			53%	1,335	6%	0.33	7%
	Effient	U.S.	2017	630	75%	470			2%	0.12	2%
	Strattera	E.U.	May-19	245			37%	90	0%	0.02	0%
	Forteo	E.U.	2019	1,675			58%	976	4%	0.25	5%
	Effient	E.U.	2019	320			25%	81	0%	0.02	0%
GSK	Agenerase	E.U.	2014	£113			48%	£54	0%	£0.00	0%
	Infanrix/Pediarix	E.U.	2014	862			67%	580	2%	0.03	3%
	Relenza	E.U.	2014	25			91%	23	0%	0.00	0%
	Avodart	U.S.	2015	840	34%	283			1%	0.02	2%
	Epzicom/Kivexa	U.S.	2016	825	36%	294			1%	0.02	2%
	Trizivir	U.S.	2016	30	14%	4			0%	0.00	0%
	Trizivir	E.U.	2016	30			86%	26	0%	0.00	0%
	Avodart	E.U.	2017	715			66%	474	2%	0.03	3%
	Infanrix/Pediarix	U.S.	2017	985	33%	322			1%	0.02	2%
	Lexiva	U.S.	2017	95	52%	50			0%	0.00	0%
	Lovaza	U.S.	2017	25	100%	25			0%	0.00	0%
	Boostrix	U.S.	2017	400	46%	183			1%	0.01	1%
	Boostrix	E.U.	2017	400			54%	217	1%	0.01	1%
	Epzicom/Kivexa	E.U.	2019	970			64%	624	2%	0.03	3%
	Lexiva	E.U.	2019	100			48%	48	0%	0.00	0%
	Cervarix	E.U.	2020	450			95%	430	1%	0.02	2%
	Cervarix	U.S.	2020	450	5%	20			0%	0.00	0%
	Rotarix	E.U.	2020	660			77%	506	2%	0.03	2%
	Volibris	E.U.	2020	265			100%	265	1%	0.01	1%

Source: Cowen and Company

PATENT EXPIRATION VULNERABILITY THROUGH 2020 – Cont'd

Company	Drug	Territory	Patent Exp. Date	U.S. Sales		Estimated U.S. Sales (\$MM)*	Non-U.S. Sales As % Of Total Sales	Estimated Non-U.S. Sales (\$MM)*	% Total Sales	% Total EPS	
				Estimated WW Sales (\$MM)	As % Of Total Sales					EPS (#)	EPS
MRK	Maxalt	U.S.	Feb-14	\$149	26%	\$38			0%	\$0.00	0%
	Temodar	U.S.	Feb-14	708	5%	38			0%	0.00	0%
	Avelox	U.S.	Mar-14	140	93%	130			0%	0.01	0%
	Remicade	E.U.	Aug-14	2,271			100%	2,271	5%	0.19	5%
	Integrelin	U.S.	Nov-14	186	91%	170			0%	0.01	0%
	Cancidas	U.S.	Jan-15	640	3%	16			0%	0.00	0%
	Nasonex	E.U.	Jan-15	1,095			45%	497	1%	0.04	1%
	PEG-Intron	U.S.	Feb-15	380	4%	14			0%	0.00	0%
	Emend	U.S.	Apr-15	535	54%	290			1%	0.02	1%
	Follistim/Puregon	U.S.	Jun-15	400	29%	118			0%	0.01	0%
	Invanz	U.S.	Nov-15	515	48%	246			1%	0.02	1%
	Zetia	U.S.	Apr-17	2,550	58%	1,472			4%	0.13	3%
	Vytorin	U.S.	Apr-17	1,215	38%	460			1%	0.04	1%
	Zetia	E.U.	Oct-17	2,550			42%	1,078	3%	0.10	3%
	NOMAC/E2	U.S.	2017	75	100%	75			0%	0.01	0%
	Foradil	U.S.	Jan-18	35	50%	18			0%	0.00	0%
	Asmanex DPI	E.U.	Mar-18	150	88%	132			0%	0.01	0%
	Nasonex	U.S.	Apr-18	750	55%	410			1%	0.04	1%
	Nuvaring	U.S.	Apr-18	910	63%	573			1%	0.05	1%
	Nuvaring	E.U.	Apr-18	910			37%	337	1%	0.03	1%
	Asmanex DPI	U.S.	Sep-18	150			12%	18	0%	0.00	0%
	PEG-Intron	E.U.	Dec-18	205			96%	198	1%	0.02	0%
	Elonva	U.S.	2018	60	100%	60			0%	0.01	0%
	Foradil	E.U.	Mar-19	30			50%	15	0%	0.00	0%
	Vytorin	E.U.	Apr-19	500			62%	311	1%	0.03	1%
	Noxafil	U.S.	Jul-19	530	36%	189			0%	0.02	0%
	Noxafil	E.U.	Dec-19	530			64%	341	1%	0.03	1%
	Intron A	U.S.	Aug-20	30	100%	30			0%	0.00	0%
NVS	Sandostatin LAR	U.S.	Jan-14	\$1,589	44%	\$705			1%	\$0.07	1%
	Gleevec	U.S.	Jul-15	4,620	45%	2,085			4%	0.22	4%
	Focalin XR	U.S.	Dec-15	440	67%	293			1%	0.03	1%
	Glivec	E.U.	2016	4,515			55%	2,478	4%	0.26	4%
	Lescol XL	E.U.	2017	25			78%	20	0%	0.00	0%
	Lotrel	U.S.	Dec-17	0	100%	0			0%	0.00	0%
	Myfortic	U.S.	Apr-17	465	29%	136			0%	0.01	0%
	Xolair	E.U.	2017	875			100%	875	1%	0.09	1%
	Lucentis	E.U.	2018	2,800			100%	2,800	4%	0.29	4%
	Tekturna/Rasilez	U.S.	2018	150	38%	57			0%	0.01	0%
	Trileptal	U.S.	2018	180	100%	180			0%	0.02	0%
	Xolair	U.S.	2018	925	0%	0			0%	0.00	0%
	Afinitor/Certican	E.U.	2018	2,425			49%	1,200	2%	0.12	2%
	Gilenya	E.U.	2018	3,350			53%	1,780	3%	0.18	2%
	Gilenya	U.S.	2019	3,600	47%	1,687			3%	0.17	2%
	Exjade	U.S.	2019	850	30%	258			0%	0.03	0%
	Exforge	U.S.	2019	550	26%	144			0%	0.01	0%
	Exforge	E.U.	2019	550			74%	406	1%	0.04	0%
	Exelon Patch	E.U.	2019	450			56%	252	0%	0.03	0%
	Exelon Patch	U.S.	2019	450	44%	198			0%	0.02	0%
	Afinitor/Certican	U.S.	2020	3,025	51%	1,528			2%	0.16	2%
PFE	Viracept	U.S.	Apr-14	\$20	100%	\$20			0%	\$0.00	0%
	Celebrex	U.S.	May-14	2,918	68%	1,991			4%	0.08	4%
	Celebrex	E.U.	Nov-14	2,918			32%	927	2%	0.04	2%
	Lyrica	E.U.	2014	4,595			54%	2,495	5%	0.10	4%
	Enbrel	E.U.	Feb-15	3,840			100%	3,840	8%	0.15	7%
	Zyvox	U.S.	May-15	1,340	49%	662			1%	0.03	1%
	Rapamune	E.U.	Jun-15	330			36%	118	0%	0.00	0%
	Relpax	E.U.	Dec-15	355			33%	116	0%	0.00	0%
	Vfend	E.U.	Jan-16	825			95%	784	2%	0.03	1%
	Zyvox	E.U.	Jan-16	1,000			51%	506	1%	0.02	1%
	Lyrica	U.S.	Dec-18	4,505	46%	2,059			4%	0.09	3%
	Chantix	U.S.	2020	635	58%	370			1%	0.02	1%

Source: Cowen and Company

PATENT EXPIRATION VULNERABILITY THROUGH 2020 – Cont'd

Company	Drug	Territory	Patent Exp. Date	Estimated WW Sales (\$MM)	U.S. Sales		Estimated U.S. Sales (\$MM)*	Non-U.S. Sales As % Of Total Sales	Estimated Non-U.S. Sales (\$MM)*	% Total Sales	% Total EPS	
					Total Sales	As % Of Total Sales					EPS (#)	EPS
ROCHE	Rituxan	E.U.	2014	CHF 6,951			52%	CHF 3,591	8%	CHF 0.93	6%	
	Herceptin	E.U.	Jul-14	6,079			70%	4,231	9%	1.10	7%	
	Rituxan	U.S.	2015	6,940	48%	3,354			7%	0.87	6%	
	Xolair	U.S.	2015	877	100%	877			2%	0.23	1%	
	Valcyte	U.S.	Sep-15	705	53%	375			1%	0.10	1%	
	Valcyte	E.U.	Sep-16	630			47%	294	1%	0.08	6%	
	Tamiflu	E.U.	Feb-16	400			49%	198	0%	0.05	7%	
	Tamiflu	U.S.	Dec-16	400	51%	202			0%	0.05	5%	
	Pegasys	E.U.	2017	595			76%	455	1%	0.12	1%	
	Avastin	U.S.	2018	6,975	42%	2,928			6%	0.76	1%	
	Actemra	E.U.	2018	1,935			68%	1,322	3%	0.34	0%	
	Actemra	U.S.	2018	1,935	32%	613			1%	0.16	0%	
	Avastin	E.U.	Dec-19	6,825			58%	3,960	7%	1.03	0%	
	Herceptin	U.S.	2019	4,285	30%	1,303			2%	0.34	1%	
SNY	Lucentis	U.S.	2019	1,830	100%	1,830			3%	0.48	4%	
	Tarceva	E.U.	Mar-20	1,050			50%	526	1%	0.14	2%	
	Mircera	E.U.	2020	645			100%	645	1%	0.17	1%	

*Estimated sales in year prior to patent expiration

**Estimated sales in the year generic competition is expected

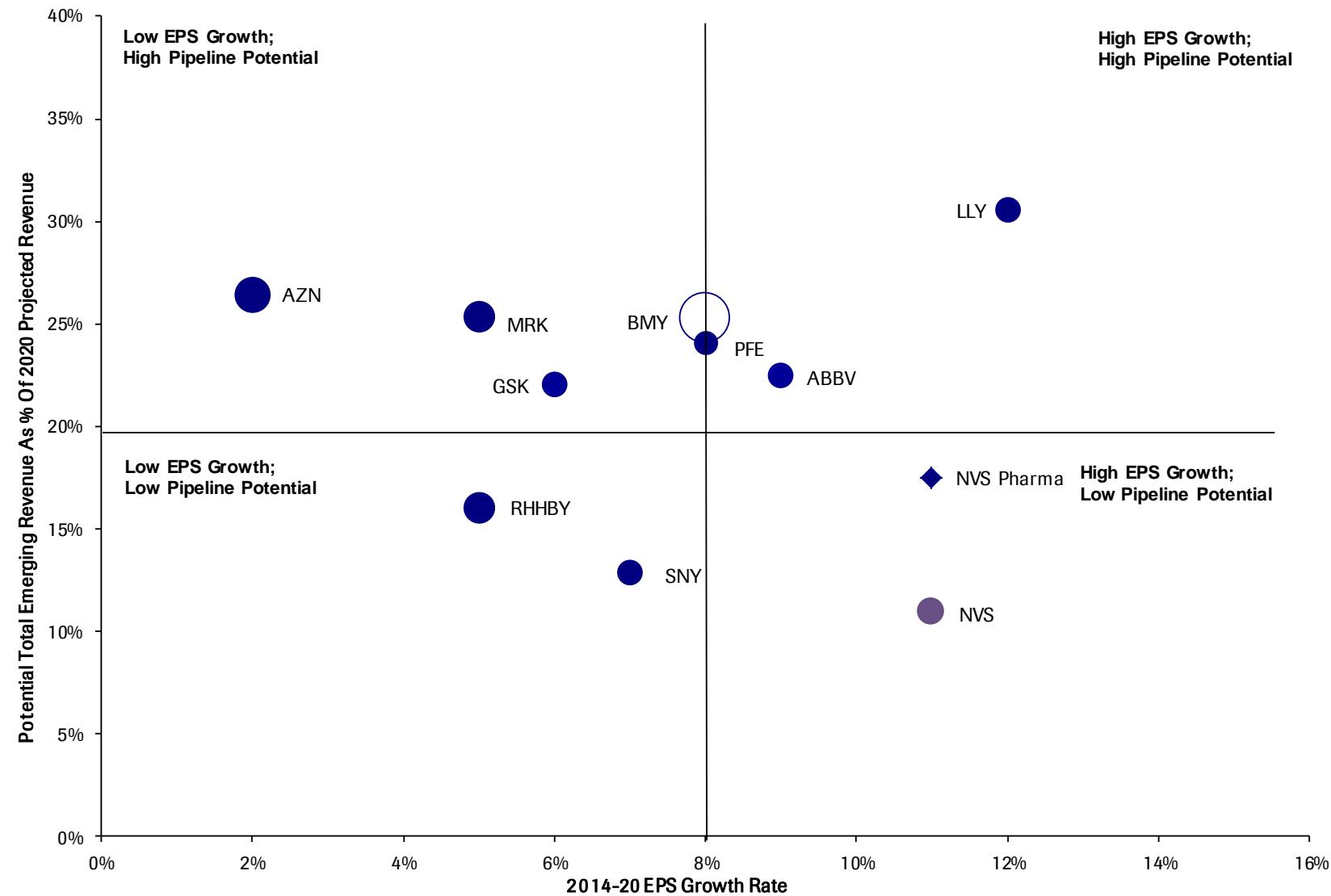
#Assumes 25% net margin

Source: Company data, FDA Orange Book, Thomson Pharma, Cowen and Company

Source: Cowen and Company

Pharma Companies Vary In “Relative Strength.” The analysis on the next page depicts estimated long-term EPS growth on the x-axis and potential total emerging revenue as a percentage of terminal year projected revenue on the y-axis. Potential total emerging revenue equals the potential of the Phase II pipeline plus potential acquired revenue (estimated to be 25% of current cash plus short-term investments). The size of each company's dot is in proportion to that company's 2020 P/E.

RELATIVE STRENGTH: COMPARISON OF EPS GROWTH AND PHASE II PIPELINES



Source: Cowen and Company.

2014 EPS HIT FROM HEALTH CARE REFORM

2014									
Company	Statements re: Impact Of U.S. Health Care Reform	Donut Hole Impact	Incremental EPS Impact	+ Rebate Impact	Incremental EPS Impact	+ SG&A Impact (Excise Tax)	Incremental EPS Impact	= Total EPS Impact	Comments
ABBV	- Total estimated impact of HC Reform will be \$400MM 2013; \$300MM for rebates and donut hole, and \$100MM for excise tax	\$100MM	\$0.05	\$200MM	\$0.10	\$100MM*	\$0.05	\$0.20	6% of 2014 EPS estimate of \$3.12
AZN	- HC Reform impact \$858MM; 2.8% hit to SG&A in 2012	\$173MM	\$0.11	\$450MM	\$0.28	\$235MM	\$0.14	\$0.53	12% of 2014 EPS estimate of \$4.40
BMY	- Medicare Part D coverage gap (~\$300MM) - Annual pharmaceutical company fee (~\$220MM+)	\$75MM	\$0.04	\$225MM	\$0.11	\$220MM	\$0.11	\$0.26	14% of 2014 EPS estimate of \$1.80
LLY	- Reduce 2013 revenue by \$380–450MM - Increase 2013 SG&A expense by \$125–175MM	\$100MM	\$0.08	\$300MM	\$0.20	\$150MM	\$0.11	\$0.40	14% of 2014 EPS estimate of \$2.80
GSK	- Impacted WW revenue by £380MM in 2011 with incremental £325MM in 2011 (majority of incremental increase in U.S.) £102MM excise tax in 2011	£50MM	£0.01	£140MM	£0.02	£110MM	£0.02	£0.05	0% of 2014 EPS estimate of 93.0p
JNJ	- Total impact of HC Reform est. at \$1B in 2013	\$150MM	\$0.05	\$450MM	\$0.10	\$400MM*	\$0.10	\$0.25	4% of 2014 EPS estimate of \$5.80
MRK	- 2011 impact of \$400–450MM incl. \$165MM industry fees - 2012 impact not provided but industry fee starts to rise	\$80MM	\$0.02	\$250MM	\$0.06	\$175MM	\$0.05	\$0.14	4% of 2014 EPS estimate of \$3.50
NVS	- % of business (which is derived from Medicare & Medicaid) in line w/peers	\$60MM	\$0.02	\$190MM	\$0.07	\$175MM	\$0.06	\$0.15	3% of 2014 EPS estimate of \$5.15
PFE	- 2013 negative impact of \$900MM (\$600MM rev.; \$300MM SI&A)	\$150MM	\$0.02	\$450MM	\$0.05	\$300MM	\$0.03	\$0.11	5% of 2014 EPS estimate of \$2.20
RHHBY	-2012 negative impact of CHF 460 (CHF 300MM rev (10% Medicare PartD coverage gap); CHF 163 G&A)	CHF 35MM	CHF 0.01	CHF 265MM	CHF 0.12	CHF 163MM	CHF 0.07	CHF 0.20	1% of 2014 EPS estimate of CHF 14.70
SNY	- 2011 sales reduced by ~\$260MM (€195MM), \$115MM from donut hole - ~\$120MM (€95MM) impact in 2011 from excise fee	€90MM	€ 0.05	€105MM	€ 0.06	€95MM	€ 0.05	€ 0.16	3% of 2013 EPS estimate of €5.20

Source: Cowen and Company.

M&A And Restructuring Likely Given Industry Fragmentation

The global pharmaceutical industry remains fragmented, with the current largest companies holding only single-digit worldwide market shares. We expect that the higher costs of remaining competitive in marketing and R&D will drive continued merger and acquisition activity, likely involving non-U.S. companies that are disproportionately exposed to weaker markets, mid-sized companies looking to expand marketing and development infrastructures, and larger companies with pipeline gaps. Our forecasts for industry sales and EPS growth do not factor in any contribution from M&A and restructuring activity, which in 2013 totaled \$210B.

HISTORICAL M&A ACTIVITY (\$MM)

1994	\$37,500	2000	\$179,928	2006	\$84,404	2012	\$146,061
1995	\$34,657	2001	\$51,519	2007	\$74,431	2013	\$210,275
1996	\$2,495	2002	\$62,306	2008	\$158,366	2014*	\$504,240
1997	\$6,449	2003	\$21,633	2009	\$192,238		
1998	\$65,952	2004	\$91,805	2010	\$147,578		
1999	\$39,882	2005	\$49,721	2011	\$194,666		

*Through August

Source: SDC/ Thomson Financial Services

2014 MAJOR PHARMACEUTICAL M&A/RESTRUCTURING ACTIVITY

Date	Acquiror	Target	Transaction Value (\$MM)	Comment
1/3/2014	NorthStar Realty Finance Corp.	Harvard Square Facility	32	- Harvard Square Facility comprises 184-unit independent and assisted living facility
1/3/2014	Meihua Holdings Group Co., Ltd.	Dalian Hissen BioPharm Co., Ltd.	116	- Dalian Hissen BioPharm Co., Ltd. manufactures hepatitis B vaccine
1/6/2014	Henry Schein, Inc.	Arseus NV, Five Businesses	68	- Arseus NV represents the combined operations of five businesses in the Netherlands
1/6/2014	Aratana Therapeutics, Inc.	Okapi Sciences NV	45	- Okapi Sciences NV, a biopharmaceutical company, focuses on licensing, development, and
1/6/2014	GE Healthcare Ltd.	Thermo Fisher Scientific Inc., HyClone(TM)	1,060	- Thermo Fisher Scientific manufactures cell culture media and sera products for cell biology research
1/6/2014	Aviv REIT, Inc. (NYSE:AVIV)	Campus In Minnesota	43	- Campus In Minnesota comprises a post-acute and long-term care skilled nursing facility
1/6/2014	Medtronic, Inc. (NYSE:MDT)	TYRX, Inc.	160	- TYRX manufactures implantable combination drug+device products
1/7/2014	Carl Zeiss Meditec, Inc.	Aaren Scientific Inc.	70	- Aaren Scientific manufactures intraocular lenses and ophthalmic surgical products
1/7/2014	Becton, Dickinson and Company	Alverix, Inc.	40	- Alverix manufactures instrument and connectivity platforms for diagnostic point-of-care testing
1/7/2014	Impax Laboratories Inc.	DURECT Corporation, Worldwide Rights of	63	- DURECT Corporation, worldwide rights to ELADUR, a transdermal bupivacaine patch
1/7/2014	Surgical Care Affiliates, Inc.	East Brunswick Surgery Center, LLC	25	- East Brunswick Surgery Center DBA University SurgiCenter owns an ambulatory surgical center
1/7/2014	American Realty Capital Properties	The Solana at Cinco Ranch	71	- The Solana at Cinco Ranch comprises a 184-unit assisted living and memory care facility
1/8/2014	Forest Laboratories Inc.	Aptalis Holdings Inc.	2,900	- Aptalis Holdings provides a range of therapies for cystic fibrosis (CF) and GI disorders
1/8/2014	Eddingpharm (Cayman) Inc.	ACT Biotech, Inc., Worldwide Rights To	95	- Acquisition of Worldwide Rights To Telatinib, ACTB1003, and ACTB1010
1/8/2014	Teva Pharmaceutical Industries	NuPathé, Inc. (NasdaqGM:PATH)	281	- NuPathé focuses on branded therapeutics for neurological and psychiatric disorders
1/9/2014	Altaris Capital Partners, LLC	HealthTronics, Inc.	140	- HealthTronics provides lithotripsy, laser treatment, cryotherapy, and laboratory solutions
1/9/2014	American Financial Group Inc.	Summit Holding Southeast Inc.	250	- Summit Holding Southeast provides managed care workers' compensation products
1/10/2014	Symrise AG (XTRA:SY1)	Probi AB (OM:PROB)	39	- Probi AB researches, develops, and sells probiotics in Sweden and internationally
1/12/2014	Alyniam Pharmaceuticals, Inc.	Sirma Therapeutics Inc.	307	- Sirma Therapeutics, Inc. develops therapeutics based on RNA interference (RNAi) technology
1/13/2014	Galena Biopharma, Inc.	Mills Pharmaceuticals, LLC	30	- Mills Pharmaceuticals, LLC develops active ingredient anagrelide, GALE-401 (Anagrelide CR)
1/13/2014	Jazz Pharmaceuticals International	Aerial BioPharma, LLC, ADX-N05	397	- ADX-N05 of Aerial BioPharma, LLC was acquired by Jazz Pharmaceuticals International III Limited
1/13/2014	Agenus Inc. (NasdaqCM:AGEN)	4-Antibody AG	51	- 4-Antibody AG discovers and develops antibody therapeutics through its technology platform
1/13/2014	The Cahill Group	Rosewood Care Center Holding Company Inc.	250	- Rosewood Care Center Holding Company Inc. owns and operates nursing care centers
1/16/2014	Lend Lease Group (ASX:LLC)	Seven Queensland Retirement Villages	60	- Acquisition of Seven Queensland Retirement Villages by Lend Lease Group
1/16/2014	The Carlyle Group LP	Ortho-Clinical Diagnostics, Inc.	4,150	- Ortho-Clinical Diagnostics, Inc. provides solutions for the transfusion medicine community
1/17/2014	Organogenesis Inc.	Shire Regenerative Medicine, Inc., Dermagraft	300	- Intellectual property rights of a living skin substitute for treatment of diabetic foot ulcers
1/17/2014	Aurobindo Pharma Limited	Actavis plc, Generics Commercial Operations	41	- Acquisition of Actavis plc, Generics Commercial Operations
1/21/2014	BioMarin Pharmaceutical Inc.	Repligen Corporation, Histone Deacetylase	162	- Acquisition of a histone deacetylase inhibitor portfolio that increases frataxin production
1/21/2014	Par Pharmaceutical Companies Inc.	JHP Pharmaceuticals, LLC	490	- JHP Pharmaceuticals, LLC acquires, develops, manufactures, and sells sterile injectable products
1/21/2014	NorthStar Realty Finance Corp.	Parkview Frisco	40	- Parkview Frisco, L.P., Parkview Frisco operates 202-unit independent living community
1/22/2014	Quest Diagnostics Inc. (NYSE:DGX)	Solstas Lab Partners Group, LLC	570	- Solstas Lab Partners Group, LLC provides clinical, anatomic pathology, and esoteric testing services
1/22/2014	Intuitive Surgical International Ltd.	Luna Innovations Incorporated, Medical Shape	30	- Luna Innovations comprises fiber optic shape sensing and localization technology
1/23/2014	IP Group Plc (LSE:IP)	Fusion IP plc (AIM:IP)	120	- Fusion IP plc, through its subsidiaries, commercializes intellectual property (IP)
1/23/2014	Tokyo Tatemono Co. Ltd.	Tokyo Electric Power Company, Incorporated,	96	- Shinjuku Ward comprises a hospital with 7 floors, 113 beds and site area of 5,609 square meters
1/24/2014	Legal & General Property Limited	Five Care Homes in Suffolk	51	- Five Care Homes in Suffolk comprises five care homes including on-site day centers
1/28/2014	Intermediate Capital Group PLC	Cura Day Hospitals Group Pty Ltd.	175	- Cura Day Hospitals Group Pty Ltd. provides healthcare services in Australia
1/29/2014	Fluidigm Corporation	DVS Sciences Inc.	208	- DVS Sciences Inc. develops analytical equipment and reagents for use in biomarker applications
1/29/2014	Atlantic Health System, Inc.	Hackettstown Regional Medical Center	54	- Hackettstown Regional Medical Center provides medical care services to patients in NJ and PA
1/30/2014	Wright Medical Group Inc.	Solana Surgical, LLC	85	- Solana Surgical, LLC develops orthopedic products
1/30/2014	Wright Medical Group Inc.	OrthoPro, LLC	36	- OrthoPro, LLC manufactures surgical products for the foot and ankle market in the United States.
1/30/2014	Organic Growth International, LLC	CEN Biotech, Inc.	64	- CEN Biotech, Inc. produces and supplies medical marijuana
1/30/2014	Organic Growth International, LLC	RXNB Inc.	72	- RXNB Inc. manufactures and distributes pharmaceuticals

Total Transaction Value, 2013 \$13,336

Source: Cowen and Company

2014 MAJOR PHARMACEUTICAL M&A/RESTRUCTURING ACTIVITY

Date	Acquirer	Target	Transaction Value (\$MM)	Comment
2/3/2014	Smith & Nephew, Inc.	ArthroCare Corporation (NasdaqGS:ARTC)	1,730	- ArthroCare Corporation develops surgical products based on its Coblation technology
2/3/2014	Mississippi Health Care Group,	Elk Valley Professional Affiliates, Inc. and	60	- Acquisition of companies offering home health care services
2/3/2014	Valeant Pharmaceuticals	Precision Dermatology, Inc.	500	- Precision Dermatology develops, manufactures, and markets skincare solutions
2/3/2014	Accelgent, Inc.	Lake Region Medical, Inc.	315	- Lake Region Medical, Inc. develops and manufactures medical devices and components
2/4/2014	Myriad Genetics Inc.	Crescendo Bioscience, Inc.	270	- Crescendo Bioscience develops biology-based tests for autoimmune and inflammatory diseases
2/6/2014	Prime Healthcare Services, Inc.	Garden City Hospital Inc.	80	- Garden City Hospital Inc. owns and operates healthcare facilities
2/7/2014	Wanzai County Shuanglong	Jilin Jinbao Pharmaceutical Co., Ltd.	178	- Jilin Jinbao Pharmaceutical Co., Ltd. manufactures pharmaceutical products
2/11/2014	Nestlé S.A. (SWX:NESN)	Galderma Pharma SA	3,740	- Galderma Pharma develops solutions for the treatment of various skin diseases and conditions
2/11/2014	Mallinckrodt plc (NYSE:MNK)	Cadence Pharmaceuticals Inc.	1,252	- Cadence Pharmaceuticals, Inc., a biopharmaceutical company, focuses on acquiring, in-licensing,
2/11/2014	21st Century Oncology, Inc.	South Florida Radiation Oncology, LLC	88	- South Florida Radiation Oncology, LLC owns and operates cancer treatment centers in South Florida
2/12/2014	Undisclosed	Greencross Limited (ASX:GXL)	36	- Mammoth Pet Pty Limited, a pet specialty retailer, owns and operates 100 pet stores in Australia
2/12/2014	Professional Compounding Centers	The Specials Laboratory Ltd. and Craig and	39	- Acquisition of the combined operations of The Specials Laboratory Ltd., Craig and Hayward Ltd., and
2/12/2014	Retrophin, Inc. (NasdaqGM:RTRX)	Manchester Pharmaceuticals, Inc.	63	- Manchester Pharmaceuticals sells therapeutic modalities for ultra-rare diseases.
2/13/2014	PhotoMedex, Inc.	LCA-Vision Inc. (NasdaqGS:LCAV)	105	- LCA-Vision Inc. provides fixed-site laser vision correction services via Laskiplus vision centers
2/17/2014	Hemis Fastighets AB	Portfolio of 15 Finnish Healthcare Properties	137	- Portfolio of 15 Finnish Healthcare Properties comprises 15 healthcare properties available for use
2/17/2014	TPG Capital, L.P.; Fosun Industrial	Chindex International Inc. (NasdaqGS:CHDX)	341	- Chindex International, Inc. provides healthcare services in China
2/17/2014	Partner Group Holding AG	MultiPlan, Inc.	4,400	- MultiPlan, Inc. operates regional preferred provider organization (PPO) networks
2/17/2014	Beijing Healthcare Technology Co.	Inner Mongolia Bigvet Biotech Co., Ltd.	69	- Inner Mongolia Bigvet Biotech Co., Ltd. Offers biological products.
2/18/2014	Stryker Corporation (NYSE:SYK)	BERCHTOLD GmbH & Co. KG	172	- BERCHTOLD GmbH & Co. KG develops, manufactures, and installs operating lights and tables
2/18/2014	Actavis plc (NYSE:ACT)	Forest Laboratories Inc. (NYSE:FRX)	25,449	- Forest Laboratories, Inc. develops, manufactures, and sells branded forms of ethical drugs
2/18/2014	Fosun Industrial Co., Ltd.; Ample	Chindex Medical Limited	45	- Chindex Medical Limited engages in medical devices and instruments in China and Hong Kong
2/18/2014	Sabra Health Care REIT, Inc.	Nye Senior Services LLC, Six Senior Housing	90	- Acquisition of Nye Senior Services LLC, Six Senior Housing Campuses
2/20/2014	Brookdale Senior Living Inc.	Emeritus Corp. (NYSE:ESC)	5,447	- Emeritus Corporation operates senior living communities in the United States
2/24/2014	Cinven Limited	Medpace, Inc.	915	- Medpace, Inc. operates as a clinical research organization
2/26/2014	Imperial Logistics	Eco Health Limited	74	- Eco Health Limited provides distribution of ethical and generic pharmaceutical products
2/27/2014	UDG Healthcare plc (LSE:UDG)	KnowledgePoint360 Group LLC, Healthcare	144	- Acquisition of healthcare communications business of KnowledgePoint360 Group LLC.
2/28/2014	Shanghai Fosun Pharmaceutical	Jinzhou Aohong Pharmaceutical Co., Ltd.	248	- Jinzhou Aohong Pharmaceutical Co., Ltd. manufactures medicines.
2/28/2014	McKesson Corporation	Celestis AG (DB:CLS1)	1,424	- Celestis AG, an international trading company, provides logistics and services in the pharmaceutical and
2/28/2014	Undisclosed	Nestle HomeCare France SAS	35	- Nestle HomeCare France SAS is based in Noisiel, France
3/3/2014	Aviv REIT, Inc. (NYSE:AVIV)	Nine Post-Acute And Long-Term Care Skilled	49	- Nine Post-Acute And Long-Term Care Skilled Nursing Facilities in Kentucky and Iowa
3/4/2014	Regal Lifestyle Communities Inc.	Birkdale Retirement Home	35	- Acquisition of a multi-unit retirement community
3/10/2014	Genomma Lab Internacional SAB	Casa Marzam S.A. de C.V.	45	- Casa Marzam S.A. de C.V. operates as a distributor of pharmaceutical products in Mexico.
3/11/2014	Undisclosed	Non Core Properties In Ontario	59	- Non Core Properties In Ontario comprises 14 retirement residences and consists of 945 suites
3/12/2014	Medix Fund Ltd. (LSE:MXF);	Lunn Healthcare Properties Limited	41	- Lunn Healthcare Properties Limited owns primary healthcare centers
3/13/2014	Vectura Group plc (LSE:VEC)	Activaero GmbH	187	- Activaero GmbH develops controlled breathing technologies
3/13/2014	Charles River Laboratories	Galapagos NV, CRO Services Division	186	- Galapagos NV, CRO Services Division comprises Argenta and BioFocus businesses
3/13/2014	Parkway Life Real Estate	Miyako Enterprise, Two Nursing Homes And	29	- Acquisition of two nursing homes and one lodging facility for the elderly in Japan
3/13/2014	Medira Inc.	Medegen Medical Products, LLC And Certain	75	- Medegen Medical Products, LLC develops, manufactures, and markets medical products
3/13/2014	Tesaro, Inc. (NasdaqGS:TSRO)	AnaptyBio, Inc., Worldwide Rights to TIM-3,	125	- Acquisition of Worldwide Rights to TIM-3, LAG-3 and PD-1 Targeting Products
3/13/2014	Islet Sciences, Inc. (OTCPK:ISLT)	Brighthaven Inc., Venture LLC	83	- Brighthaven is developing Remoglitofin-etabonate, a selective sodium glucose co-transporter 2
3/13/2014	Hospital De Madrid, S.A.	Sanatorio Quirúrgico Modelo, S.L.	118	- Sanatorio Quirúrgico Modelo, S.L. operates hospitals and a children's specialist centre in Galicia
3/17/2014	Formation Capital, L.L.C.; Eclipse	Healthcare Real Estate Portfolio	1,050	- Healthcare Real Estate Portfolio comprises 43 primarily private pay senior housing facilities
3/17/2014	HealthLease Properties Real Estate	Clearavista Lake Health Campus And Arlington	37	- Acquisition of 100-unit senior housing and care facilities with 100 short-stay rehabilitation suites
3/17/2014	Griffin-American Healthcare REIT	Medical Office Building, Senior Housing	85	- Acquisition of a medical office building, a senior housing facility, and a skilled nursing facility
3/18/2014	United Gene High-Tech Group	Smart Ascent Limited	100	- Smart Ascent Limited is an investment holding company
3/19/2014	Horizon Pharma, Inc.	Vidara Therapeutics International Limited	660	- Vidara Therapeutics International Limited develops specialty pharmaceutical products
3/20/2014	EKF Diagnostics Holdings plc	SELAH Genomics Inc	73	- SELAH Genomics Inc. develops nanotechnology-enabled products for the biomedical industry
3/20/2014	EKF Diagnostics Holdings plc	DiaSpect Medical AB	34	- DiaSpect Medical AB develops hemoglobin measurement systems in the European Union
3/20/2014	Concordia Healthcare Corp.	Revive Pharmaceuticals, Donnatal	265	- Donnatal is an adjunctive therapy in the treatment of IBS and acute enterocolitis
3/20/2014	Aratana Therapeutics, Inc.	Adaxis, Inc., Worldwide License For Adxs-Cedarburg Pharmaceuticals, Inc.	53	- Acquisition of license for design of an immunotherapy utilizing live attenuated Listeria monocytogenes
3/24/2014	Albany Molecular Research Inc.	AQTIS Medical BV	41	- Cedarburg Pharmaceuticals engages in the contract of commercial small molecule APIs
3/25/2014	Sinclair Is Pharma plc (AIM:SPH)	PACK Pharmaceuticals, LLC	64	- AQTIS Medical BV specializes in medical devices for minimal invasive aesthetics therapies
3/27/2014	Rising Pharmaceuticals, Inc.	Nordion Inc. (TSX:NDN)	100	- PACK Pharmaceuticals, LLC markets and sells generic medications in North America
3/28/2014	Sterigenics International, Inc.	Aptiv Solutions, Inc.	766	- Nordion Inc. provides products and services for disease prevention, diagnosis, and treatment
3/31/2014	ICON Public Limited Company	Two Long-Term Acute Care Hospitals Located	144	- Aptiv Solutions, Inc. operates as a clinical research organization that offers clinical trial services
3/31/2014	Physicians' Realty L.P.	Prestige Care, One Assisted Living Community	40	- Acquisition of two long-term acute care hospitals in Pittsburgh and Fort Worth
3/31/2014	National Health Investors Inc.	CDMI, LLC	40	- Acquisition of 105 assisted living units in Idaho and three skilled nursing facilities in Oregon
4/1/2014	Magellan Rx Management, LLC	Integrated Medical Systems International, Inc.	370	- CDMI, LLC operates as a medical and pharmacy benefit management company
4/1/2014	Steris Corp. (NYSE:STE)	Silommedical Co.,Ltd.	165	- Integrated Medical Systems International, Inc. provides surgical instrument repair services.
4/1/2014	Actavis plc (NYSE:ACT)	AccessClosure, Inc.	100	- Silommedical manufactures and distributes generics pharmaceutical products in Thailand.
4/2/2014	Cardinal Health, Inc. (NYSE:CAH)	Acceleron Pharma, Inc. (NasdaqGM:XLRN)	320	- AccessClosure, Inc. designs, manufactures, and distributes access site management devices
4/2/2014	Celgene Corporation	Long Island College Hospital Inc.	47	- Acceleron Pharma focuses on protein therapeutics for cancer and rare diseases
4/3/2014	Undisclosed	BioFarb SA (BVB:BIO)	250	- Long Island College Hospital Inc. operates as a community hospital and medical school
4/4/2014	Muntenia Sif (BVB:SIF4)	Ranbaxy Laboratories Ltd. (BSE:500359)	47	- Biofarb S.A. manufactures pharmaceutical products primarily for human use in Romania
4/6/2014	Sun Pharmaceutical Industries	Iquum, Inc.	4,305	- Ranbaxy Laboratories engages in the manufacture, marketing, and sale of pharmaceuticals
4/7/2014	Roche Molecular Systems, Inc.	Questcor Pharmaceuticals, Inc.	450	- Iquum, Inc. provides biological sample testing technology to the bioassay market
4/7/2014	Mallinckrodt plc (NYSE:MNK)	THI Beacon Court Limited	5,137	- Questcor provides drugs for the treatment of autoimmune and inflammatory disorders
4/7/2014	Undisclosed	Guizhou Baite Pharmaceutical Co., Ltd.	48	- THI Beacon Court Limited (UPMC Beacon Hospital) provides acute care services in South Dublin
4/7/2014	Zhejiang Conba Pharmaceutical	Smiles Dental	160	- Guizhou Baite manufactures and distributes Rx and OTC Chinese herbal medicine and chemical medicine
4/8/2014	Oasis Healthcare Limited	Prism UK Medical Ltd.	50	- Smiles Dental owns and operates a chain of dental care clinics in Ireland and the United Kingdom.
4/11/2014	LDC Ltd.	Oral Hammaslääkärit Plc (HLSE:ORA1V)	47	- Prism UK Medical manufactures medical equipment for the mobility disadvantaged in the UK
4/14/2014	CapMan Oyi (HLSE:CPMBV); Atine	California Stem Cell, Inc.	94	- Oral Hammaslääkärit Plc provides dental health care services in Finland
4/14/2014	Neostem, Inc. (NasdaqCM:NBS)	Seniors Housing and Care Property Portfolio	74	- California Stem Cell engages in human cell populations
4/15/2014	HealthLease Properties Real Estate	TopoTarget A/S (CPSE:TOPO)	49	- Seniors Housing and Care Property Portfolio: skilled nursing/assisted living facilities in NC, VA, PA
4/16/2014	BioAlliance Pharma (ENXTPA:BIO)	Scanned Multimedis S.A. (WSE:SCM)	105	- Topotarget A/S, develops and commercializes a portfolio of oncology product candidates
4/16/2014	Dadley Investments Sp. z.o.o.	Chengdu Yingde Bio-Engineering Co., Ltd.	57	- Scanned Multimedis S.A. provides medical care services in Poland
4/18/2014	Shinva Medical Instrument Co., Ltd.	Novartis Animal Health Inc.	59	- Chengdu Yingde Bio-Engineering provides pharmaceutical engineering and technical services
4/22/2014	Elanco Animal Health, Inc.	GlaxoSmithKline plc, Marketed Oncology	5,350	- Novartis Animal Health Inc. researches, develops, and commercializes animal treatments
4/22/2014	Novartis AG (SWX:NOVN)	Novartis AG, Global Vaccines Business	16,000	- GSK Marketed Oncology Portfolio provides development, and production of oncology drugs
4/22/2014	GlaxoSmithKline plc (LSE:GSK)	Allergan Inc. (NYSE:AGN)	7,050	- Novartis AG, Global Vaccines Business develops and supplies vaccines
4/22/2014	Valeant Pharmaceuticals	47,866	- Allergan, Inc. operates as a multi-specialty health care company	

Source: Cowen and Company

2014 MAJOR PHARMACEUTICAL M&A/RESTRUCTURING ACTIVITY

Date	Acquiror	Target	Transaction Value (\$MM)	Comment
4/23/2014	The Medicines Company	Tenaxis Medical, Inc.	170	- Tenaxis Medical develops and markets sealants and anti-adhesion agents for surgical markets
4/24/2014	Hyperion Therapeutics, Inc.	Andromeda Biotech Ltd.	571	- Andromeda Biotech Ltd. develops treatment for autoimmune diabetes
4/24/2014	Zimmer Holdings, Inc. (NYSE:ZMH)	LVB Acquisition, Inc.	13,926	- LVB Acquisition, through its subsidiary Biomet, manufactures and distributes surgical products
4/24/2014	Endo Ventures Limited	Zogenix, Inc., Worldwide Rights to Sumavel®	105	- As of 5/16/14, Worldwide Rights to Sumavel® DosePro® of Zogenix were acquired by Endo
4/25/2014	Medtech Products, Inc.	INSIGHT Pharmaceuticals, LLC	750	- INSIGHT Pharmaceuticals manufactures non-prescription medications, personal care products
4/28/2014	Pfizer Inc. (NYSE:PFE)	AstraZeneca PLC (LSE:AZN)	127,094	- AstraZeneca PLC discovers, develops, and commercializes pharmaceuticals
4/28/2014	Forest Laboratories Inc.	Furiex Pharmaceuticals, Inc. (NasdaqGS:FURX)	1,558	- Furiex Pharmaceuticals, Inc. operates as a drug development company that is involved in compound
4/29/2014	Bristol-Myers Squibb Company	iPerian, Inc.	725	- iPerian engages in the industrialization of induced pluripotent stem cell technology
4/29/2014	Endo Netherlands B.V.	Grupo Farmacéutico Somar, Sociedad	269	- Grupo Farmacéutico Somar, Sociedad Anónima Promotora de Inversión de Capital Variable
4/29/2014	The Carlyle Group LP	Haier Bio-Medical and Laboratory Co., Ltd.	65	- Haier Bio-Medical and Laboratory Co. manufactures laboratory equipment
5/1/2014	St Ives plc (LSE:SIV)	The Health Hive Group Ltd	85	- The Health Hive Group Ltd. operates as a patient centric communication agency to the healthcare sector
5/1/2014	Shire plc (LSE:SHP)	Fibrotech Therapeutics Pty Ltd.	75	- Fibrotech Therapeutics Pty Ltd., a drug development company, develops novel drug candidates to treat the
5/2/2014	Aviv REIT, Inc. (NYSE:AVIV)	Four Post-Acute And Long-Term Care Skilled	54	- Acquisition of four post-acute and long-term care skilled nursing facilities
5/4/2014	Kingworld (Hong Kong) Holdings	Shenzhen Dong Di Xin Technology Company	32	- Shenzhen Dong Di Xin Technology manufactures and distributes medical devices in China
5/6/2014	Bayer AG (DB:BAYN)	Merck & Co., Inc., Merck Consumer Care	14,200	- Merck Consumer Care business unit develops products for everyday consumer care ailments
5/6/2014	Hongkong Tigermed Consulting	Frontage Laboratories, Inc.	50	- Frontage Laboratories provides R&D services to pharmaceutical and biotech companies
5/6/2014	Boston Scientific Corporation	logyn, Inc.	65	- logyn develops hysteroscopic morcellator systems to remove uterine fibroids and polyps
5/8/2014	H. Lundbeck A/S (CPSE:LUN)	Chelsea Therapeutics International Ltd.	635	- Chelsea Therapeutics International focuses on pharmaceutical products for various diseases
5/9/2014	Eurofins Scientific SA	Viracor-IBT Laboratories, Inc.	255	- Viracor-IBT Laboratories, Inc. provides testing, immune monitoring, and bioanalytical services
5/9/2014	Akorn, Inc. (NasdaqGS:AKRX)	VersaPharm Incorporated	440	- VersaPharm develops multi-source Rx, specialty Rx, and generic pharmaceutical products
5/12/2014	Ramsay Santé SA	Générale de Santé Société Anonyme	1,949	- Générale de Santé Société Anonyme operates a network of private hospitals and clinics
5/12/2014	Shire plc (LSE:SHP)	Lumenis Pharmaceuticals, Inc.	295	- Lumenis focuses on products for cholesterol liver diseases and metabolic disorders
5/12/2014	The Advisory Board Company	HealthPost, Inc.	26	- HealthPost provides web-based appointment scheduling software for the health care industry
5/13/2014	Santen Pharmaceutical Co. Ltd.	Merck & Co., Inc., Assets in Ophthalmology in	600	- Merck & Co., Inc., Ophthalmology Products in Japan and key Markets in Europe and Asia Pacific includes
5/13/2014	BNP Paribas Real Estate	Clinique Geoffroy Saint-Hilaire, Clinique	78	- Sale to Health property fund 1 and BNP Paribas Real Estate Investment Management
5/14/2014	Navigant Consulting Inc.	Navigant Healthcare Cymetrix	100	- Navigant provides revenue cycle management solutions to the healthcare industry
5/15/2014	Kindred Healthcare Inc.	Gentiva Health Services Inc. (NasdaqGS:GTIV)	1,685	- Gentiva Health Services provides home health, hospice, and community care services in the U.S.
5/15/2014	Boston Scientific Corporation	Bayer HealthCare AG, Interventional Division	415	- Bayer Interventional Division offers technologies to treat coronary, peripheral vascular disease
5/15/2014	Ohr Pharmaceutical, Inc.	SKS Ocular, LLC	30	- SKS Ocular, LLC is a biopharmaceutical company that develops drugs for ocular disease
5/16/2014	Synergy Health plc (LSE:SYR)	Bioster S.p.A.	40	- Bioster S.p.A. provides medical device sterilization services to healthcare facilities and industries
5/16/2014	Abbott Investments Luxembourg	CFR Pharmaceuticals S.A. (SNSE:CFR)	2,659	- CFR Pharmaceuticals S.A. focuses on specialty generics, complex injectables in Latin America
5/16/2014	Abbott Investments Luxembourg	CFR Pharmaceuticals S.A. (SNSE:CFR)	798	- CFR Pharmaceuticals S.A. focuses on specialty generics, complex injectables in Latin America
5/16/2014	West Corporation	Health Advocate, Inc.	265	- Health Advocate, Inc. provides healthcare advocacy and assistance services
5/16/2014	GIC Special Investments Pte. Ltd.	Neptune Stroika Holdings, Inc.	84	- Neptune Stroika Holdings, Inc. owns and operates hospitals and is based in the Philippines
5/19/2014	Japan Wastech Corporation	Fuji Medical Instruments Mfg. Co., Ltd.	77	- Acquisition of Fuji Medical Instruments Mfg.
5/19/2014	CHP Partners LP	Mercy Rehabilitation Hospital, LLC	26	- Mercy Rehabilitation Hospital, LLC provides inpatient rehabilitation services
5/19/2014	CHP Partners LP	Victory Medical Center Beaumont, LP	34	- Victory Medical Center Beaumont, LP is a surgical hospital
5/19/2014	CHP Partners LP	Southwest Surgical Hospital	30	- Southwest Surgical Hospital provides surgical and emergency services in Texas
5/20/2014	Regal Lifestyle Communities Inc.	A Portfolio Of Seven Multi-Unit Retirement	147	- Acquisition of seven multi-unit retirement communities located in The Province Of Quebec
5/21/2014	Beijing Fert Technology Co., Ltd.; Clayton Dubilier & Rice, Inc.	Beijing Tian Xin Fu Medical Appliances Co. Ltd	129	- Beijing Tian Xin Fu Medical Appliances Co. Ltd markets and distributes medical devices
5/21/2014	The Peebles Corporation; The	Healogics, Inc.	910	- Healogics, Inc. is a wound care management company
5/22/2014	Long Island College Hospital Inc.	Long Island College Hospital Inc.	260	- Long Island College Hospital Inc. operates as a community hospital and medical school
5/23/2014	Siopharm Industrial Investment	Siopharm Holding Medical Investment	32	- Siopharm Holding Medical Investment Management offers medical equipment leasing services
5/26/2014	Volati AB	Naturamed-Pharma AB and NaturaMed	47	- Acquisition of combined operations of Naturamed-Pharma AB and NaturaMed Pharma AS
5/27/2014	Undisclosed	CSPC Pharmaceutical Group Limited	569	- CSPC Pharmaceutical Group Limited manufactures and sells pharmaceutical products
5/27/2014	The Spectranetics Corporation	AngioScore, Inc.	230	- AngioScore, Inc. designs, develops, manufactures, and markets scoring balloon catheters
5/27/2014	Volcano Corporation	AtheroMed, Inc.	130	- AtheroMed, Inc. develops treatments for peripheral arterial disease
5/28/2014	Galderma Pharma SA	Valeant Pharmaceuticals International, Inc.	1,400	- Acquisition of Valeant Pharmaceuticals International, Inc., Filler And Toxin Assets, in Canada
5/28/2014	Hikma Pharmaceuticals plc	Bedford Laboratories	300	- Bedford Laboratories engages in the manufacture and distribution of generic injectables
5/28/2014	Bangkok Dusit Medical Services	Sanamchan Hospital Company Limited	112	- Sanamchan Hospital Company Limited operates a hospital
5/28/2014	St. Jude Medical Inc. (NYSE:STJ)	CardioMEMS, Inc.	375	- CardioMEMS develops and commercializes a wireless sensing and communication technology
5/29/2014	AmSurg Corp. (NasdaqGS:AMSG)	Sheridan Healthcare, Inc.	2,350	- Sheridan Healthcare, Inc. provides clinical solutions to hospitals and outpatient centers
5/30/2014	Agena Bioscience, Inc.	Sequenom Inc., Bioscience Business	36	- Bioscience Business of Sequenom Inc. provides technology and research use only tools
6/2/2014	PetVivo Holdings, Inc.	Gel-Del Technologies, Inc.	40	- Gel-Del Technologies designs and produces biomedical products in the United States
6/2/2014	Albany Molecular Research Inc.	OSO BioPharmaceuticals Manufacturing, LLC	110	- OSO BioPharmaceuticals, a CMO, provides pharmaceutical manufacturing services
6/2/2014	Ventas, Inc. (NYSE:VTR)	29 Independent Living Seniors Housing	899	- Acquisition of 29 seniors housing communities with 3,354 independent living units
6/2/2014	Cross Country Healthcare, Inc.	Medical Staffing Network Healthcare, LLC	48	- Medical Staffing Network Healthcare, LLC provides healthcare staffing solutions in the U.S.
6/3/2014	Teva Pharmaceutical Industries	Labrys Biologics, Inc.	825	- Labrys Biologics and develops antibody treatments for chronic migraines
6/3/2014	DCC Vital Ltd.	Williams Medical Supplies Ltd.	75	- Williams Medical supplies medical equipment and services to the primary care market in the UK
6/3/2014	Repligen Corporation	Refine Technology, LLC	33	- Refine Technology develops equipment for the enhancement of cell culture processes
6/3/2014	Acadia Healthcare Company, Inc.	Partnerships in Care Limited	660	- Partnerships in Care Limited provides specialist care services in the United Kingdom
6/4/2014	Kelun International Development	Lijun International Pharmaceutical (Holding)	273	- Lijun International Pharmaceutical develops pharmaceuticals in Mainland China
6/6/2014	HCP, Inc. (NYSE:HCP)	Maria Mallaband Care Group Limited, 23	151	- Acquisition of 23 Purpose-Built and Converted Care Homes with 965 beds
6/9/2014	Merck & Co. Inc. (NYSE:MRK)	Idenix Pharmaceuticals Inc. (NasdaqGS:IDIX)	3,849	- Idenix Pharmaceuticals develops drugs for human viral diseases in the United States and France
6/10/2014	Celsion Corp. (NasdaqCM:CLSN)	Expression Genetics, Inc.	44	- Expression Genetics develops therapeutics based on genes, inhibitory RNA, and small molecules
6/10/2014	EmCare Inc.	Phoenix Physicians, LLC	170	- Phoenix Physicians, LLC provides hospital-based physician practice management services
6/11/2014	Teijin Ltd. (TSE:3401)	KYORIN Holdings, Inc. (TSE:4569)	159	- KYORIN Holdings produces ethical, generic, OTC drugs, and others in Japan and internationally
6/11/2014	Icade Santé SAS	Clinique Saint Pierre and Clinique Saint Michel	96	- Acquisition of three healthcare facilities in Port-Barcarès
6/11/2014	Meiji Seika Pharma Co., Ltd	Medreich Limited	290	- Medreich Limited manufactures and markets generic and branded drugs
6/11/2014	Euromezanine Conseil; Temasek	Ceva Sante Animale S.A.	2,165	- Ceva Sante Animale develops veterinary medicines
6/11/2014	Ardian	SELARL BIO 7	195	- SELARL BIO 7 owns and operates clinical pathology laboratories
6/12/2014	Town Health International Medical	Dr. Vio & Partners Limited	53	- Acquisition of Dr. Vio & Partners Limited
6/12/2014	Merro Pharmaceutical Co.,Ltd.	Suzhou Industrial Park Nuoxin Bio-Technology	56	- Suzhou Industrial Park Nuoxin Bio-Technology Co., Ltd. undertakes pharmaceutical R&D
6/13/2014	Assura Group Ltd (LSE:AGR)	28 Medical Centers	181	- Acquisition of 28 medical centers.
6/15/2014	Medtronic, Inc. (NYSE:MDT)	Covidien plc (NYSE:COV)	48,056	- Covidien plc develops, manufactures, and sells healthcare products
6/16/2014	HR Europe B.V.; Hill-Rom Holdings	TRUMPF Medical	260	- Acquisition of diversified TRUMPF Medical operations
6/16/2014	WEX Inc. (NYSE:WEX)	Evolution1, Inc.	533	- Evolution1 provides electronic payment, on-premise, and cloud computing healthcare solutions
6/16/2014	AlphaRx Corp. (OTCBB:ALPC)	FV Pharma Inc.	75	- FV Pharma Inc. focuses on the development and production of pharmaceutical-grade cannabis
6/17/2014	Aqualis ASA (OB:AQUA)	Weifa AS	184	- Weifa AS operates as a pharmaceutical company
6/17/2014	Techne Corp. (NasdaqGS:TECH)	ProteinSimple	312	- ProteinSimple, a life sciences instrumentation company, develops and commercializes proprietary systems

Source: Cowen and Company

2014 MAJOR PHARMACEUTICAL M&A/RESTRUCTURING ACTIVITY

Date	Acquiror	Target	Transaction Value (\$MM)	Comment
6/18/2014	Focus Healthcare Partners;	Portfolio of Four Properties Located in	136	- Portfolio of Four Properties Located in Alabama, Michigan, Oklahoma and Tennessee
6/18/2014	AviaRent Capital management S.á	Wohnpark Dimbeck Facility in Mülheim an der	48	- Acquisition of a retirement village: a 95-bed full-care residence, 2 and 51 apartments for assisted living
6/19/2014	Nordic Capital	GHD GesundHeits GmbH Deutschland	679	- GHD GesundHeits GmbH Deutschland provides homecare services
6/19/2014	AbbVie Inc. (NYSE:ABBV)	Shire plc (LSE:SHP)	47,353	- Shire plc. is a biopharmaceutical company
6/20/2014	Valeant Pharmaceuticals	E. Claiborne Robins Company, Inc.	41	- E. Claiborne Robins Company sells pharmaceutical products
6/21/2014	Estia Health Pty Ltd	Cook Care Group Pty Ltd	188	- Cook Care Group owns and manages aged care facilities in New South Wales and Queensland
6/23/2014	Emdeon Inc.	Capario, Inc.	115	- Capario provides revenue cycle management solutions for healthcare providers and payers
6/23/2014	Huadong Medicine Co., Ltd	Hangzhou Zhongmei Huadong Pharmaceutical	144	- Hangzhou Zhongmei Huadong manufactures bulk drugs, healthcare products
6/23/2014	China Grand Pharmaceutical and	Shanghai Weicon Optics Co., Ltd.	79	- Shanghai Weicon Optics Co., Ltd. manufactures contact lenses
6/24/2014	Generics International (US), Inc.	DAVA Pharmaceuticals, Inc.	600	- DAVA Pharmaceuticals develops and markets pharmaceutical products
6/25/2014	Owens & Minor Inc. (NYSE:OMI)	Medical Action Industries Inc.	287	- Medical Action Industries Inc. develops disposable medical products
6/25/2014	Klinik Hirrländern AG	Clinique La Colline SA	146	- Clinique La Colline SA operates a hospital
6/25/2014	Fresenius Medical Care AG & Co.	Sound Inpatient Physicians, Inc.	600	- Sound Inpatient Physicians provides hospitalist and post-acute physicians
6/26/2014	Merz North America, Inc.	Ulthera, Inc.	600	- Ulthera develops various technologies for aesthetic and medical applications
6/29/2014	Real Nutriceutical Group Limited	Magic Galaxy Worldwide Limited	32	- Magic Galaxy Worldwide Limited is an investment holding company
6/30/2014	Stryker Corporation (NYSE:SYK)	Small Bone Innovations, Inc.	375	- Small Bone Innovations, Inc. manufactures and supplies orthopedics devices and instruments
6/30/2014	The Cooper Companies Inc.	Sauflon Pharmaceuticals Limited	1,200	- Sauflon Pharmaceuticals manufactures, and markets contact lenses and aftercare products
7/1/2014	Capital Senior Living Corp.	Three Senior Living Communities in Ohio	84	- Acquisition of 3 Senior Living Communities in Ohio
7/1/2014	ABIOMED Europe GmbH	ECP Entwicklungsgesellschaft mbH	28	- ECP Entwicklungsgesellschaft mbH develops a percutaneous, expandable catheter pump
7/1/2014	Genentech, Inc.	Seragon Pharmaceuticals Inc.	1,725	- Seragon Pharmaceuticals develops pharmaceutical products for estrogen-driven cancers
7/2/2014	Nicox SA (ENXTPA:COX)	Acix Therapeutics Inc.	116	- Acix Therapeutics Inc. operates as an ophthalmic pharmaceutical company in the United States
7/2/2014	Techne Corp. (NasdaqGS:TECH)	Novus Biologicals, LLC	60	- Novus Biologicals, LLC licenses, develops, and markets research tools
7/2/2014	Thoratec Switzerland GmbH	Apica Cardiovascular Ltd.	75	- Apica Cardiovascular Ltd. manufactures cardiovascular devices
7/8/2014	Salix Pharmaceuticals Ltd.	Cosmo Technologies Ltd	2,642	- Cosmo develops oral formulation of mesalamine for first-line treatment of colitis
7/8/2014	Undisclosed	A Portfolio of Seven Care Homes	29	- Acquisition of portfolio of seven care homes
7/9/2014	Hemsö Fastighets AB	179 Beds at Ullsteinstrasse 159 and	34	- Acquisition of 179 Beds at Ullsteinstrasse 159 and Seniorencentrums Christian Runkel Facility
7/10/2014	Juniper Communities, LLC	Juniper Village at Brookline	36	- Juniper Village provides retirement living and healthcare services in Central Pennsylvania
7/10/2014	Aviv REIT, Inc. (NYSE:AVIV)	Two ALFs, One SNF And Two Parcels Of Land	94	- Acquisition of 2 ALFs, 1 SNF And 2 parcels of land In Massachusetts
7/11/2014	ProStrakan Group PLC	Archimedes Pharma Limited	393	- Archimedes Pharma Limited operates as a pharmaceutical company
7/14/2014	Target Healthcare REIT Limited	Three Purpose-Built Care Homes and Four	35	- Acquisition of three purpose-built care homes and four specialist care bungalows
7/14/2014	Bridgepoint Development Capital	Bridgepoint Development Capital	72	- Phlegxglobal Ltd. provides electronic trial master file (TMF) solutions and services
7/14/2014	Mylan, Inc. (NasdaqGS:MYL)	Abbott Laboratories, Non-U.S. Developed	5,271	- Acquisition of ABT manufacturing operations of specialty and generic pharmaceuticals
7/14/2014	Medica Properties Trust Inc.	Health Properties (Bath) Limited	50	- Health Properties (Bath) Limited owns and operates Bath hospital
7/14/2014	St. Jude Medical Inc. (NYSE:STJ)	NeuroTherm, Inc.	200	- NeuroTherm develops, manufactures, and markets minimally invasive solutions for pain management
7/14/2014	Ares Life Sciences SA	Esaote SpA	26	- Esaote SpA specializes in non-invasive diagnostics and healthcare info tech applications
7/15/2014	Undisclosed	Biosensors International Group, Ltd. (SGX:B20)	33	- Biosensors International develops medical devices for interventional cardiology, critical care
7/16/2014	Pfizer Inc. (NYSE:PFE)	InnoPharma, LLC	360	- InnoPharma develops niche generic and specialty pharmaceutical/bio-pharmaceutical products
7/17/2014	Eurazeo PME	Colisés Patrimoine Group SAS	237	- Colisés Patrimoine Group SAS owns retirement homes as Les Jardins de Cybèle SAS in France
7/17/2014	Undisclosed	Gentiva Health Services Inc. (NasdaqGS:GTIV)	1,805	- Gentiva Health Services provides home health, hospice, and community care services in the U.S.
7/18/2014	Vinda International Holdings	SCA Tissue And SCA Shanghai And	148	- Acquisition of combined operations of SCA Tissue, SCA Healthcare, Everbeauty Ind., PRC assets
7/18/2014	Formation Capital, L.L.C.;	Fourteen Skilled Nursing Facilities in the Mid-	150	- Fourteen Skilled Nursing Facilities in the Mid-Atlantic Region comprises 14 nursing facilities
7/22/2014	Primonial REIM	Clinique du Parc Healthcare Asset In The Sixth	75	- Clinique du Parc Healthcare Asset In The Sixth Arrondissement Of Lyon comprises a healthcare property
7/22/2014	Sentio Healthcare Properties, Inc	St. Andrews Village	43	- St. Andrews Village operates a retirement community for active, independent seniors in Maine
7/22/2014	Black Toro Capital LLP	Antibioticos, S.A.	34	- Antibioticos, S.A. specializes in developing antibiotics and pharmaceutical active ingredients
7/24/2014	Reckitt Benckiser (India) Ltd	Reckitt Benckiser Healthcare India Ltd.	121	- Reckitt Benckiser Healthcare India Ltd. sells pharmaceutical products for Paras Pharmaceutical
7/28/2014	Retrophin, Inc. (NasdaqGM:RTRX)	Clinuvel Pharmaceuticals Limited (ASX:CUV)	82	- Clinuvel Pharmaceuticals focuses on drugs for treatment of skin disorders in Australia
7/28/2014	Royston Hospital Trust Board,	Acurity Health Group Limited (NZSE:ACY)	28	- Acurity Health Group private surgical healthcare services in New Zealand
7/28/2014	Medtronic, Inc. (NYSE:MDT)	Visualase, Inc.	99	- Visualase develops laser and image-guided technology devices
7/28/2014	ALPHAEON Corporation	LifeGuard Health, LLC	55	- LifeGuard Health, LLC develops and offers omega-based dietary supplements
7/28/2014	Packaging Coordinators, Inc.	Penn Pharmaceutical Services Limited	216	- Penn Pharmaceutical Services provides services to the healthcare industry
7/30/2014	AstraZeneca PLC (LSE:AZN)	Almirall, S.A. Respiratory Franchise	2,095	- Almirall, S.A. Respiratory Franchise provides treatments for bronchitis and emphysema
7/30/2014	Tecan Group Ltd. (SWX:TECN)	IBL International GmbH	39	- IBL International GmbH develops, produces, and distributes in-vitro diagnostic test systems
7/30/2014	Sinopharm Group Co. Ltd.	Sichuan Medical Limited Corporation	41	- Sichuan Medical Limited Corporation was founded in 1953 and is based in Chengdu, China
7/30/2014	Pfizer Inc. (NYSE:PFE)	Baxter International Inc., Two Commercially	635	- Acquisition of vaccine production facilities
7/30/2014	3D Systems Corporation	Simbionix USA Corporation	120	- Simbionix USA Corporation provides simulation, training, and education for medical professionals
7/31/2014	Meda AB (OM:MEDA A)	Rottapharm S.p.A.	3,161	- Rottapharm S.p.A. provides consumer healthcare products, Rx products, and natural extracts
8/4/2014	Tecomet, Inc.	Symmetry Medical, Inc. (NYSE:SMA)	457	- Symmetry Medical produces medical device solutions and surgical instruments
8/4/2014	Nordson Medical Corporation	Avalon Laboratories, LLC	180	- Avalon Laboratories, LLC engages in the development and manufacture of medical devices for surgical
8/4/2014	Beecken Petty O'Keefe & Company	himagine solutions, Inc.	119	- himagine solutions offers staffing, consulting, outsourcing, and medical coding services
8/4/2014	Roche Holding AG (SWX:ROG)	Santaris Pharma A/S	450	- Santaris Pharma A/S operates as a biopharmaceutical company
8/5/2014	Premier Healthcare Solutions, Inc.	TheraDoc, Inc.	117	- TheraDoc develops and implements electronic surveillance systems for injury detection
8/5/2014	Duke Street; Partners Group	Voyage Healthcare Group Ltd.	633	- Voyage Healthcare provides home care and support services in the UK, Scotland, and Wales
8/5/2014	Capital Senior Living Corp.	Two Senior Living Communities in Virginia and	34	- Acquisition of two senior living communities in Virginia and Wisconsin
8/6/2014	Walgreen Co. (NYSE:WAG)	Alliance Boots GmbH	2,989	- Alliance Boots provides various products and services in the UK, France, Germany, Switzerland
8/6/2014	The Carlyle Group LP	Lianyungang Jiatai Construction Co. Ltd.	122	- Lianyungang Jiatai invests, manages, and operates hospitals and medical institutions
8/6/2014	American Realty Capital Healthcare	Platinum Health Care LLC, Portfolio Of Ten	52	- Acquisition of portfolio of ten skilled nursing facilities In Missouri
8/7/2014	Undisclosed	TMC Life Sciences Berhad (KLSE:TMCCLIFE)	56	- TMC Life Sciences Berhad operates a tertiary care centre and fertility center in Malaysia
8/11/2014	Sanofi-Aventis Deutschland GmbH	MannKind Corp., Global Rights of Afrezza	925	- MannKind Corp., Global Rights of Afrezza comprises licenses for development and commercialization of
8/11/2014	Oncothyreon Inc	Alpine Biosciences, Inc.	27	- Alpine Biosciences develops therapies for cancer and rare diseases using nanoparticles
8/13/2014	MedAssets, Inc.	Sg2, LLC	142	- Sg2, LLC offers analytics, intelligence, consulting, educational solutions to the healthcare industry
8/13/2014	Allergan Inc. (NYSE:AGN)	TARIS BioMedical, Inc., LiRIS Program in	588	- Acquisition of LiRIS Program in Phase 2 for the treatment of interstitial cystitis
8/13/2014	NorthStar Healthcare Income	Four Senior Living Facilities in Nassau and	125	- Acquisition of four Senior Living Facilities in Nassau and Suffolk Counties
8/13/2014	Carter Validus Mission Critical	Bay Area Regional Medical Center Property	198	- Bay Area Regional Medical Center owns and operates a nine-story acute-care hospital
8/14/2014	Undisclosed	United Medical Systems (DE), Inc.	75	- United Medical Systems (DE), Inc. offers transportable and mobile medical solutions
8/15/2014	Sinopharm Group Co. Ltd.	Sichuan Medical Limited Corporation	33	- Sichuan Medical Limited Corporation was founded in 1953 and is based in Chengdu, China
8/18/2014	Alliance Boots Holdings Limited	Unidrug Distribution Group Ltd.	110	- Unidrug Distribution Group Ltd. provides supply chain solutions in the United Kingdom
8/19/2014	IMMAG Holding AG	Three Nursing Homes In Ascheberg, Gütersloh	36	- Acquisition of three nursing homes in Ascheberg, Gütersloh And Rödermark In Western Germany
8/19/2014	Recipharm AB (publ) (OM:RECI B)	Corvette Pharmaceutical Services Group SpA	161	- Corvette manufactures sterile injectable, API and finished dose form of beta lactam antibiotics
8/19/2014	Grupo Angeles Servicios de Salud	Espirito Santo Saúde SGPS, SA. (ENXTLS:ESS)	804	- Espírito Santo Saúde-SGPS, S.A. operates a network of healthcare facilities in Portugal
8/24/2014	Roche Holding AG (SWX:ROG)	InterMune, Inc. (NasdaqGS:ITMN)	8,250	- InterMune focuses on therapies for pulmonology and orphan fibrotic diseases

Source: Cowen and Company

2014 MAJOR PHARMACEUTICAL M&A/RESTRUCTURING ACTIVITY

Date	Acquiror	Target	Transaction Value (\$MM)	Comment
8/25/2014	Japara Healthcare Limited	Whelan Care, Four Aged Care Facilities	37	- Acquisition of four aged care facilities
8/25/2014	Guangxi Dali Biotechnology Co.	Guizhou TaiBang Biological Products Co. Ltd.	87	- GuiZhou TaiBang sells Human Albumin, Human Immunoglobulin, Human IV Immunoglobulin
8/25/2014	Premier, Inc. (NasdaqGS:PINC)	Aperek, Inc.	49	- Aperek, Inc. provides Web-based analytics and savings solutions for the healthcare supply chain
8/25/2014	Medtronic, Inc. (NYSE:MDT)	Sapiens Steering Brain Stimulation GmbH	200	- Sapiens Steering Brain Stimulation GmbH, a medical device company, develops deep brain stimulation
8/25/2014	Sequoia Capital	Jiangsu Yuyue Medical Equipment & Supply	139	- Jiangsu Yuyue Medical Equipment & Supply Co., Ltd. is a medical equipment company
8/26/2014	Clearlake Capital Group, LLC	First Physicians Capital Group, Inc.	25	- First Physicians Capital provides management, financial, and ancillary healthcare and IT services
8/27/2014	Bangkok Dusit Medical Services	Phuket International Hospital Company	126	- Phuket International Hospital Company Limited provides acute care hospital services
8/27/2014	Medtronic, Inc. (NYSE:MDT)	N.G.C. Medical S.p.A.	238	- N.G.C. Medical S.p.A. designs, manufactures, and markets medical and surgical devices
8/27/2014	Shandong Luye Pharmaceutical Co.	Beijing Jialin Pharmaceutical Co., Ltd.	599	- Beijing Jialin develops and manufactures drugs for cardiovascular problems
8/28/2014	Medequities Realty Trust Inc	Vibra Healthcare LLC, A Long-Term Acute	51	- Acquisition of a long-term acute care hospital in Kentfield, California
8/28/2014	Medequities Realty Trust Inc	Fundamental Healthcare, Acute Care Hospital	40	- Fundamental Healthcare, Acute Care Hospital in Nevada and A Nursing Facility in South Carolina
8/29/2014	Prime United Industries Limited	Xi'an Lijun Pharmaceutical Co., Ltd.	100	- Xi'an Lijun Pharmaceutical Co., Ltd. manufactures and distributes pharmaceutical products
Total Transaction Value, 2014			\$504,240	

Source: Cowen and Company

Appendix: Tables Of Industry Fundamentals

INDUSTRY EMPLOYMENT ANALYSIS

	2012	Sales/ Employee		2013	Sales/ Employee		2014P	Sales/ Employee		2015P	Sales/ Employee		2016P	Sales/ Employee		2017P	Sales/ Employee		2018P	Sales/ Employee		2019P	Sales/ Employee		2020P	Sales/ Employee	
ABBV	21,500	\$837,767		21,500	\$873,953		21,500	\$911,163		21,500	\$1,246,512		21,500	\$1,357,907		21,500	\$1,444,651		21,500	\$1,461,860		21,500	\$1,498,605		21,500	\$1,525,349	
AZN	51,700	\$541,064		59,500	\$432,118		59,500	\$434,706		59,500	\$426,050		59,500	\$434,034		59,500	\$399,328		59,500	\$414,706		59,500	\$445,630		59,500	\$481,849	
BMY	28,000	\$629,321		27,000	\$606,852		27,000	\$573,333		27,000	\$538,519		27,000	\$548,519		27,000	\$585,741		27,000	\$633,704		27,000	\$685,556		27,000	\$768,148	
GSK	100,000	\$428,307		100,000	\$414,952		100,000	\$380,040		100,000	\$403,007		100,000	\$426,427		100,000	\$439,880		100,000	\$467,676		100,000	\$501,307		100,000	\$536,721	
LLY	38,100	\$593,255		34,808	\$664,014		34,808	\$565,675		34,808	\$602,591		34,808	\$632,757		34,808	\$664,215		34,808	\$653,873		34,808	\$674,558		34,808	\$712,624	
MRK	81,000	\$583,543		86,000	\$512,012		86,000	\$493,023		86,000	\$449,186		86,000	\$446,919		86,000	\$441,163		86,000	\$450,756		86,000	\$464,419		86,000	\$484,419	
NVS	110,000	\$515,164		133,000	\$431,241		133,000	\$438,038		133,000	\$437,444		133,000	\$436,278		133,000	\$455,489		133,000	\$470,113		133,000	\$498,797		133,000	\$539,323	
PFE	79,000	\$746,658		78,400	\$656,288		78,400	\$621,811		78,400	\$606,569		78,400	\$608,355		78,400	\$633,099		78,400	\$654,528		78,400	\$651,339		78,400	\$694,643	
RHHBY	80,500	\$632,966		80,500	\$677,213		80,500	\$641,906		80,500	\$647,229		80,500	\$669,411		80,500	\$690,731		80,500	\$717,481		80,500	\$742,973		80,500	\$767,273	
SNY	112,000	\$413,435		101,000	\$447,133		101,000	\$427,432		101,000	\$446,814		101,000	\$452,234		101,000	\$470,787		101,000	\$490,807		101,000	\$512,421		101,000	\$537,159	
Total	701,800	\$5,921,481		721,708	\$5,715,775		721,708	\$5,487,127		721,708	\$5,803,921		721,708	\$6,012,839		721,708	\$6,225,084		721,708	\$6,415,504		721,708	\$6,675,604		721,708	\$7,047,508	
Average	70,180	\$592,148		72,171	\$571,578		72,171	\$548,713		72,171	\$580,392		72,171	\$601,284		72,171	\$622,508		72,171	\$641,550		72,171	\$667,560		72,171	\$704,751	
% Change/CGR	-13.7%	+5.9%		+2.8%	-1.8%		+0.0%	-0.8%		+0.0%	+0.7%		+0.0%	+1.4%		+0.0%	+1.0%		+0.0%	+2.3%		+0.0%	+4.0%		+0.0%	+4.0%	

Source: Company reports, Cowen and Company

CURRENT SALES FORCE HEADCOUNT COMPARISON

	U.S.	Foreign	Worldwide
AstraZeneca	4,250	9,500	13,750
Bristol-Myers Squibb	2,500	6,500	9,000
Eli Lilly	4,000	8,500	12,500
GlaxoSmithKline	4,750	26,250	31,000
Merck	6,000	NP	NP
Novartis	1,800	16,700	18,500
Pfizer	4,500	24,900	29,400
Roche	1,500	8,300	9,800
Sanofi	5,000	28,000	33,000
Average	3,811	16,081	19,619

NP=Not Provided

Source: Company reports; Cowen and Company

PHARMACEUTICAL INDUSTRY COMPOSITE P&L (\$MM)

	1990	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	1990-13 CAGR	2013-16 CAGR	2013-20 CAGR	2014-20 CAGR
Sales	\$50,937	\$378,011	\$362,882	\$369,561	\$378,216	\$389,051	\$402,676	\$419,765	\$444,551	+9%	+0%	+2%	+3%
COGS	<u>14,842</u>	<u>94,461</u>	<u>92,734</u>	<u>91,181</u>	<u>91,390</u>	<u>93,990</u>	<u>95,988</u>	<u>99,044</u>	<u>103,291</u>	+8%	-1%	+1%	+2%
Gross Profit	\$36,095	\$284,735	\$271,474	\$279,579	\$287,812	\$296,160	\$307,819	\$321,883	\$342,454	+9%	+0%	+3%	+4%
Gross Margin	70.9%	75.3%	74.8%	75.7%	76.1%	76.1%	76.4%	76.7%	77.0%				
SG&A	\$18,274	\$104,955	\$100,894	\$99,866	\$99,657	\$101,464	\$104,314	\$108,177	\$114,689	+8%	-2%	+1%	+2%
% Sales	35.9%	27.8%	27.8%	27.0%	26.3%	26.1%	25.9%	25.8%	25.8%				
R&D	\$5,053	\$61,397	\$60,516	\$62,082	\$62,575	\$63,608	\$64,717	\$66,423	\$68,939	+11%	+1%	+2%	+2%
% Sales	9.9%	16.2%	16.7%	16.8%	16.5%	16.3%	16.1%	15.8%	15.5%				
Op. Expenses	\$23,327	\$166,189	\$161,890	\$162,463	\$162,805	\$165,716	\$169,686	\$175,267	\$184,307	+9%	-1%	+1%	+2%
% Sales	45.8%	44.0%	44.6%	44.0%	43.0%	42.6%	42.1%	41.8%	41.5%				
Op. Income	\$12,768	\$118,577	\$110,432	\$117,801	\$125,698	\$131,239	\$139,053	\$147,641	\$159,278	+10%	+2%	+4%	+6%
% Sales	25.1%	31.4%	30.4%	31.9%	33.2%	33.7%	34.5%	35.2%	35.8%				
Non-Op. Income	\$383	(\$4,382)	(\$2,975)	(\$3,276)	(\$2,626)	(\$1,913)	(\$847)	\$45	\$941	NM	NM	NM	NM
Pretax Income	\$13,151	\$114,367	\$107,598	\$114,650	\$123,172	\$129,426	\$138,307	\$147,786	\$160,319	+10%	+3%	+5%	+7%
% Sales	25.8%	30.3%	29.7%	31.0%	32.6%	33.3%	34.3%	35.2%	36.1%				
Taxes	\$4,062	\$25,112	\$24,042	\$25,106	\$26,770	\$28,004	\$29,973	\$31,955	\$34,692	+8%	+2%	+5%	+6%
Tax Rate	30.9%	22.0%	22.3%	21.9%	21.7%	21.6%	21.7%	21.6%	21.6%				
Minority Interest	(\$48)	\$596	\$542	\$846	\$1,195	\$1,323	\$1,440	\$1,569	\$1,701				
Net Income	\$9,041	\$89,156	\$83,555	\$89,809	\$96,936	\$102,003	\$108,971	\$116,526	\$126,385	+10%	+3%	+5%	+7%
EPS	\$0.53	\$3.57	\$3.43	\$3.66	\$4.00	\$4.26	\$4.60	\$4.98	\$5.46	+9%	+4%	+6%	+8%
Shares Outstanding	17,098	24,950	24,393	24,508	24,251	23,962	23,678	23,409	23,140	+2%	-+1%	-1%	-1%

Includes ABBV, AZN, BMY, GSK, LLY, MRK, NVS, PFE, RHHBY, SNY

Source: Cowen and Company.

ESTIMATES 2013 WORLDWIDE PHARMACEUTICAL SALES BREAK OUT

	ABBV	AZN	BMY	GSK	LLY	MRK	NVS	PFE	Roche	SNY	IMS MAT Value Share 9/13*	Value MAT Growth % 9/13*
U.S.	56%	38%	50%	34%	57%	44%	34%	41%	33%	35%	40%	-0.1%
U.K.	3	3	5	7	3	3	6	4	4	4	2.7	3.7
Germany	4	6	6	6	4	6	9	6	6	6	4.8	4.5
France	3	5	4	5	3	5	6	5	5	4	4.1	-1.7
Italy	2	3	3	5	3	3	4	3	5	3	3.1	1.3
Canada	3	2	3	5	3	3	3	2	2	3	2.6	-0.5
Central/South America	4	4	4	6	5	7	6	6	7	9	5.0	11.7
Japan	4	10	7	7	6	9	8	10	7	7	10.8	2.4
Asia Ex-Japan	6	9	3	12	4	11	7	8	8	9	11.6	8.3
Rest of World	15	21	15	13	12	10	17	15	23	20	15.5	4.1
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	2.5%

*Estimation based off net sales for Pharmaceutical divisions where applicable; excludes sales generated in JVs, and other license arrangements

* Average is calculated for territories with more than one country; Sterling used to calculate IMS data

Source: Company Figures, IMS

Q3:14 OUTLOOK

Company	close	Reporting Date	Quarter	Cowen	Street Consensus	Prior Year	% Chg.	Sales % chg	Q3 Key Product Trends
AbbVie	ABBV	\$58	10/24	Q3:14	\$0.78	\$0.77	\$0.82	-5%	3% - Humira (+15% to \$3,185MM); Kaletra (-14% to \$205MM); Androgel (-19% to \$200MM); Lupron (-8% to \$180MM); Synthroid (+9% to \$175MM); Ultane/Sevoflurane (+9% to \$150MM); Creon (+9% to \$110MM); Zemplar (+10% to \$110MM); Norvir (-28% to \$75MM); Niaspan (-93% to \$15MM); Tricor/Trilipix (-62% to \$15MM)
AstraZeneca	AZN	71	11/06	Q3:14	1.06	0.99	1.21	-12%	3% - Crestor (-1% to \$1,345MM); Symbicort (+9% to \$915MM), Nexium (-9% to \$835MM), Seroquel XR (-7% to \$315MM), Onglyza (+185% to \$265MM), Pulmicort (+8% to \$190MM), Brilinta (+67% to \$125MM), Bydureon \$140MM, Foxiga \$15MM
Bristol-Myers Squibb	BMY	51	10/24	Q3:14	0.40	0.42	0.46	-13%	NM - Orencia (+13% to \$425MM), Baraclude (+6% to \$400MM), Abilify (-34% to \$375MM), Sprycel (+16% to \$365MM), Reyataz (-7% to \$350MM), Atripla/Sustiva (-14% to \$335MM), Yervoy (+32% to \$315MM), Eliquis (\$200MM), Erbitux (+4% to \$190MM), Avapro (-30% to \$50MM), Plavix (-5% to \$40MM)
Eli Lilly	LLY	65	10/23	Q3:14	0.77	0.70	1.11	-31%	-16% - Alimta (+8% to \$745MM), Humalog (+7% to \$660MM), Cialis (+11% to \$585MM), Cymbalta (-78% to \$305MM), Zyprexa (-17% to \$230MM), Straterra (-2% to \$170MM), Effient (+12% to \$140MM), Trajenta (+55% to \$100MM), Evista (-67% to \$85MM)
GlaxoSmithKline	GSK	46	10/22	Q3:14	25.0p	NA	28.0p	-10%	-6% - Pharma (-6% to £4,765MM), Consumer (-7% to £1,105MM), Advair (-22% to £945MM), Infanrix (-1% to £255MM), Epizicom (+3% to £195MM), Flovent (-7% to £160MM), Hepatitis Vaccine (-11% to £150MM), Rotarix (+2% to £110MM), Synflorix (+13% to £90MM), Boostrix (+2% to £85MM), Cervarix (+48% to £60MM), Tivicay (£60MM), Veramyst (+9% to £60MM), Benlysta (+7% to £45MM), Anoro £20MM, Breo/Relvar (£15MM), Lovaza (-89% to £15MM)
Merck	MRK	59	10/27	Q3:14	0.88	0.88	0.92	-5%	-5% - Januvia (+3% to \$1,415MM), Gardasil (+13% to \$750MM), Zetia (flat @ \$660MM), Remicade (+9% to \$625MM), Isentress (+7% to \$455MM), Vytorin (-5% to \$375MM), Nasonex (-16% to \$250MM), Singulair (-18% to \$230MM), Zostavax (+3% to \$190MM), Simponi (+31% to \$165MM), PEG-Intron (-23% to \$80MM), Temodar (-54% to \$75MM), Victrelis (-63% to \$45MM)
Novartis	NVS	94	10/28	Q3:14	1.34	1.30	1.24	8%	2% - Gleevec (-1% to \$1,125MM), Diovan (-48% to \$435MM), Lucentis (+8% to \$625MM), Gilenya (+24% to \$640MM), Exforge (-3% to \$350MM), Tasigna (+22% to \$385MM), Afinitor (+17% to \$395MM), Exelon (+3% to \$260MM), Exjade (+8% to \$230MM), Zometa (-42% to \$60MM), Ultibro (\$30MM), Alcon (+7% to \$2,715MM), Consumer (+8% to \$1,120MM), Sandoz (+6% to \$2,405MM), Vaccines (+12% to \$505MM)
Pfizer	PFE	30	10/28	Q3:14	0.54	0.55	0.58	-8%	-4% - Lyrica (-6% to \$1,070MM), Prevnar (+9% to \$1,045MM), Enbrel foreign (+2% to \$955MM), Celebrex (-1% to \$745MM), Lipitor (-17% to \$445MM), Viagra (-12% to \$405MM), Zyvox (+2% to \$325MM), Sutent (+4% to \$290MM), Premarin (+3% to \$285MM), Champix (+1% to \$155MM), Zosyn (-18% to \$85MM)
Roche	RHHBY	37	10/16	Q3:14	NA	NA	NA	--	-2% - Rituxan (-1% to CHF1,795M), Avastin (flat at CHF1,620MM), Herceptin (-1% to CHF1,495MM), Actemra (+12% to CHF300M), Xeloda (-57% to CHF170MM), Pegasys (-16% to CHF255MM), Perjeta (CHF235MM), Kadcylla (+105% to CHF150MM), Gazyva (CHF15MM)
Sanofi	SNY	56	10/28	Q3:14	€ 1.43	NA	€ 1.36	5%	5% - Lantus (+12% to €1,625MM), Flu (+9% to €610MM), Plavix (-5% to €400MM), Lovenox (-5% to €380MM), Pedi combo (+21% to €295MM), Meningitis (+9% to €230MM), Travel (+14% to €115MM), Aubagio (€110MM), Booster (+13% to €95MM), Ambien CR (-31% to €65MM), Allegra (-37% to €45MM), Lemtrada (€10MM)

Source: Cowen and Company.

AbbVie

Price: \$57.76 (09/30/2014)
Price Target: \$65.00

OUTPERFORM (1)

Steve Scala, R.Ph., CFA
617.946.3923
steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA
617.946.3857
kathy.miner@cowen.com

Jean Perreault
617.946.3967
jean.perreault@cowen.com

Key Data	
Symbol	NASDAQ: ABBV
52-Week Range:	\$60.02 - 44.03
Market Cap (MM):	\$92,026.6
Net Debt (MM):	\$4,828.0
Cash/Share:	\$6.23
Dil. Shares Out (MM):	1,593.3
Enterprise Value (MM):	\$96,521.6
ROIC:	NA
ROE (LTM):	NA
BV/Share:	\$3.28
Dividend:	\$1.68
Yield:	2.91%

FY (Dec)	2013A	2014E	2015E
Earnings Per Share			
Q1	\$0.68	\$0.71A	\$0.81
Q2	\$0.82	\$0.82A	\$0.96
Q3	\$0.82	\$0.78	\$0.93
Q4	\$0.82	\$0.81	\$1.05
Year	\$3.14	\$3.12	\$3.75
P/E	18.4x	18.5x	15.4x
Consensus EPS	\$3.14	\$3.16	\$3.90

Consensus source: Thomson Reuters

Revenue (MM)			
Year	\$18,790.0	\$19,590.0	\$26,800.0
Prior Year	-	-	\$20,915.0
EV/S	5.1x	4.9x	3.6x

Shire Acquisition Very Accretive; Helps Offset Eventual Humira Pressure

The Cowen Insight

Shire acquisition boosts near-term earnings and provides a longer-term cushion to Humira competitive pressure.

The acquisition of Shire appears substantially accretive, decreases concentration of sales and EPS from Humira, and utilizes a tax benefit which may not be available in the future. Key upcoming events include hep C's approval and rollout, and more data on ABT-199. Risks include execution, politics, and competitive threats to Humira. We believe opportunities greatly outweigh risks over the next 12 months.

Post 2014, Strong Double-Digit EPS Growth 2015-17

Given lingering patent expiration pressures, 2014 EPS is forecast to be down 1% to \$3.12. For 2015-17, we anticipate 11-20% EPS growth keyed to benefits (both operating synergies and tax-related) from the Shire acquisition which we assume is consolidated on 1/1/15.

Humira Growth Story Intact Through 2017

Humira is the leading TNF inhibitor in sales and offers the broadest range of indications in the class, with more on the way. Threats from other TNF inhibitors, orally delivered alternatives, and biosimilars are real but not expected to impact Humira until 2017 when patent expirations begin. We estimate Humira WW sales of \$12.505B (+17%) in 2014 \$15.1B (+10%) in 2016, before slowing to \$15.7B (+4%) in 2017, and declining to \$14.7B (-6%) in 2018, and \$12.7B (-7%) in 2020 reflecting threats mentioned above.

Pipeline Offers At Least A Few Promising Assets

AbbVie's 16 compounds in Phase II/III should contribute meaningfully commencing in 2015-16. We project combined new drug sales of \$1.55B in 2016, rising to \$6.8B in 2020. Duopa for Parkinson's disease (PDUFA Q1:15), AbbVie's HCV antiviral combinations that successfully completed Phase III trials (filed Q2:14), daclizumab for multiple sclerosis (positive Phase III data; submission H1:15), elagolix for endometriosis (Phase III data by YE) and uterine fibroids (Phase IIb data by mid-2015), and ABT-199 (CLL) are most visible.

Shire A Leader In ADHD And Rare Diseases

Shire will bring diversification to the AbbVie portfolio, most notably in the CNS area with ADHD leader Vyvanse (FDA accepted sNDA for added indication of binge eating disorder in September with priority review), and in Rare Diseases with a line-up that includes products for Hunter's, HAE, Fabry, Gaucher as well as a number of compounds and new indications in the pipeline.

AbbVie/Shire Pro Forma Model Thru 2020 Shows Substantial Accretion

EPS Anticipated To Be Down 1% In 2014

EPS are estimated at \$3.12 (-1%) in 2014. This reflects revenue growth of 4% to \$19.590B and a modest improvement in gross PM (+0.5 pp to 78.9%). This is offset by R&D spend which is expected to increase 13% to \$3.2B (+1.2pp to 16.3% of sales) and SG&A which is expected to rise 8% to \$5.505B (+1.0pp to 28.1% of sales). The tax rate is expected to remain at 22.2% and shares outstanding stable at 1.6B. Strong H1 Humira trends are expected to continue for the year (+17% to \$12.505B) but sales growth will be tempered by erosion in Tricor/Trilipix (-77%) and Niaspan (-85%). In June, management raised EPS guidance by six cents to \$3.06-3.16.

AbbVie 2014 Guidance Versus Our Expectations

	ABBV Guidance	Cowen Estimates
Sales	\$19B*	\$19.505B
Gross P.M.	Approaching 79%	78.9%
SG&A	Approaching 28% of sales	28.1%
R&D	Somewhat above 16% of sales	16.3%
Net Interest	(\$270MM)	(\$270MM)
Tax Rate	22%	22.2%
EPS	\$3.06 - 3.16	\$3.12

Bold=revised

* Estimated 1% negative impact from exchange

Source: Cowen and Company

Shire-Driven Accretion Boosts EPS Growth By 11-20% In 2015-17

For 2015 (assuming Shire consolidated as of 1/1/15), we estimate EPS of \$3.75 (+20%) for the combined entity, versus \$3.40 for ABBV alone, which assumes \$600MM in synergies (\$400MM in SG&A, \$100MM in COGS and \$100MM in R&D) and a tax rate of 13% (ABBV tax rate guidance is 13% in 2016; no guidance provided for 2015). Our synergy target represents 18% of Shire's 2015 expense base (first year synergies projected for MRK/SGP and PFE/WYE were 18% and 21%, respectively, of the target's forecast expense base). Total revenue for the combined entity is estimated at \$26.8B, versus \$20.9B for ABBV alone. Humira sales are estimated at \$13.8B (+10%). We estimate hep C revenue in 2015 of only \$350MM, as ABBV appears not willing to compete on price. Should ABBV launch its hep C regimen at a significant discount, 2015 hep C revenue could increase by \$1-2B. We assume 528MM new ABBV shares outstanding (589MM Shire shares x 0.8960 new ABBV shares/Shire share) and additional interest expense of \$940MM/year (589MM Shire shares x £24.44/Shire share x \$1.6329/£1 = \$23,505MM * 4% interest rate).

For 2016, we forecast EPS of \$4.40 (+17%) for the combined entity, versus \$3.70 for ABBV alone, assuming \$700MM in synergies (\$450MM in SG&A,\$125MM in COGS and \$125MM in R&D) and a tax rate of 13%. Total revenue for the combined entity is

forecast at \$29.2B (+9%), versus \$22.9B for ABBV alone. Humira sales are estimated at \$15.1B (+10%). In 2017, we forecast EPS of \$4.90 (+11%) on sales growth of 6% to \$31.06B. Humira sales are estimated at \$15.7B (+4%) as biosimilars begin to make inroads. Continued synergies should drive a 1.4pp increase in operating margin to 42.4%.

Low-Single Digit Growth Anticipated At End Of Decade Reflecting Competition For Humira

We estimate sales growth of 1-3% and EPS growth of +1-3% for 2018-20. The top-line trends reflect our forecast of declining annual Humira sales starting in 2018, partially offset by an increasing pipeline contribution. The pipeline is expected to generate an incremental \$1.6B in 2019 and \$1.4B in 2020, although visibility on these contributions is not high. Gross margin is expected to contract by 0.4pp per year during this time as ABT-199 becomes larger and the profit sharing with Roche grows. We forecast slightly declining SG&A and flat R&D (as a percentage of sales), with the tax rate estimated to remain at 13.0% and share count at 2.136B. We estimate 2018 EPS at \$4.95 (+1%) and 2019 at \$5.10 (+3%). In 2020, we forecast EPS of \$5.20 (+2%), versus our prior \$4.80 estimate for ABBV alone, which assumed \$1.1B in synergies (\$650MM in SG&A, and \$225MM in COGS and \$225MM in R&D) and a tax rate of 13%. ABBV management has guided to \$1.00 in accretion whereas our model shows \$0.40 in accretion.

AbbVie 2013-20 EPS Buildup (\$MM)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2013-16 CGR	2013-20 CGR	2014-20 CGR Comments
Humira	\$1.92	\$2.29	\$1.93	\$2.12	\$2.21	\$2.06	\$1.92	\$1.78	3%	-1%	-4% - RA, PA, AS, Crohn's, psoriasis, JIA, UC; 4 additional indications in development
Lupron	0.08	0.08	0.06	0.05	0.05	0.05	0.04	0.04	-12%	-9%	-10% - Leads market, despite generics; line extensions boost
Synagis	0.08	0.09	0.07	0.07	0.07	0.07	0.07	0.07	-7%	-2%	-3% - Prevention of RSV; rights in foreign markets
Kaletra	0.10	0.08	0.06	0.05	0.04	0.04	0.03	0.03	-20%	-17%	-17% - Lopinavir/low-dose ritonavir combo for HIV; patent expires 6/26/16
Androgel	0.10	0.09	0.05	0.04	0.03	0.02	0.01	0.00	-26%	-36%	-39% - Testosterone replacement; generics of 1% form launch in 2015; 1.62% is 60% of franchise
Tricor/Trilipix	0.03	0.01	0.00	0.00	0.00	0.00	0.00	0.00	-59%	-45%	-37% - Generics launched 11/12
Niaspan	0.06	0.01	0.00	0.00	0.00	0.00	0.00	0.00	-71%	-51%	-40% - Generics launched 9/2013 via settlement with TEVA/BRL
Pipeline	0.02	0.02	0.05	0.13	0.23	0.33	0.48	0.62	93%	66%	72% - Duopa, ABT-199, HCV combos, daclizumab, elagolix, elotuzumab, veliparib, atrasentan, others
CNS		0.33	0.37	0.41	0.46	0.50	0.54	NM	NM	NM	NM - Vyvanse (patent thru 2023); Adderall XR (generic competition)
HGT		0.40	0.43	0.46	0.49	0.51	0.53	NM	NM	NM	NM - Human genetic Therapies: Elaprase, Firazyr, Cinryze, Replagal, Vipriv
GI		0.16	0.17	0.19	0.20	0.21	0.19	NM	NM	NM	NM - Lialda, Pentasa, Resolor
Other	0.75	0.45	0.64	0.96	1.22	1.24	1.32	1.38	9%	9%	21%
ABBV EPS	\$3.14	\$3.12	\$3.75	\$4.40	\$4.90	\$4.95	\$5.10	\$5.20	12%	7%	9% - Versus industry average of +4%, +6% and +8%
% Change	-4%	-1%	20%	17%	11%	1%	3%	2%			

Source: Cowen and Company

AbbVie Estimated Quarterly Revenues (\$MM)

	Q1	Q2	Q3	Q4	2013		Q1	Q2	Q3E	Q4E	2014E	Q1E	Q2E	Q3E	Q4E	2015E
Wtd ave currency impact (%) - as of 9/5/14							1,000	0.9891			0.9904	0.9876	0.9949	1.0000		
PHARMACEUTICALS																
Humira WW							\$1,192	\$1,661	\$1,640	\$1,875	\$6,370	\$1,350	\$1,825	\$1,800	\$2,050	\$7,025
U.S.	\$956	\$1,224	\$1,389	\$1,667	\$5,236	5,423	1,445	1,627	1,545	1,520	6,135	1,585	1,755	1,690	1,700	6,730
Foreign	1,288	1,382	1,381	1,372					1,545	1,535		1,600	1,775	1,700	1,700	
Foreign (lc, ex fx)																
Humira WW	\$2,244	\$2,606	\$2,770	\$3,039	\$10,659		\$2,637	\$3,288	\$3,185	\$3,395	\$12,505	\$2,935	\$3,580	\$3,490	\$3,750	\$13,755
Synagis							\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	
U.S.	\$0	\$0	\$0	\$0	\$0		354	74	100	345	875	295	75	75	400	
Foreign	345	70	98	314	827				100	350		300	75	75	400	845
Foreign (lc, ex fx)																
Synagis WW	\$345	\$70	\$98	\$314	\$827		\$354	\$74	\$100	\$345	\$875	\$295	\$75	\$75	\$400	\$845
Kaletra							\$52	\$66	\$63	\$63	\$244	\$54	\$56	\$55	\$45	\$210
U.S.	167	212	174	165	718		141	160	160	140	590	140	130	130	120	\$180
Foreign									150	140		140	130	130	120	520
Foreign (lc, ex fx)																
Kaletra WW	\$219	\$278	\$237	\$228	\$962		\$195	\$216	\$205	\$185	\$800	\$190	\$180	\$170	\$160	\$700
Tricor/Trilipix							\$128	\$107	\$39	\$29	\$303	\$23	\$17	\$15	\$15	\$70
U.S.	\$128	\$107	\$39	\$29	\$303		\$23	\$17	\$15	\$15	\$70	\$10	\$10	\$5	\$5	\$30
Tricor/Trilipix																
Niaspan							\$186	\$232	\$201	\$31	\$650	\$47	\$21	\$15	\$15	\$100
U.S.	0	0	0	0	0		0	0	0	0	0	0	0	0	0	\$30
Foreign																0
Foreign (lc, ex fx)																
Niaspan WW	\$186	\$232	\$201	\$31	\$650		\$47	\$21	\$15	\$15	\$100	\$10	\$10	\$5	\$5	\$30
Lupron (Leuprolide)							\$125	\$144	\$141	\$156	\$566	\$140	\$133	\$130	\$140	\$545
U.S.	56	55	55	53	219		49	53	50	50	200	45	50	45	45	\$135
Foreign									50	50		50	45	45	45	185
Foreign (lc, ex fx)																
Lupron (Leuprolide) WW	\$181	\$199	\$196	\$209	\$785		\$189	\$186	\$180	\$190	\$745	\$180	\$175	\$165	\$180	\$700
AndroGel							\$240	\$258	\$248	\$289	\$1,035	\$254	\$218	\$200	\$190	\$860
U.S.	\$240	\$258	\$248	\$289	\$1,035											\$660
AndroGel WW																
Zemplar							\$41	\$63	\$57	\$57	\$218	\$10	\$60	\$60	\$60	\$190
U.S.	40	44	43	44	171		42	40	50	50	180	45	45	45	45	\$225
Foreign									50	50		50	45	45	45	200
Foreign (lc ex fx)																
Zemplar WW	\$81	\$107	\$100	\$101	\$389		\$52	\$100	\$110	\$110	\$370	\$75	\$110	\$120	\$120	\$425
Norvir							\$52	\$30	\$74	\$98	\$254	\$70	\$35	\$35	\$30	\$30
U.S.	30	130	30	30	220		30	80	40	40	190	40	40	40	40	\$120
Foreign									40	40		40	40	40	40	160
Foreign (lc ex fx)																
Norvir WW	\$82	\$160	\$104	\$128	\$474		\$100	\$115	\$75	\$70	\$360	\$70	\$70	\$70	\$70	\$280
Ultane/Sevoflurane							\$15	\$19	\$19	\$23	\$76	\$19	\$22	\$20	\$20	\$80
U.S.	120	118	119	133	490		123	132	130	145	530	130	140	140	140	\$70
Foreign									130	145		130	140	140	140	565
Foreign (lc ex fx)																
Ultane/Sevoflurane WW	\$135	\$137	\$138	\$156	\$566		\$142	\$154	\$150	\$165	\$610	\$145	\$160	\$155	\$175	\$635
Synthroid							\$119	\$153	\$161	\$189	\$622	\$157	\$166	\$175	\$200	\$700
U.S.	\$119	\$153	\$161	\$189	\$622											\$735
Synthroid WW																
Creon							\$90	\$106	\$101	\$115	\$412	\$107	\$110	\$110	\$125	\$450
U.S.	\$90	\$106	\$101	\$115	\$412											\$490
Creon WW																
Depakote							\$23	\$30	\$43	\$50	\$146	\$46	\$30	\$45	\$55	\$175
US Only																\$185
Biaxin							\$5	\$0	\$0	\$0	\$5	\$5	\$0	\$0	\$0	\$5
US Only																
Other							\$90	\$193	\$80	\$51	\$414	\$102	\$117	\$90	\$60	\$370
U.S.	122	12	96	133	363		101	58	90	90	370	105	75	90	120	\$400
Foreign									90	120		105	75	90	120	390
Foreign (lc ex fx)																
Other WW	\$212	\$205	\$176	\$184	\$777		\$203	\$175	\$180	\$180	\$740	\$205	\$175	\$190	\$220	\$790

Source: Company data, Cowen and Company

AbbVie Estimated Quarterly Revenues (\$MM) (continued)

	Q1	Q2	Q3	Q4	2013	Q1	Q2	Q3E	Q4E	2014E	Q1E	Q2E	Q3E	Q4E	2015E
Pipeline															
Duoopa															
U.S.															
Foreign															
Foreign (fc ex fx)															
Duoopa WW	39	44	46	49	178	52	56	60	60	230	\$10 60	\$10 60	\$15 65	\$15 65	\$50 250
ABT-199															
U.S.															
Foreign															
Foreign (fc ex fx)															
ABT-199 WW	\$39	\$44	\$46	\$49	\$178	\$52	\$56	\$60	\$60	\$230	\$70 60	\$70 60	\$80 65	\$80 65	\$300 250
HCV Combinations															
U.S.															
Foreign															
Foreign (fc ex fx)															
HCV Combinations WW															
Dacizumab															
U.S.															
Foreign															
Foreign (fc ex fx)															
Dacizumab WW															
Elagolix															
U.S.															
Foreign															
Foreign (fc ex fx)															
Elagolix WW															
Elotuzumab															
U.S.															
Foreign															
Foreign (fc ex fx)															
Elotuzumab WW															
Veliparib (PARP inhibitor)															
U.S.															
Foreign															
Foreign (fc ex fx)															
Veliparib WW															
Duvelisib															
U.S.															
Foreign															
Foreign (fc ex fx)															
Duvelisib WW															
Atrasentan															
U.S.															
Foreign															
Foreign (fc ex fx)															
Atrasentan WW															
ABT-126															
U.S.															
Foreign															
Foreign (fc ex fx)															
ABT-126 WW															
Total Pipeline	<u>39</u>	<u>44</u>	<u>46</u>	<u>49</u>	<u>180</u>	<u>52</u>	<u>56</u>	<u>60</u>	<u>60</u>	<u>230</u>	<u>\$55 70</u>	<u>\$75 70</u>	<u>\$100 80</u>	<u>\$120 80</u>	<u>\$350 300</u>
TOTAL PHARMACEUTICALS															
U.S.	<u>2,122</u>	<u>2,625</u>	<u>2,616</u>	<u>2,818</u>	<u>10,181</u>	<u>2,226</u>	<u>2,646</u>	<u>2,590</u>	<u>2,830</u>	<u>10,290</u>	<u>2,295</u>	<u>2,810</u>	<u>2,790</u>	<u>3,125</u>	<u>11,020</u>
Foreign	<u>2,207</u>	<u>2,067</u>	<u>2,042</u>	<u>2,293</u>	<u>8,809</u>	<u>2,337</u>	<u>2,280</u>	<u>2,215</u>	<u>2,470</u>	<u>9,300</u>	<u>2,455</u>	<u>2,380</u>	<u>2,345</u>	<u>2,715</u>	<u>9,885</u>
WW	<u>\$4,329</u>	<u>\$4,692</u>	<u>\$4,658</u>	<u>\$5,111</u>	<u>\$18,790</u>	<u>\$4,563</u>	<u>\$4,926</u>	<u>4,805</u>	<u>5,300</u>	<u>\$19,590</u>	<u>\$4,750</u>	<u>\$5,190</u>	<u>\$5,135</u>	<u>\$5,840</u>	<u>\$20,915</u>
% Change	+9%	+10%	+8%	-6%	+4%	+5%	+5%	+3%	+4%	+4%	+4%	+4%	+5%	+7%	+10%

Source: Company data, Cowen and Company

Shire Estimated Quarterly Revenues (\$MM)

	Q1	Q2	Q3	Q4	2013	Q1	Q2	Q3E	Q4E	2014E	Q1E	Q2E	Q3E	Q4E	2015E	
Shire Products:																
CNS																
Vyvanse											\$375	\$395	\$385	\$445	\$1,600	
Adderall XR											80	80	70	70	300	
Equasym											15	15	15	15	60	
Intuniv											10	10	10	5	35	
Carbatrol											10	10	10	5	35	
Total CNS											490	510	490	540	2,030	
GI																
Lialda												\$160	\$160	\$165	\$165	\$650
Pentasa											70	70	70	70	280	
Resolor											10	10	10	15	45	
Colazide											0	0	0	5	5	
Total GI											240	240	245	255	980	
General Products																
Fosrenol												\$45	\$45	\$50	\$50	\$190
Agrilyin and Xagrid											25	25	25	25	100	
Calcichew											0	0	5	5	10	
Remimyl/Remimyl XL											0	0	0	5	5	
Total General Products											70	70	80	85	305	
Human Genetic Therapies																
Elaprase												\$150	\$155	\$155	\$160	\$620
Firazyr											80	90	100	110	380	
Cinryze											125	130	130	135	520	
Replagal											115	115	115	115	460	
Vpriv											85	85	85	90	345	
Plenadren											10	10	15	15	50	
Buccolam											10	10	10	10	40	
Other Viropharma											0	0	0	0	0	
Total HGT											575	595	610	635	2,415	
Other Shire											40	40	40	35	155	
Total Shire												\$1,415	\$1,455	\$1,465	\$1,550	\$5,885
Total AbbVie + Shire	\$4,329	\$4,692	\$4,658	\$5,111	\$18,790	\$4,563	\$4,926	\$4,805	\$5,300	\$19,590	\$6,165	\$6,645	\$6,600	\$7,390	\$26,800	

Source: Cowen and Company

AbbVie Estimated Annual Revenues (\$MM)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
<i>Wtd ave currency impact (%) - as of 9/5/14</i>											
PHARMACEUTICALS											
Humira WW	\$5,236	\$6,370	\$7,025	\$7,700	\$8,000	\$7,500	\$7,000	\$6,500	0%	3% - RA, PA, AS, Crohn's, Psoriasis, JIA; UC	- Adalimumab; anti-TNF monoclonal antibody
U.S.	5,423	6,135	6,730	7,400	7,700	7,200	6,700	6,200	0%	2% - Pushing into Brazil, Japan, China, Russia	- 4 add'l indications in development, incl. uveitis
Foreign											- Biosimilars possible - U.S. H1:17, E.U. H1:18 but IP could delay
Foreign (lc ex fx)											- Mkt targets new indications adding \$1B incremental sales by '15
Humira WW	\$10,659	\$12,505	\$13,755	\$15,100	\$15,700	\$14,700	\$13,700	\$12,700	0%	0%	- Humanized Mab binds to F-protein of RSV
Synagis	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	NM	NM - Guidelines could pressure use	
U.S.	827	875	845	800	800	800	800	800	-1%	0%	
Foreign											
Foreign (lc ex fx)											
Synagis WW	\$827	\$875	\$845	\$800	\$800	\$800	\$800	\$800	-1%	0%	
Kaletra	\$244	\$210	\$180	\$150	\$100	\$80	\$60	\$40	-24%	-23% - Lopinavir/low-dose ritonavir combo for HIV; patent exp. 6/26/16	
U.S.	718	590	520	450	400	350	300	250	-13%	-14% - Marketed in EM as Aluvia; combo protease inhibitor	
Foreign											
Foreign (lc ex fx)											
Kaletra WW	\$962	\$800	\$700	\$600	\$500	\$430	\$360	\$290	-16%	-16% - Emerging markets slowing sales decline	
Tricor/Trilipix	\$303	\$70	\$30	\$25	\$20	\$15	\$10	\$5	-36%	-44%	
U.S.	\$303	\$70	\$30	\$25	\$20	\$15	\$10	\$5	-36%	-44% - Generics launched 11/12	
Niaspan	\$650	\$100	\$30	\$20	\$10	\$5	\$5	\$5	-39%	-50% - Generics launched 9/2013 via settlement with TEVA/BRL	- ER Niacin for raising HDL, reducing LDL; acquired w/KOSPI '07
U.S.	0	0	0	0	0	0	0	0	NM	NM	
Foreign											
Foreign (lc ex fx)											
Niaspan WW	\$650	\$100	\$30	\$20	\$10	\$5	\$5	\$5	-39%	-50%	
Lupron (Leuproreotide)	\$566	\$545	\$515	\$485	\$455	\$425	\$395	\$365	-6%	-6% - Line extensions (central precocious puberty in '11) boost	
U.S.	219	200	185	165	145	125	105	85	-13%	-13% - Assuming flat units OUS in 2012-16	
Foreign											
Foreign (lc ex fx)											
Lupron (Leuproreotide) WW	\$785	\$745	\$700	\$650	\$600	\$550	\$500	\$450	-8%	-8% - No growth projected	
AndroGel	\$1,035	\$860	\$660	\$500	\$350	\$200	\$100	\$50	-38%	-35% - Generics of 1% form launch in 2015; 1.62% is 60% of franchise	- Testosterone gel for hypergonadism; market in decline
U.S.	\$1,035	\$860	\$660	\$500	\$350	\$200	\$100	\$50	-38%	-35%	
AndroGel WW											
Zemplar	\$218	\$190	\$225	\$250	\$275	\$300	\$325	\$350	11%	7% - Teva generics launched in U.S. 10/2013	- Paricalacitin; tx of secondary hyperparathyroidism in pts with CKF
U.S.	171	180	200	225	250	270	290	310	9%	9%	
Foreign											
Foreign (lc ex fx)											
Zemplar WW	\$389	\$370	\$425	\$475	\$525	\$570	\$615	\$660	10%	8%	
Norvir	\$254	\$170	\$120	\$100	\$80	\$60	\$40	\$20	-30%	-30% - U.S. patent expires in January 2015	- Ritonavir; HIV protease inhibitor; used as a booster combo
U.S.	220	190	160	130	100	80	40	20	-31%	-29% - Inhibits cytochrome P450-3A4 metabolism of other PI's	
Foreign											
Foreign (lc ex fx)											
Norvir WW	\$474	\$360	\$280	\$230	\$180	\$140	\$80	\$40	-31%	-30% - OUS sales growing through 2014	
Ultane/Sevoflurane	\$76	\$80	\$70	\$60	\$50	\$40	\$30	\$20	-21%	-17% - Induction, maintenance of general anesthesia	- Fluorinated isopropyl ether for anesthesia
U.S.	490	530	565	600	630	650	680	720	5%	6% - U.S. patents expired, but Abbott maintains share via service	
Foreign											
Foreign (lc ex fx)											
Ultane/Sevoflurane WW	\$566	\$610	\$635	\$660	\$680	\$700	\$720	\$740	3%	4% - Steady OUS sales	
Synthroid	\$622	\$700	\$735	\$775	\$815	\$850	\$885	\$925	5%	6% - Steady sales in U.S.; generics difficult to formulate	- Levothyroxine for overactive thyroid
U.S.	\$622	\$700	\$735	\$775	\$815	\$850	\$885	\$925	5%	6%	
Synthroid WW											
Creon	\$412	\$450	\$490	\$525	\$555	\$585	\$615	\$645	6%	7% - Acquired with Solvay in 2/2010	- Pancrelipase: enzyme replacement for pancreatic insufficiency
U.S.	\$412	\$450	\$490	\$525	\$555	\$585	\$615	\$645	6%	7%	
Creon WW											
Depakote	\$146	\$175	\$185	\$195	\$205	\$215	\$225	\$235	5%	7% - U.S. IR patent expired 7/08; ER patent expired 12/08	- Divalproex acid for seizure control, bipolar mania
US Only											
Biaxin	\$5	\$5	\$5	\$5	\$5	\$5	\$5	\$5	0%	0% - U.S. patent expired 2005	- Clarithromycin for Gram positive bacterial infections
Other	\$414	\$370	\$400	\$425	\$450	\$475	\$500	\$525	6%	3% - Includes Simcor, Advicor, Cardizem LA, etc.	
U.S.	363	370	390	410	430	450	470	490	5%	4% - Includes Nimbex, Vicodin, etc.; emerging mkt growth	
Foreign											
Foreign (lc ex fx)											
Other WW	\$777	\$740	\$790	\$835	\$880	\$925	\$970	\$1,015	5%	4% - Modest growth projected, via OUS	

Source: Company data, Cowen and Company

AbbVie Estimated Annual Revenues (\$MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
Pipeline											
Duopa											- Gel formulation of carbidopa/levodopa for Parkinson's
U.S.		\$50	\$100	\$150	\$200	\$250	\$300	NM	NM	NM - Infused directly to small intestine via portable pump; PDUFA Q1:15	
Foreign	178	230	250	270	290	310	330	350	NM	NM	NM - Likely a niche product for refractory PD
Foreign (lc ex fx)											
Duopa WW	\$178	\$230	\$300	\$370	\$440	\$510	\$580	\$650	NM	NM	NM - Marketed by Solvay OUS
ABT-199											- Bcl-2 selective inhibitor; CLL
U.S.			\$150	\$300	\$550	\$1,000	\$1,250	NM	NM	NM - 50% of profits to Roche	
Foreign			100	175	250	500	750	NM	NM	NM - Royalty on sales to Roche	
Foreign (lc ex fx)			100	175	250	500	750	NM	NM	NM - Royalty on sales to Roche	
ABT-199 WW			\$250	\$475	\$800	\$1,500	\$2,000	NM	NM	NM - 17p deletion global filings 2015; standard refractory filing in 2017	
HCV Combinations											- Combination of ABT-450 (PI) + ABT-267 (NS5A inhibitor) +
U.S.	\$300	\$500	\$700	\$700	\$700	\$700	\$700	NM	NM	NM - ABT-072 and ABT-333 (non-nuc polymerase inhibitors) for HCV	
Foreign	50	200	300	400	500	600	600	NM	NM	NM - Interim Ph II data show good SVR @12 weeks	
Foreign (lc ex fx)			200	300	400	500	600	NM	NM	NM - All-oral regimen for genotype 1, IFN-naïve HCV patients	
HCV Combinations WW	\$350	\$700	\$1,000	\$1,100	\$1,200	\$1,300	NM	NM	NM	NM - NDA filed 4/14 US and 5/14 EU	
Dacizumab											- Anti-IL-2 alpha MAB; Phase III for MS (DECIDE Trial); Q-monthly inj
U.S.		\$100	\$200	\$300	\$400	\$500	NM	NM	NM	NM - Good efficacy in Phase IIb trial; safety will be key; NDA 2014	
Foreign		20	40	60	80	100	NM	NM	NM	NM - Marketed as Zenepax for kidney X-plant rejection by Roche	
Foreign (lc ex fx)		20	40	60	80	100	NM	NM	NM	NM - Efficacy profile positions as salvage Tx in JCV(+) MS patients	
Dacizumab WW		\$120	\$240	\$360	\$480	\$600	NM	NM	NM	NM - Acquired via Facet Biotech in 4/2010; partnered w/BIIb (50/50)	
Elagolix											- Oral GnRH antagonist; partial estrogen suppression
U.S.			\$100	\$200	\$300	\$400	\$400	NM	NM	NM - Starting Ph III for endometriosis; Ph II for uterine fibroids	
Foreign			50	100	200	300	300	NM	NM	NM - Partnership with Neurocrine	
Foreign (lc ex fx)			50	100	200	300	300	NM	NM	NM - Similar to Lupron, Zoladex	
Elagolix WW			\$150	\$300	\$500	\$700	NM	NM	NM	NM - ABT holds WW rights to Elagolix and other GnRH antagonists	
Elotuzumab											- Anti-CS1 antibody; Phase III for multiple myeloma
U.S.		\$100	\$200	\$300	\$400	\$500	NM	NM	NM	NM - Partnered with BMY; ABBV records 30% of profit in the U.S.	
Foreign		10	20	30	40	50	NM	NM	NM	NM - ABBV records royalty ex-U.S.	
Foreign (lc ex fx)		10	20	30	40	50	NM	NM	NM	NM - ABBV records royalty ex-U.S.	
Elotuzumab WW		\$110	\$220	\$330	\$440	\$550	NM	NM	NM	NM	
Veliparib (PARP inhibitor)											- Ph IIb trials in breast cancer started H2:11
U.S.			\$100	\$200	\$300	\$400	\$400	NM	NM	NM - BID oral dosing; crosses BBB	
Foreign		0	0	0	0	0	NM	NM	NM	NM - Evaluating in brain, NSC lung, colorectal cancers	
Foreign (lc ex fx)		0	0	0	0	0	NM	NM	NM	NM - PARP inhibitors so far have been failures in breast	
Veliparib WW			\$100	\$200	\$300	\$400	NM	NM	NM	NM	
Duvetisib											- Oral PI3K-delta and gamma
U.S.											NM - Infinity books sales; ABBV shares profits
Foreign											NM - ABBV books sales, Infinity receives 23.5-30.5% royalty
Foreign (lc ex fx)											
Duvetisib WW											NM - Phase III in CLL, Phase II in iNHL; other tumor types
Atrasentan											- Phase III underway; single, global registration trial
U.S.											NM - Approval anticipated 2018
Foreign											NM - Approval anticipated 2018
Foreign (lc ex fx)											
Atrasentan WW											NM - Chronic kidney disease; Phase III underway
ABT-126											- Phase III to start in 2014
U.S.											NM - Approval anticipated 2017
Foreign											NM - Approval anticipated 2018
Foreign (lc ex fx)											
ABT-126 WW											NM - Cognitive deficits of schizophrenia
Pipeline											
U.S.											
Foreign	180	230	\$350	\$950	\$1,800	\$2,625	\$3,675	\$4,550	49%	NM	
Total Pipeline	\$180	\$230	\$650	\$1,550	\$2,675	\$3,800	\$5,400	\$6,800	76%	NM	
TOTAL PHARMACEUTICALS											
U.S.	10,181	10,290	11,020	12,165	13,170	13,380	13,870	14,240	6%	5%	
Foreign	8,809	9,300	9,885	10,780	11,330	11,185	11,270	11,425	3%	4%	
Foreign (lc ex fx)											
WW	\$18,790	\$19,590	\$20,915	\$22,945	\$24,500	\$24,585	\$25,140	\$25,865	5%	5%	
% Change	+4%	+4%	+7%	+10%	+7%	+0%	+2%	+2%			

Source: Company data, Cowen and Company

Shire Estimated Annual Revenues (\$MM)

2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20	2013-20	CGR Comments
								CGR	CGR	
Shire Products:										
CNS										
Vyvanse	\$1,600	\$1,800	\$1,975	\$2,150	\$2,300	\$2,450				- Amphetamine derivative; patent protection through 2023
Adderall XR	300	300	300	300	300	300				- Mixture of amphetamine salts; once-daily; generic launched 1/10
Equasym	60	70	80	90	100	110				- Once-daily methylphenidate; launched in Europe
Intuniv	35	25	25	25	25	25				- Modified release guanfacine; generics assumed in late 2015
Carbatrol	35	15	15	15	15	15				- Carbamazepine extended release; epilepsy; co-promote with Impax
Total CNS	2,030	2,210	2,395	2,580	2,740	2,900	NM	NM		
GI										
Lialda	\$650	\$675	\$700	\$720	\$740	\$565				- Reformulated mesalamine; ulcerative colitis; once-daily advantage
Pentasa	280	280	280	280	280	310				- Reformulated mesalamine; ulcerative colitis; no patent protection
Resolor	45	75	85	95	105	115				- Acquired via Movetis; international launches underway
Colazide	5	5	10	10	10	10				- Balsalazide; ulcerative colitis
Total GI	980	1,035	1,075	1,105	1,135	1,000	NM	NM		
General Products										
Fosrenol	\$190	\$190	\$190	\$190	\$190	\$190				- Hyperphosphatemia in end stage renal; patents through 2016
Agrylin and Xagrid	100	100	90	90	85	85				- Thrombocythemia; generics entered U.S. in 2005; still brand in Europe
Calcichew	10	10	10	10	10	10				- Calcium carbonate; osteoporosis; marketed in U.K.
Reminy/Reminy XL	5	5	5	5	5	5				- Galantamine; Alzheimer's Disease; marketed by Shire in U.K.
Total General Products	305	305	295	295	290	290	NM	NM		
Human Genetic Therapies										
Elaprase	\$620	\$645	\$670	\$695	\$720	\$745				- Idursulfase; Hunters
Firazyr	380	440	480	520	540	560				- Icatibant
Cinryze	520	540	560	580	550	525				- Acquired from Viropharma; HAE
Replagal	460	460	460	460	460	460				- Alglalsidase alfa; Fabry Disease; continued Ex-U.S. growth
Vpriv	345	330	320	310	300	290				- Gaucher disease; launch proceeding well but capacity constrained
Plenadren	50	85	100	115	130	145				- Acquired from Viropharma
Buccolam	40	55	70	80	90	100				- Acquired from Viropharma; HAE
Other Viropharma	0	0	0	0	10	10				- Acquired from Viropharma
Total HGT	2,415	2,555	2,660	2,760	2,800	2,835	NM	NM		
Other Shire	155	145	135	125	115	105				- Royalties, licensing, other
Total Shire	\$5,885	\$6,250	\$6,560	\$6,865	\$7,080	\$7,130	NM	NM		
Total AbbVie + Shire	\$18,790	\$19,590	\$26,800	\$29,195	\$31,060	\$31,430	\$32,220	\$32,795		

Source: Cowen and Company

AbbVie P&L Buildup 2013-20 (\$MM)

	Total Sales	% Chg.	Gross P.M.	SG&A		R&D		Op. P.M.	Other	Pretax P.M.	Tax Rate	Net Income	EPS (Dil.)	Y/Y % Chg.	Shares (MM)
Q1	\$4,329	--	76.2%	\$1,206	27.9%	\$632	14.6%	33.7%	\$52	32.5%	22.2%	\$1,095	\$0.68	--	1,605
Q2	4,692	--	80.7%	1,310	27.9%	695	14.8%	37.9%	82	36.2%	22.3%	1,319	0.82	--	1,609
Q3	4,658	--	79.7%	1,215	26.1%	709	15.2%	38.4%	82	36.7%	22.3%	1,327	0.82	--	1,605
Q4	<u>5,111</u>	--	77.1%	1,353	26.5%	795	15.6%	35.1%	93	33.3%	22.2%	1,325	0.82	--	1,608
2013	\$18,790	4%	78.4%	\$5,084	27.1%	\$2,831	15.1%	36.3%	\$309	34.7%	22.2%	\$5,066	\$3.14	-4%	1,607
Q1	\$4,563	5%	78.4%	\$1,261	27.6%	\$771	16.9%	33.9%	\$65	32.4%	22.3%	\$1,150	\$0.71	5%	1,609
Q2	4,926	5%	79.6%	1,336	27.1%	793	16.1%	36.4%	82	34.7%	22.2%	1,330	0.82	0%	1,608
Q3E	4,805	3%	79.5%	1,340	27.9%	810	16.9%	34.8%	65	33.4%	22.2%	1,249	0.78	-5%	1,608
Q4E	<u>5,300</u>	4%	78.0%	1,568	29.6%	826	15.6%	32.8%	66	31.6%	22.2%	1,302	0.81	-2%	1,608
2014E	\$19,590	4%	78.9%	\$5,505	28.1%	\$3,200	16.3%	34.4%	\$278	33.0%	22.2%	\$5,031	\$3.12	-1%	1,608
Q1E	\$6,165	--	80.5%	\$1,635	26.5%	\$1,035	16.8%	37.2%	\$300	32.3%	13.0%	\$1,735	\$0.81	14%	2,136
Q2E	6,645	--	81.4%	1,705	25.7%	1,035	15.6%	40.2%	300	35.7%	13.0%	2,061	0.96	18%	2,136
Q3E	6,600	--	81.3%	1,695	25.7%	1,085	16.4%	39.2%	300	34.7%	13.0%	1,991	0.93	20%	2,136
Q4E	<u>7,390</u>	--	80.0%	1,925	26.0%	1,120	15.2%	38.8%	300	34.8%	13.0%	2,236	1.05	29%	2,136
2015E	\$26,800	--	80.8%	\$6,960	26.0%	\$4,275	16.0%	38.9%	\$1,200	34.4%	13.0%	\$8,024	\$3.75	20%	2,136
2016P	\$29,195	9%	80.9%	\$7,320	25.1%	\$4,320	14.8%	41.0%	\$1,175	37.0%	13.0%	\$9,391	\$4.40	17%	2,136
2017P	\$31,060	6%	80.9%	\$7,450	24.0%	\$4,495	14.5%	42.4%	\$1,150	38.7%	13.0%	\$10,468	\$4.90	11%	2,136
2018P	\$31,430	1%	80.8%	\$7,555	24.0%	\$4,570	14.5%	42.3%	\$1,125	38.7%	13.0%	\$10,577	\$4.95	1%	2,136
2019P	\$32,220	3%	80.4%	\$7,640	23.7%	\$4,645	14.4%	42.3%	\$1,100	38.9%	13.0%	\$10,892	\$5.10	3%	2,136
2020P	\$32,795	2%	80.0%	\$7,695	23.5%	\$4,720	14.4%	42.2%	\$1,075	38.9%	13.0%	\$11,100	\$5.20	2%	2,136

Source: Company data, Cowen and Company

Anti-Inflammatory

Humira A Lesser, But Still Sizable, Portion Of Sales And EPS Of Combined Entity

We estimate that 64% of ABBV sales and 74% of ABBV profits will come from Humira in 2014. On a standalone bases, Humira was estimated to contribute 66% of sales and 75% of profits in 2015, and 49% of sales and 49% of profits in 2020. As a combined entity, Humira is estimated to contribute 51% of sales and 52% of profits in 2015, and 39% of sales and 34% of profits in 2020. While Humira will still be a big part of the combined entity, its profit contribution will be significantly less than that of ABBV standalone in 2020.

Percentage Concentration Of Humira

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P
ABBV Standalone								
Humira Sales	57%	64%	66%	66%	64%	60%	54%	49%
Humira Profits	61%	74%	75%	76%	72%	64%	56%	49%
ABBV + Shire								
Humira Sales			51%	52%	51%	47%	43%	39%
Humira Profits			52%	48%	45%	42%	38%	34%

Source: Company data; Cowen and Company

Increased Visibility Of Biosimilars Expected To Pressure Humira Sales Growth

Humira is a powerful franchise, although it faces patent expirations in the U.S. in 12/16 and in the EU in 4/18. At least two companies are in Phase III with a biosimilar of Humira (NVS for psoriasis and Amgen for psoriasis and RA), and this represents a significant risk to ABBV. NVS indicates that it has a plan in place to extrapolate to other indications beyond psoriasis without the need to generate clinical data.

On the other hand, biosimilars of most biologics have not had an easy go of it; ABBV has over 100 patents beyond the substance patent protecting Humira and we have very little visibility on these patents (although NVS claims they have been following the patent filings closely); ABBV pays a 10% royalty on sales of Humira which ceases with the expiration of certain patents, substantially bolstering ABBVs profits in a few years, by up to an estimated \$1.5B annually. This gives ABBV significant flexibility to compete on price if necessary. Rebates to PBMs further strengthen the case that Humira should remain a preferred entity on formularies.

We estimate Humira sales at \$12.505B (+17%) in 2014, \$13.755B in 2015, \$15.1B in 2016, \$15.7MM in 2017, and then declining to \$14.7B in 2018, \$13.7B in 2019, and \$12.7B in 2020.

Humira The Leading TNF Antibody

Humira (adalimumab) is a fully human monoclonal TNF antibody that has FDA approval for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, moderate to severe plaque psoriasis and axial spondyloarthritis (SpA; EU only). Sales of \$10.6B in 2013 make Humira the largest-selling therapeutic on the market today. Globally about

35-40% of sales are in rheumatoid arthritis and 20-22% in Crohn's. Psoriasis ranks third in the U.S., contributing about 15% of sales, and a similar percentage OUS. Ulcerative colitis is a very small contributor of Humira sales globally.

Humira Sales By Indication And Geography

	U.S.	Foreign
Rheumatoid Arthritis	40%	35%
Crohn's	22%	20%
Psoriasis	15%	15%
AS/PsA*	20%	25%
Ulcerative Colitis	5%	1%

*Includes Axial SpA in foreign markets.

Source: Cowen and Company

Our physician consultants consider Humira to be as safe and effective as Enbrel in RA and modestly more efficacious than Enbrel in psoriasis. Humira's main differentiating features are less frequent injectable dosing (40mg subcutaneously every other week vs. once weekly 50mg injection with Enbrel). Humira can also be dose-escalated to 40mg weekly (another benefit over Enbrel). In Crohn's disease, Humira is viewed as having more modest efficacy than Remicade but with a better safety profile and more convenient administration.

Over the next few years, we expect Humira to continue its growth in RA, IBD, and psoriasis, as well as the smaller indications. AbbVie is also developing Humira in six additional indications that are in Phase III: axial SpA (U.S.), peripheral SpA, hidradenitis suppurativa (HS; results from Phase III PIIONEER 1 trial, announced September 2014, showed Humira met primary endpoint with a 48% improvement compared to 26% for placebo in moderate-to-severe HS), uveitis (Phase III data and filing expected 2015), pediatric Crohn's disease (approved in U.S. in September), and most recently, fingernail psoriasis (Phase III started Q2:14, 26-week trial; n=200).

The key U.S. composition-of-matter patent covering Humira (#6,090,382: Human antibodies that bind human TNF-alpha) expires December 31, 2016 and the equivalent EU patent expires in February 2018. These patents claim high affinity antibodies for human TNF alpha with a slow off-rate for dissociation both in vitro and in vivo. Methods for expressing and synthesizing recombinant human antibodies that directly relate to Humira or related antibodies are also covered by the composition of matter patents. AbbVie continues to prosecute new intellectual property around Humira, and has many granted or pending patents.

Humira has 27% patient share, followed by Enbrel with 20% patient share. Remicade leads with 32% share. The next five drugs (RoActemra, MabThera/Rituxan, Orencia, Simponi, and Cimzia) combined hold a 20% patient share.

TNF Inhibitor Quarterly Market Buildup (\$MM)

	Q1	Q2	Q3	Q4	2013	Q1	Q2	Q3E	Q4E	2014E	Q1E	Q2E	Q3E	Q4E	2015E
Humira															
U.S.	\$956	\$1,224	\$1,389	\$1,667	\$5,236	\$1,192	\$1,661	\$1,640	\$1,875	\$6,370	\$1,350	\$1,825	\$1,800	\$2,050	\$7,025
Foreign	1,288	1,362	1,381	1,372	5,423	1,445	1,627	1,545	1,520	6,135	1,585	1,755	1,690	1,700	6,730
Humira WW	\$2,244	\$2,606	\$2,770	\$3,039	\$10,659	\$2,637	\$3,288	\$3,185	\$3,395	\$12,505	\$2,935	\$3,580	\$3,490	\$3,750	\$13,755
Blended price (indications and geographies)					\$25,200					\$25,200					\$25,200
Implied number of patients (MM)					423					496					546
Patient Share					26%					28%					29%
Enbrel															
U.S.	\$1,039	\$1,157	\$1,155	\$1,200	\$4,551	\$988	\$1,243	\$1,175	\$1,225	\$4,630	\$1,025	\$1,250	\$1,250	\$1,275	\$4,800
Foreign	877	960	932	1,005	3,774	914	1,010	980	1,045	3,950	965	1,060	1,030	1,095	4,150
Enbrel WW	\$1,916	\$2,117	\$2,087	\$2,205	\$8,825	\$1,902	\$2,253	\$2,155	\$2,270	\$8,580	\$1,990	\$2,310	\$2,280	\$2,370	\$8,950
Blended price (indications and geographies)					\$25,000					\$25,000					\$25,000
Implied number of patients (MM)					333					343					358
Patient Share					21%					19%					19%
Remicade															
U.S.	\$1,319	\$1,258	\$1,304	\$1,349	\$5,230	\$1,164	\$1,378	\$1,350	\$1,408	\$5,300	\$1,225	\$1,460	\$1,425	\$1,490	\$5,600
Foreign (JNJ)	281	414	385	363	1,443	446	426	415	413	1,700	470	450	440	440	1,800
Foreign (MRK)	549	527	574	620	2,270	604	607	625	675	2,510	580	580	600	650	2,410
Remicade WW	\$2,149	\$2,199	\$2,263	\$2,332	\$8,943	\$2,214	\$2,411	\$2,390	\$2,496	\$9,510	\$2,275	\$2,490	\$2,465	\$2,580	\$9,810
Blended price (indications and geographies)					\$16,500					\$16,500					\$16,500
Implied number of patients (MM)					542					576					595
Patient Share					34%					33%					31%
Simponi															
U.S.	\$94	\$87	\$111	\$112	\$404	\$104	\$132	\$125	\$139	\$500	\$135	\$145	\$155	\$165	\$600
Foreign (JNJ)	143	88	155	142	528	155	150	160	160	625	170	180	185	190	725
Foreign (MRK)	108	120	126	146	500	157	174	165	175	670	180	200	190	200	770
Simponi WW	\$345	\$295	\$382	\$400	\$1,432	\$416	\$456	\$450	\$474	\$1,795	\$485	\$525	\$530	\$555	\$2,095
Blended price (indications and geographies)					\$20,000					\$20,000					\$20,000
Implied number of patients (MM)					72					90					105
Patient Share					4%					5%					6%
Cimzia															
U.S. (Euro)	€ 76	€ 90	€ 105	€ 115	€ 386	€ 102	€ 112	€ 125	€ 135	€ 474	€ 120	€ 135	€ 145	€ 155	€ 555
U.S. (US)	\$77	\$92	\$111	\$121	\$400	\$106	\$118	\$126	\$130	\$480	\$115	\$129	\$142	\$155	\$540
Foreign (Euro)	€ 46	€ 60	€ 46	€ 60	€ 212	€ 58	€ 81	€ 70	€ 85	€ 294	€ 70	€ 95	€ 85	€ 100	€ 350
Foreign (US)	46	61	48	63	219	60	85	70	82	295	67	91	84	100	340
Cimzia WW	\$123	\$153	\$159	\$184	\$618	\$166	\$203	\$196	\$211	\$775	\$181	\$219	\$226	\$255	\$880
Blended price (indications and geographies)					\$21,500					\$21,500					\$21,500
Implied number of patients (MM)					29					36					41
Patient Share					2%					2%					2%
Rituxan															
U.S. (CHF)	CHF 135	CHF 130	CHF 145	CHF 120	CHF 530	CHF 125	CHF 130	CHF 150	CHF 125	CHF 530	CHF 130	CHF 125	CHF 145	CHF 125	CHF 525
U.S. (US)	\$134	\$129	\$149	\$124	\$536	\$130	\$138	\$154	\$122	\$545	\$126	\$120	\$143	\$125	\$515
Foreign (CHF)	135	144	142	158	579	140	140	140	160	580	135	140	140	155	570
Foreign (US)	134	143	146	163	585	146	148	143	157	595	131	135	138	155	560
Rituxan WW	\$267	\$272	\$295	\$286	\$1,121	\$276	\$286	\$297	\$279	\$1,140	\$256	\$255	\$281	\$280	\$1,075
Blended price (indications and geographies)					\$17,050					\$17,050					\$17,050
Implied number of patients (MM)					66					67					63
Patient Share					4%					4%					3%
Orencia															
U.S.	\$214	\$238	\$246	\$256	\$954	\$229	\$254	\$270	\$280	\$1,035	\$250	\$280	\$295	\$305	\$1,130
Foreign	108	114	129	141	490	134	148	155	165	600	160	170	180	190	700
Orencia WW*	\$320	\$352	\$375	\$397	\$1,444	\$363	\$402	\$425	\$445	\$1,635	\$410	\$450	\$475	\$495	\$1,830
Blended price (indications and geographies)					\$19,000					\$19,000					\$19,000
Implied number of patients (MM)					76					86					96
Patient Share					5%					5%					5%
Actemra															
U.S. (CHF)	CHF 73	CHF 77	CHF 83	CHF 81	CHF 314	CHF 86	CHF 94	CHF 95	CHF 100	CHF 375	CHF 105	CHF 110	CHF 115	CHF 120	CHF 450
U.S. (US)	\$72	\$77	\$85	\$83	\$318	\$90	\$100	\$97	\$98	\$385	\$102	\$106	\$113	\$120	\$440
Foreign (CHF)	165	181	184	193	723	187	201	205	230	825	230	240	250	265	985
Foreign (US)	163	180	190	200	733	195	215	210	225	845	225	230	245	265	965
Actemra WW*	\$236	\$257	\$275	\$283	\$1,051	\$285	\$315	\$307	\$323	\$1,230	\$327	\$338	\$358	\$385	\$1,405
Blended price (indications and geographies)					\$19,100					\$19,100					\$19,100
Implied number of patients (MM)					55					64					74
Patient Share					3%					4%					4%
Xeljanz															
U.S.	\$11	\$22	\$35	\$46	\$114	\$50	\$60	\$70	\$80	\$260	\$90	\$100	\$110	\$120	\$420
Foreign					2	5	5	5	5	15	10	10	15	15	50
Xeljanz WW	\$11	\$22	\$35	\$46	\$114	\$52	\$65	\$75	\$85	\$275	\$100	\$110	\$125	\$135	\$470
Blended price (indications and geographies)					\$21,000					\$21,000					\$21,000
Implied number of patients (MM)					5					13					22
Patient Share					0%					1%					1%
Total Market	\$7,611	\$8,272	\$8,651	\$9,173	\$33,707	\$8,311	\$9,679	\$9,480	\$9,978	\$37,445	\$8,959	\$10,276	\$10,230	\$10,805	\$40,270
% Change	11%	10%	14%	12%	12%	9%	17%	10%	9%	11%	8%	6%	8%	8%	8%

Source: Company data, Cowen and Company

TNF Inhibitor Annual Market Buildup (\$MM)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CAGR	2013-20 CAGR	Comments
Humira											
U.S.	\$5,236	\$6,370	\$7,025	\$7,700	\$8,000	\$7,500	\$7,000	\$6,500	0%	3% - RA, PA, AS, Crohn's, Psoriasis, JIA; UC	
Foreign	5,423	6,135	6,730	7,400	7,700	7,200	6,700	6,200	0%	2% - Pushing into Brazil, Japan, China, Russia	
Humira WW	\$10,659	\$12,505	\$13,755	\$15,100	\$15,700	\$14,700	\$13,700	\$12,700	0%	3% - Adalimumab; biosimilars possible - US H1:17, EU H1:18; AbbVie	
Blended price (indications and geographies)	\$25,200	\$25,200	\$25,200	\$25,200	\$25,200	\$25,200	\$25,200	\$25,200		- Expect U.S. price increases to be offset by fgn price erosion	
Implied number of patients (MM)	423	496	546	599	623	583	544	504			
Patient Share	26%	28%	29%	30%	29%	27%	25%	23%			
Enbrel											
U.S.	\$4,551	\$4,630	\$4,800	\$4,900	\$5,000	\$5,150	\$5,250	\$5,350	2%	2% - RA, JIA, PA, AS, adult plaque psoriasis; new patent extends exclusivity to 2020+; Amgen	
Foreign	3,774	3,950	4,150	4,250	4,375	4,500	4,625	4,750	3%	3% - Pfizer	
Enbrel WW	\$8,325	\$8,580	\$8,950	\$9,150	\$9,375	\$9,650	\$9,875	\$10,100	3%	3% - 'Etanercept	
Blended price (indications and geographies)	\$25,000	\$25,000	\$25,000	\$25,000	\$25,000	\$25,000	\$25,000	\$25,000		- Expect U.S. price increases to be offset by fgn price erosion	
Implied number of patients (MM)	333	343	358	366	375	386	395	404			
Patient Share	21%	19%	19%	18%	18%	18%	18%	19%			
Remicade											
U.S.	\$5,230	\$5,300	\$5,600	\$5,750	\$6,000	\$6,300	\$5,950	\$5,600	1%	1% - RA, AS, psoriasis, PA, Crohn's acute, maintenance, fistula closure and prevention), UC, -	
Foreign (JNJ)	1,443	1,700	1,800	1,900	2,050	2,150	2,250	2,350	6%	7%	
Foreign (MRK)	2,270	2,510	2,410	2,300	2,200	2,100	2,000	1,900			
Remicade WW	\$8,943	\$9,510	\$9,810	\$9,950	\$10,1250	\$10,550	\$10,200	\$9,850	1%	1% - Infliximab	
Blended price (indications and geographies)	\$16,500	\$16,500	\$16,500	\$16,500	\$16,500	\$16,500	\$16,500	\$16,500		- Expect U.S. price increases to be offset by fgn price erosion	
Implied number of patients (MM)	542	576	595	603	621	639	618	597			
Patient Share	34%	33%	31%	30%	29%	29%	28%	28%			
Simponi											
U.S.	\$404	\$500	\$600	\$750	\$850	\$950	\$1,050	\$1,150	15%	16% - RA, PA, AS; JNJ	
Foreign (JNJ)	528	625	725	850	950	1,050	1,150	1,250	12%	13%	
Foreign (MRK)	500	670	770	875	975	1,075	1,175	1,275	11%	14%	
Simponi WW	\$1,432	\$1,795	\$2,095	\$2,475	\$2,775	\$3,075	\$3,375	\$3,675	13%	14% - Golimumab; once-monthly	
Blended price (indications and geographies)	\$20,000	\$20,000	\$20,000	\$20,000	\$20,000	\$20,000	\$20,000	\$20,000		- Expect U.S. price increases to be offset by fgn price erosion	
Implied number of patients (MM)	72	90	105	124	139	154	169	184			
Patient Share	4%	5%	6%	6%	7%	7%	8%	8%			
Cimzia											
U.S. (Euro)	€ 386	€ 474	€ 555	€ 650	€ 750	€ 850	€ 950	€ 1,050			
U.S. (US)	\$400	\$480	\$540	\$650	\$750	\$850	\$950	\$1,050	14%	15% - Moderate to severe RA; Crohn's, PsA, AS, axSpA every 2-4 weeks	
Foreign (Euro)	€ 212	€ 294	€ 350	€ 425	€ 500	€ 575	€ 650	€ 725			
Foreign (US)	219	295	340	425	500	575	650	725	16%	19% - Every 2 weeks	
Cimzia WW	\$618	\$775	\$880	\$1,075	\$1,250	\$1,425	\$1,600	\$1,775	15%	16% - Certolizumab pegol; once monthly anti-TNF; UCB Pharma	
Blended price (indications and geographies)	\$21,500	\$21,500	\$21,500	\$21,500	\$21,500	\$21,500	\$21,500	\$21,500		- Expect U.S. price increases to be offset by fgn price erosion	
Implied number of patients (MM)	29	36	41	50	58	66	74	83			
Patient Share	2%	2%	2%	2%	3%	3%	3%	4%			
Rituxan											
U.S. (CHF)	CHF 530	CHF 530	CHF 525	CHF 495	CHF 450	CHF 400	CHF 360	CHF 320	-8%	-7% - Moderate to severe RA; monox or in combo with DMARDs	
U.S. (US)	\$536	\$545	\$515	\$495	\$450	\$400	\$360	\$320			
Foreign (CHF)	579	580	570	535	505	475	465	435			
Foreign (US)	585	595	560	535	505	475	465	435	-5%	-4%	
Rituxan WW	\$1,121	\$1,140	\$1,075	\$1,030	\$955	\$875	\$825	\$755	-7%	-5% - Rituximab; estimated 16% of sales are in RA; Roche	
Blended price (indications and geographies)	\$17,050	\$17,050	\$17,050	\$17,050	\$17,050	\$17,050	\$17,050	\$17,050		- Expect U.S. price increases to be offset by fgn price erosion	
Implied number of patients (MM)	66	67	63	60	56	51	48	44			
Patient Share	4%	4%	3%	3%	3%	2%	2%	2%			
Orencia											
U.S.	\$954	\$1,035	\$1,130	\$1,250	\$1,350	\$1,450	\$1,550	\$1,650	8%	8% - RA, JIA	
Foreign	490	600	700	840	910	980	1,050	1,050	10%	12%	
Orencia WW*	\$1,444	\$1,635	\$1,830	\$2,020	\$2,190	\$2,360	\$2,530	\$2,700	9%	9% - Abatacept; IV T-cell co-stimulator; Bristol-Myers Squibb	
Blended price (indications and geographies)	\$19,000	\$19,000	\$19,000	\$19,000	\$19,000	\$19,000	\$19,000	\$19,000		- Expect U.S. price increases to be offset by fgn price erosion	
Implied number of patients (MM)	76	86	96	106	115	124	133	142			
Patient Share	5%	5%	5%	5%	5%	6%	6%	7%			
Actemra											
U.S. (CHF)	CHF 314	CHF 375	CHF 450	CHF 550	CHF 650	CHF 750	CHF 850	CHF 950			
U.S. (US)	\$318	\$385	\$440	\$550	\$650	\$750	\$850	\$950	16%	17% - Moderate to severe RA; monox or in combo with DMARDs	
Foreign (CHF)	723	825	985	1,135	1,285	1,435	1,510	1,585			
Foreign (US)	233	245	965	1,135	1,285	1,435	1,510	1,585	11%	12%	
Actemra WW*	\$1,051	\$1,230	\$1,405	\$1,685	\$1,935	\$2,185	\$2,360	\$2,535	13%	13%	
Blended price (indications and geographies)	\$19,100	\$19,100	\$19,100	\$19,100	\$19,100	\$19,100	\$19,100	\$19,100		- Expect U.S. price increases to be offset by fgn price erosion	
Implied number of patients (MM)	55	64	74	88	101	114	124	133			
Patient Share	3%	4%	4%	4%	5%	5%	6%	6%			
Xeljanz											
U.S.	\$114	\$260	\$420	\$600	\$800	\$1,000	\$1,200	\$1,400	32%	43% - RA; Phase III psoriasis, UC; Phase II transplant, AS, PA, Crohn's	
Foreign	15	50	75	100	125	150	175	NA		NA	
Xeljanz WW	\$114	\$275	\$470	\$675	\$900	\$1,125	\$1,350	\$1,575	34%	46% - Tofacitinib; oral JAK3 inhibitor; Pfizer	
Blended price (indications and geographies)	\$21,000	\$21,000	\$21,000	\$21,000	\$21,000	\$21,000	\$21,000	\$21,000		- Expect U.S. price increases to be offset by fgn price erosion	
Implied number of patients (MM)	5	13	22	32	43	54	64	75			
Patient Share	0%	1%	1%	2%	2%	2%	3%	3%			
Total Market	\$33,707	\$37,445	\$40,270	\$43,160	\$45,330	\$45,945	\$45,815	\$45,665			
% Change	12%	11%	8%	7%	5%	1%	0%	0%			

Source: Company data, Cowen and Company

Anti-TNFs And Other Biologics Approved In The U.S. For The Treatment Of RA

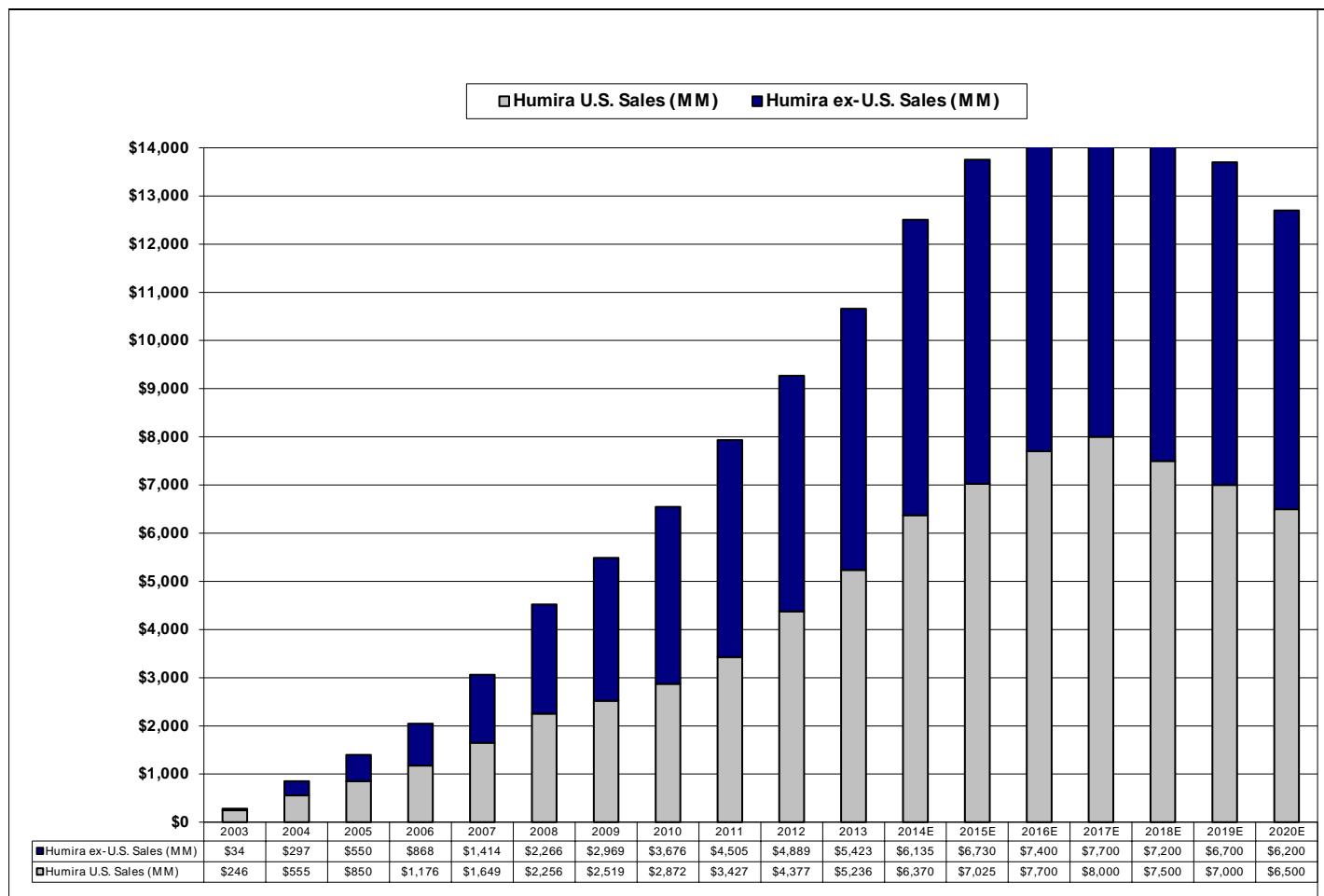
Drug	Company	Description/ Class	Indications (U.S. and/or International)	Route of admin	Dose in RA	Annual cost of therapy	Initial U.S. approval
Remicade (infliximab)	JNJ/MRK	TNF antagonist	RA w MTX, AS, PsA, Ps, CD, UC, pCD	IV infusion	3mg/kg at 0,2 & 6 weeks, then every 8 weeks	\$15-30K	1998
Enbrel (etanercept)	AMGN/PFE	TNF antagonist	RA, JIA, AS, PsA, Ps, pPs	S/C injection	50mg once weekly	\$29K	1998
Humira (adalimumab)	ABBV	TNF antagonist	RA, JIA, AS, PsA, Ps, CD, UC, aSpA; Ph III for HS, Uvt, pSpA, pCD, pPs	S/C injection	40mg every other week; 40mg every week in MTX non-responders	\$28-57K	2002
Simponi (golimumab)	JNJ/MRK	TNF antagonist	RA, AS, PsA; Filed for UC	S/C injection; sBLA filed for IV form	50mg every 4 weeks	\$29K	2009
Cimzia (certolizumab pegol)	UCB	TNF antagonist	RA, CD; Ph III in JIA, aSpA, PsA, pCD	S/C injection	400mg at 1, 2 & 4 weeks, then 200 mg every other week or 400mg every 4 weeks	\$27K	2008
Orencia (abatacept)	BYM	T cell costimulation modulator	RA but not w TNF antagonist, JIA	IV infusion or S/C injection	500-1,000mg at 0,2 & 4 weeks, then every 4 weeks; or 125 mg S/C weekly	\$16K-31K (IV); \$27K (S/C)	2005
Actemra (tocilizumab)	Roche/Chugai	IL-6 inhibitor	RA; SJIA	IV infusion	4-8mg/kg every 4 weeks	\$19-37K	2010
Rituxan (rituximab)	BIIB/Roche	Anti CD20 antibody	RA but only in TNF non-responders	IV infusion	two-1000 mg IV infusions separated by 2 weeks (one course) every 24 weeks	\$26K	2006
Kineret (anakinra)	SOBI	IL-1 antagonist	RA but not w TNF antagonist	S/C injection	100mg daily	\$25K	2001
Xeljanz (tofacitinib)	Pfizer	JAK inhibitor	RA but not w other biologics; Ph III for UC, pPs, JIA	Oral	5 mg twice daily	\$25K	2012

RA- Rheumatoid arthritis, JIA- Juvenile idiopathic arthritis, AS- Ankylosing spondylitis, PsA- Psoriatic arthritis, UC- Ulcerative colitis, CD- Crohn's disease, Ps- Psoriasis, aSpA- axial spondyloarthritis, pSpA- peripheral spondyloarthritis, pPs- plaque psoriasis, pCD- pediatric Crohn's disease, Uvt- uveitis, HS- hidradenitis suppurativa

Source: Cowen and Company, Company data

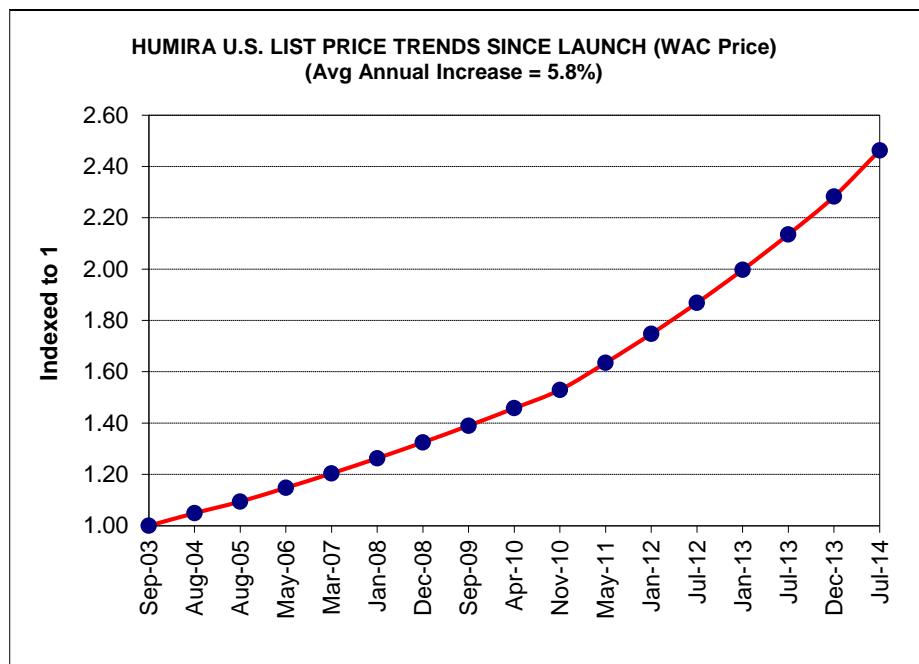
Humira sales growth in the OUS markets has outpaced U.S. growth over the past few years, yet the TNF inhibitor penetration of international RA, Crohn's, and psoriasis treatment markets remains relatively low, at less than 30%. AbbVie continues to focus its OUS Humira sales efforts on the rapidly-growing biologics markets in Brazil, Japan, China, and Russia.

Humira WW Sales Growth Since Launch



Source: Cowen and Company

Humira U.S. Price Has Doubled Since Launch



Source: Walters Kluwer Health

TNF Inhibitors Are Entrenched As The Go-To Biologic Agents...

Tumor necrosis factor alpha (TNF α), a cytokine produced by T-lymphocytes and macrophages, is a central player in the inflammatory cascade and a primary mediator of immune reactions. TNF α inhibitors (anti-TNFs) block TNFs' ability to attach to cell receptors. The net result is a dramatic decline in inflammation. Anti-TNF agents are highly effective in treating a multitude of inflammatory diseases including: RA, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel diseases, psoriasis, and spondyloarthritis.

Evidence-based clinical trials support the use of anti-TNFs as an early second-line therapy. Anti-TNFs can be used as monotherapy or in combination with traditional disease-modifying antirheumatic drugs (DMARDs) in treatment naïve or treatment failure patients. Issues with anti-TNFs include their high cost and their contraindication in patients with CHF, old/latent tuberculosis, or a history of cancer or demyelinating disease. All anti-TNF labels were updated in 2008 to include a black box for fungal infections and TB reactivation. In 2009, the FDA announced that anti-TNFs in children and adolescents lead to "an increased risk of lymphoma and other cancers" (e.g., leukemia) and is associated with new-onset psoriasis. Black-box warnings and medication guides associated with all biologics from this class were updated to reflect these safety concerns. According to the ACR, the FDA's analysis was based on reports of 48 malignancies (including lymphoma) in children and adolescents, 147 cases of leukemias (primarily in adults, few in children), and 69 cases of new-onset psoriasis. In April 2011, the FDA issued an additional warning indicating that it continues to receive reports of cases of Hepatosplenic T-Cell Lymphoma (HSTCL), primarily in adolescents and young adults being treated with anti-TNFs. In September 2011, the FDA updated the black box on all anti-TNFs to reflect increased risk of infection by *Legionella* and *Listeria*.

Although the FDA has become more aggressive in detailing the risks associated with anti-TNFs, specialists remain eager to use these drugs for the following three reasons: (1) Anti-TNFs have demonstrated robust efficacy in halting or slowing disease progression (clinically and radiographically); (2) The serious adverse events associated with these drugs are very rare; and (3) Evidence-based medicine suggests that anti-TNFs lead to a decrease in associated co-morbidities (i.e. acute coronary syndrome, stroke). Thus, rheumatologists believe the benefits of TNF inhibitors continue to far outweigh the risks and expect these agents to remain the dominant therapy in RA. In fact, TNF inhibitors are so well-entrenched and highly regarded that doctors usually try a second anti-TNF in patients who fail on initial therapy.

What Will Keep Humira Growing?

- New indications:** In addition to the ten approved Humira indications, AbbVie is seeking four additional indications. The four new indications include: uveitis, peripheral and axial spondyloarthropathies (joint disease of the spine; axial approved in EU), and hidradenitis suppurativa (skin disease from clogging of apocrine glands). In May 2014, Humira received orphan drug designation for certain forms of non-infectious uveitis. Management estimates the WW incremental sales opportunity of these new indications at \$1.5B by 2016.

Humira Indications Summary And Market Projections

Disease Category	Indications	Timing	Potential WW Market Opportunity
Rheumatology	Rheumatoid Arthritis (RA)	Approved in 2002	~\$15B
	Psoriatic Arthritis (PsA)	Approved in 2005	~\$1.5B
	Ankylosing Spondylitis (AS)	Approved in 2006	~\$1.2B
	Juvenile Idiopathic Arthritis (JIA)	Approved in 2008	~\$2.0B
	Peripheral Spondyloarthropathies	Evaluating next steps	\$100-150MM
	Axial Spondyloarthropathies	EU approved 2012; evaluating next steps in U.S.	\$100-150MM
Gastroenterology	Crohn's Disease (CD)	Approved in 2007	~\$1.0B
	Ulcerative Colitis	Approved in Q4:12	\$300-400MM
	Pediatric Crohn's Disease	Approved September 2014	\$100-150MM
Dermatology	Psoriasis (Ps)	Approved in 2008	~\$1.5B
	Hidradenitis Suppurativa	Expect filing H2:14; approval in 2015	\$25-50MM
	Fingernail Psoriasis	Phase III started Q2:14	\$50-100MM
Ophthalmology	Uveitis	Expect filing 2015; approval in 2106	\$50-100MM

Source: Cowen and Company

- Rheumatoid Arthritis, Crohn's, and psoriasis markets remain underpenetrated:** Penetration rates for TNF inhibitors remain relatively low in both the U.S. and international markets. AbbVie plans to continue to expand Humira use by: (1) driving earlier diagnosis and faster cycling times from conventional therapies; (2) launching Humira in new indications in Brazil, Japan, China, and Russia; and (3) continuing to implement best-in-class support programs to improve patient adherence.

Biologic Penetration Rates

	(% of moderate-to severe patients treated with biologics)	
	U.S. Penetration	Ex-U.S. Penetration
Rheumatology	~26%	~20%
Dermatology	~6%	~4%
Gastroenterology	~28%	~25%

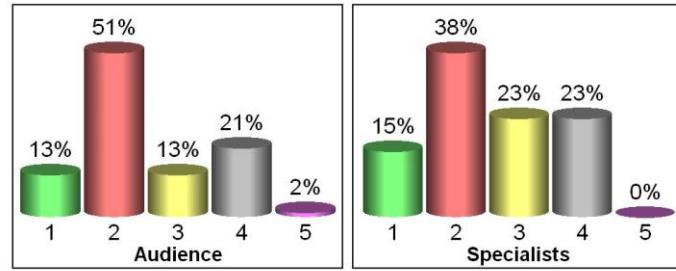
Source: Company data

3. U.S. specialists prefer the established TNF inhibitors: During Cowen's October 2013 Therapeutics Conference, our rheumatology physician panelists continued to laud biologic anti-TNFs as excellent drugs for RA, having shown benefits on the three critical domains of disease in RA: (1) signs and symptoms; (2) patient reported outcomes; and (3) structural progression. The physicians projected that the anti-TNF class would continue to grow modestly over the next three years. One source of growth might be the group of rheumatologists currently using nonbiologic DMARD "triple therapy" (sulfasalazine/MTX/hydroxychloroquine) coming around to the view that this regimen is inferior to biologics in that it has not shown a benefit on structural progression.

Rheumatology Panel Survey Question – October 2013

1) All things considered (population growth, penetration gains, competition, etc), in 3 years' time the number of RA patients in the U.S. on TNF inhibitors will be:

1. 15%+ higher than today
2. 0-15% higher than today
3. unchanged
4. 0-15% lower than today
5. 15%+ lower than today



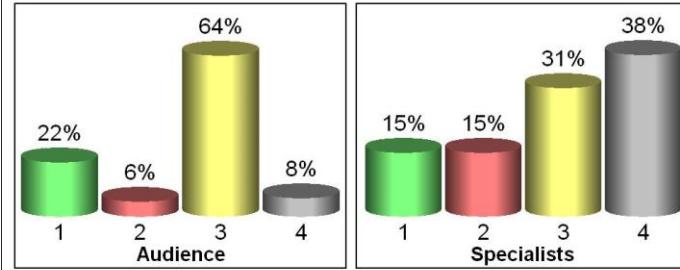
Source: Cowen and Company Therapeutics Conference – October 2013

Specialist panelists expect Humira to capture over 31% of new patients next year, below prior high-30% estimates, but still well ahead of all but JNJ's Simponi. This uptick in expected Simponi use reflects, in our panelist's view, that most Simponi users view it as a substitute for Remicade, and now that Simponi is available as an IV infusion as well as subQ, those Remicade infusers are more naturally able to convert to Simponi.

Rheumatology Panel Survey Question – October 2013

2) Which of the following TNF inhibitors will gain the most new patients in the U.S. in 2014?

1. Cimzia (UCB)
2. Enbrel (Amgen/Pfizer)
3. Humira (Abbott)
4. Simponi (JNJ)



Source: Cowen and Company Therapeutics Conference – October 2013

4. Oral RA agents not expected to have a major impact on Humira, but will have a role:

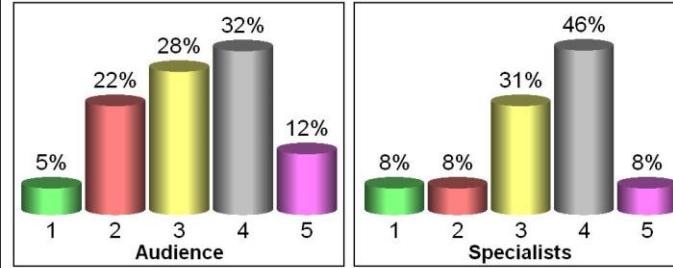
Multiple oral RA drugs are now approved or in clinical development (4 in Phase III, 15+ in Phase II), led by Pfizer's Xeljanz (JAK 1/3 inhibitor). Overall, our clinical consultants are not optimistic for the potential of orals to be used ahead of TNFs, until long-term safety and radiographic progression data are documented – in contrast to the wealth of clinical experience and data for the TNF inhibitors. They believe that it may take as long as five years for oral agents to gain significant traction in the RA market.

During our October 2013 Therapeutics Conference rheumatology panel, Xeljanz was not viewed as a particularly attractive option in RA, with 77% of surveyed specialists citing lingering safety concerns as the major barrier (e.g. reactivation of herpes zoster). Our surveyed physicians are mostly using Xeljanz only after patients have failed two TNFs, and usually another biologic as well. Our panelist noted that Xeljanz is also wanting on efficacy, as it has not demonstrated a benefit on structural progression at the approved 5mg dose.

Rheumatology Panel Survey Question – October 2013

7) In the next year, I plan to prescribe Xeljanz mostly to patients who:

1. Are TNF-inhibitor naïve
2. Have failed one TNF inhibitor
3. Have failed two TNF inhibitors
4. Have failed two TNF inhibitors and another biologic (i.e. Orencia or Actemra)
5. I do not plan to prescribe Xeljanz in the next year



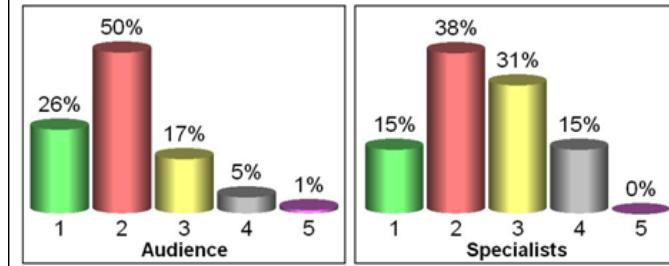
Source: Cowen and Company Therapeutics Conference – October 2013

That said, it is somewhat surprising that over three quarters of surveyed physicians say they are ready to use Xeljanz in the first line today, or will be within one to two years. Our panelist noted that there is a place for Xeljanz in certain patients, such as those living far from their physicians and unable to access in-office injection/infusion services on a regular basis.

Rheumatology Panel Survey Question – October 2013

11) In three years' time, Xeljanz will capture approximately what percent of the methotrexate refractory RA market? (current share: Enbrel (30%), Humira (25%), other TNFs (25%), Orencia (10%), Actemra (10%))

1. <5%
2. 10%
3. 15%
4. 20%
5. >25%



Source: Cowen and Company Therapeutics Conference – October 2013

TNF Inhibitors Stack Up Well Against The Orals

Oral Arthritis Drugs Approved And In Development

Therapeutic	Mechanism	Company	Status
Xeljanz (tofacitinib)	JAK Inhibitor	Pfizer	FDA approved 11/2012
T-614 (iguratimod)	Multi-Cytokine Inhibitor	Eisai	Approved in Japan 6/2012
Iremod (iguratimod)	Multi-Cytokine Inhibitor	Simcere	SFDA approved 8/2011
Apremilast	PDE4 Inhibitor	Celgene	Phase III
Baricitinib (INC028050)	JAK1/2 Inhibitor	Incyte/LLY	Phase III
Masitinib (AB1010)	c-Kit Inhibitor	AB Science	Phase IIb/III
GLPG0634	selective JAK1 inhibitor	AbbVie/Galapagos	Phase IIb
ASP015K	JAK Inhibitor	JNJ/Astellas	Phase IIb
LX2931	S1P lyase inhibitor	Lexicon	Phase II
CF101	A3 Adenosine Receptor Agonist	Can-Fite Biopharma	Phase II
CCX354	CCR1 Receptor	ChemoCentryx/GSK	Phase II

Source: Cowen and Company

5. Long-term data from PREMIER and DE019 trials were impressive. Abbott presented long-term data from the open-label extension studies of PREMIER and DE019 at the 2011 American College of Rheumatology (ACR) meeting. Both trials evaluated disease activity, improvement in physical function and inhibition of radiographic progression in patients treated with Humira plus methotrexate for up to eight years in patients with moderate-to-severe RA and up to ten years in patients with long-standing moderate-to-severe RA. Neither trial showed any new safety signals for Humira after eight and ten years of treatment.

The PREMIER long-term extension study evaluated 299 patients for eight years: 103 were initially treated with Humira plus methotrexate, 96 were treated with methotrexate monotherapy, and 100 were initially treated with Humira in the controlled portion of the study. The completers analysis showed that the 299 patients achieved a mean change in mTSS (mean change in modified total Sharp score) of 8.6, a mean DAS28 (Disease Activity Score 28 joint counts) of 2.6, and a mean Health Assessment Questionnaire Disability Index (HAQ-DI) of 0.6. 52.5% of patients in the extension study experienced an absence of swollen joints and 47.9% of patients experienced an absence of tender joints. Most notable was >40% of patients had no further radiographic progression, defined as change in mTSS of ≤0.5. 71% of patients achieved a DAS28 of < 2.6, and 60% of patients achieved an HAQ-DI score of <0.5.

Premier Extension Trial Demonstrates Long-Term Benefits Of Humira...

Study duration: up to 8 years in patients with moderate-to-severe RA	
Endpoint Measured	Humira 40mg Sub-Q biweekly + MTX
completers analysis @ 8 years:	(n=299)
mean change in mTSS	8.6
mean DAS28 composite	2.6
mean HAQ-DI	0.6
%achieving change in mTSS ≤0.5	>40%
%achieving DAS28 <2.6	71%
%achieving HAQ-DI score <0.5	60%
%achieving absence of swollen joints	52.5%
%achieving absence of tender joints	47.9%

Source: Company Presentation ACC 2011; Cowen and Company

The DE019 study evaluated Humira 40mg every other week and Humira 20mg once weekly vs placebo injections in patients with long-standing RA that showed an inadequate response to methotrexate. The controlled portion of the study showed that Humira plus methotrexate achieved clinical and radiographic superiority over placebo plus methotrexate.

In the extension study of DE019, 202 patients continued on Humira plus methotrexate therapy through year ten: 80 patients were initially treated with Humira 40 mg every other week; 66 were initially treated with Humira 20 mg weekly, and 56 were initially treated with placebo. Patients initially randomized to Humira 40 mg every other week plus methotrexate achieved mean change in mTSS of 0.7, and close to 50% of patients had no radiographic progression (defined as change in mTSS of less than or equal to 0.5) after ten years of treatment.

Biosimilars May Become A Threat Starting In 2017

Our clinical consultants indicate that the possibility of biosimilar TNF inhibitors is of increasing interest among rheumatologists, given the availability of biosimilar versions of Enbrel and/or Remicade in China, India, and South America. We do not anticipate biosimilar anti-TNFs to enter the U.S. market before 2017-18, given clinical trial requirements and ongoing patent activity (Enbrel). However, at least two companies are in Phase III with a biosimilar of Humira (NVS for psoriasis and Amgen for psoriasis and RA), and this represents a significant risk to AbbVie. NVS indicates that it has a plan in place to extrapolate to other indications beyond psoriasis without the need to generate clinical data.

While biosimilar regulatory guidelines have been in place in Europe since 2004 and were first published in Japan in 2008, the U.S. has yet to outline a definitive path to approval of biosimilars. Close to 20 biosimilars have been approved in Europe, but several of these would not be considered biosimilars in the U.S. due to differences in definitions. Our regulatory consultants indicate that the FDA may set minimum statutory guidelines for biosimilar development and approvals, but ultimately will set specific requirements on a drug-by-drug basis.

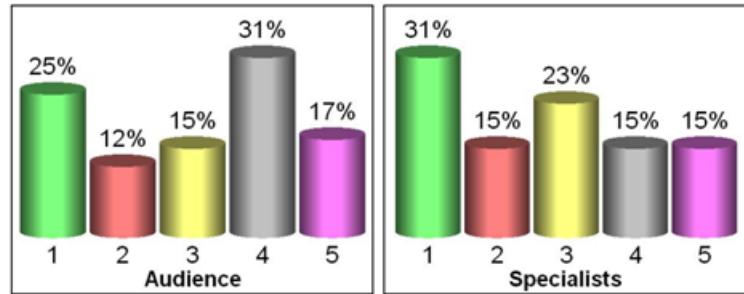
Interestingly, about a third of surveyed specialists from our October 2013 Therapeutics Conference would be ready to prescribe a biosimilar in the U.S. market for any indication, were it approved on a similar clinical package, with about another quarter of surveyed doctors satisfied with the efficacy data but wanting to see more safety

data. The remaining 45% would have issues with efficacy, safety, and/or cost. Some panelists noted skepticism that interchangeability would ever be achievable with antibodies and cited concerns about potential safety differences in terms of immunogenicity.

Rheumatology Panel Survey Question – October 2013

3) Celltrion's Inflectra, a biosimilar infliximab, was approved by the EMA (for all Remicade's indications) following demonstration of noninferiority to Remicade, with comparable safety and tolerability, in a 580-patient Phase III trial for RA and a 230-patient Phase I trial for ankylosing spondylitis. If biosimilars eventually become available in the U.S., what would you want to see to feel comfortable prescribing the biosimilars?

1. A clinical efficacy and safety data package similar to Inflectra's would suffice to prescribe the biosimilar in all labeled indications
2. Safety is adequate, but I would want efficacy trials for each specific indication in question before prescribing
3. Efficacy is adequate to prescribe for all indications, but I would want more safety data
4. Both more efficacy data and more safety data would be needed for me to feel comfortable
5. Price is the most important factor



Source: Cowen and Company Therapeutics Conference – October 2013

The EMEA has outlined specific clinical and non-clinical guidelines for four major biosimilar categories: recombinant insulin, human growth factor, erythropoietin, and colony stimulating factors. The most important guidelines include: (1) the molecular property conformance of biosimilars need to be rigorously confirmed via physicochemical and biological characterization; (2) prior to initiating clinical trials, *in vitro* studies must be performed to detect any significant differences between the biosimilar being evaluated and its reference (cell-based functional assay comparisons; toxicity and toxicokinetics studies in animal models such as primates); (3) clinical trials must include comparative pharmacokinetic profiles for reference, and the biosimilar must be evaluated in the appropriate patient population; (4) comparative efficacy must be assessed in clinical trials; and (5) biosimilar safety and immunogenicity must be assessed in a post-approval setting.

Comparison Of Regional Biosimilar Guidelines

	Europe	United States	Japan
Product Characterization	Establish comparability in reactivity through relevant physicochemical characterization studies; receptor-binding, structural characterization.	Analytical studies required. Complexities of protein therapeutics require sophisticated evaluation of amino acid sequence, amino acid modifications (glycosylation, side chain analysis), and higher-order structure (protein folding and protein-protein interactions).	Stability testing required; comparison to reference product.
Non-Clinical Studies	Animal studies to assess PD effect relative to clinical application. Non-clinical toxicity as determined in at least one repeat dose toxicity study, including toxicokinetic measurements (antibody titer, cross reactivity, and neutralizing capacity).	In-vitro functional characterization. Animal studies; PK/PD, immunogenicity. Human PK/PD studies. Clinically relevant PD markers should be evaluated to provide scientific justification for type/duration of clinical studies.	Comparative studies with reference product; animal models, in-vitro/in-vivo bioactivity, immunologic response, PK/PD.
Clinical Trials	Comparative clinical trials usually required. Requirements dependent upon existing knowledge of reference product and claimed therapeutic indications. In certain cases, PK/PD studies may be appropriate for demonstrating clinical comparability.	Comparative PD studies required unless sponsor provides adequate scientific justification. Where surrogate PD markers of efficacy are not well established, clinical safety and efficacy must be established through clinical trials; non-inferiority designs appropriate. Sufficient immunogenicity data required.	Required, but flexible; results of animal work and human PK/PD will determine type, length, and number of trials required. Surrogate markers of efficacy may substitute for true endpoints where appropriate.
Post-Marketing	Required	Required	Required

Source: FDA, CHMP, PMDA, Cowen and Company

Humira Protected By Composition-Of-Matter Patents At Least Through 2016

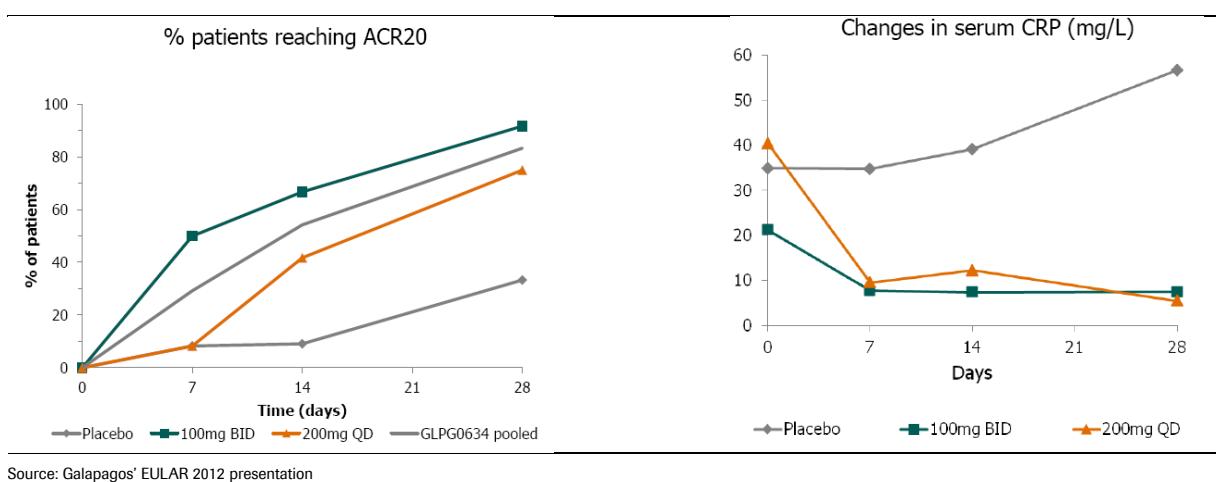
The key U.S. composition-of-matter patent covering Humira (#6,090,382: Human antibodies that bind human TNF-alpha) expires December 31, 2016 and the equivalent EU patent expires in February 2018. These patents claim high affinity antibodies for human TNF alpha with a slow off-rate for dissociation both in vitro and in vivo. Methods for expressing and synthesizing recombinant human antibodies that directly relate to Humira or related antibodies are also covered by the composition of matter patents.

AbbVie continues to prosecute new intellectual property around Humira, so biosimilars may be delayed beyond 2017. And Amgen's new patent for Enbrel is a positive signal that antibodies can be improved and gain new exclusivity.

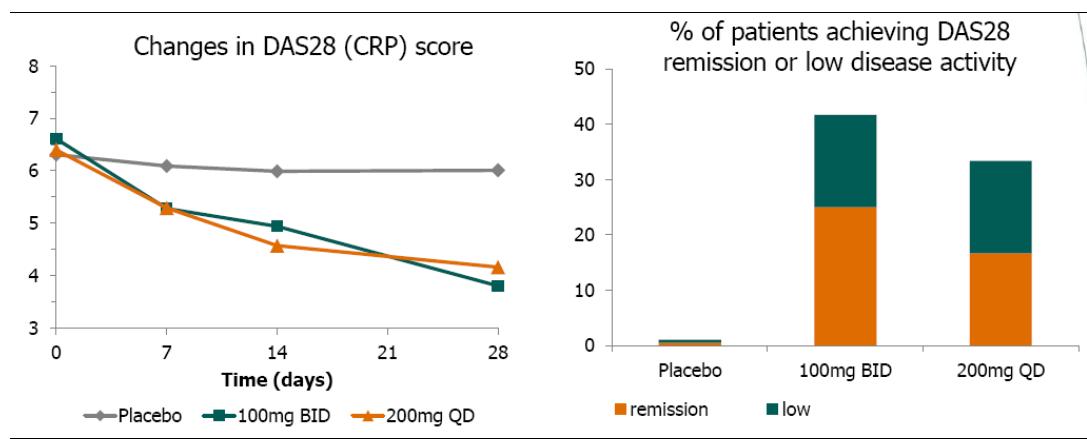
GLPG0634 Shows Promise In Race For Oral Alternative

Abbott and Galapagos (Belgium; GLPG) announced in February 2012 a global partnership to develop Galapagos' GLPG0634, an oral selective JAK-1 inhibitor in Phase IIa trials for rheumatoid arthritis (RA). In November 2011, Galapagos reported positive results from a 36-patient, placebo-controlled, four-week Phase IIa single-center trial. The trial tested twelve methotrexate-failure RA patients on each of three arms: placebo, 100mg drug BID, and 200mg drug QD. Pooling the two drug arms, at four weeks ACR20/50/70 was achieved by 83%/42%/21% of patients, vs. 33%/8%/0% on placebo. This efficacy appears at least on par with anti-TNFs, and GLP0634 is the first JAK1-selective agent to show efficacy in this indication. The safety profile was quite clean overall: modest declines in neutrophils and platelets were observed, though there was no anemia (in fact there was a dose dependent *increase* in Hb levels over the course of the study), while LDL was unchanged, and there were no liver or CV signals (including blood pressure) or SAEs. Still, we believe the drug's longer term efficacy and safety remain to be established in larger, longer trials.

GLP0634's Four-Week Efficacy Data- ACR20



GLP0634's Four-Week Efficacy Data – DAS28



Galapagos reported success in an additional Phase IIa multi-center dose ranging trial in November 2012. This trial was intended to confirm the initial single-center results and to further refine dosing. The trial was conducted at 19 sites in Eastern Europe. The 91-patient trial tested 10mg, 25mg, 50mg, and 100mg capsules dosed three times daily vs. placebo, all on background MTX. The primary endpoint was ACR20 response at 4 weeks. In each of the 25mg TID through 100 mg TID arms, the trial achieved statistical significance on ACR response, DAS28, HAQ-DI, and CRP level. There were no discontinuations for AEs and no SAEs. As in the single-center Phase IIa, there was no anemia, LDL increase, or effects on liver enzymes, and an increase in hemoglobin level. We speculate that the motivation for the TID trial may be that the 100mg BID dose, in general, appeared superior on efficacy vs. the 200 mg QD dose in the initial trial, while producing lesser changes in certain lab values. However, we question the commercial viability of a TID dosing scheme in light of less-frequently dosed alternatives.

Galapagos initiated a 24-week global Phase IIb program in RA in Q213 exploring once and twice daily dosing formats. The total number of patients to be included in the Phase IIb program will be expanded to 875, which will facilitate a final dose and

regimen selection for Phase III clinical studies. Galapagos expects to report topline data from the Phase IIb program in Q4:2014.

Darwin 1 – Add-On To MTX

200 mg QD	85 patients (pt)
100 mg QD	85 pt
50 mg QD	85 pt
100 mg BID	85 pt
50 mg BID	85 pt
25 mg BID	85 pt
Placebo	85 pt
TOTAL	595 pt

Source: Galapagos NV

Darwin 2 – Monotherapy

200 mg QD	70 patients (pt)
100 mg QD	70 pt
50 mg QD	70 pt
Placebo	70 pt
TOTAL	280 pt

Source: Galapagos NV

Under the terms of the agreement, Abbott paid Galapagos a \$150MM upfront fee. Galapagos remains responsible for completing Phase II development. Assuming the Phase IIb studies are completed and meet certain agreed-upon criteria (expected in 2014), AbbVie will license GLP0604 for a further \$200MM fee. AbbVie will then assume full Phase III development and manufacturing responsibility and global commercial rights, with Galapagos retaining co-promotion rights in Belgium, the Netherlands, and Luxembourg. Galapagos will be eligible for development and commercial milestone payments totaling a further \$1.0B, as well as tiered double-digit royalties on sales. In addition, the collaboration was recently expanded to include Crohn's disease (Phase II studies initiated Q1:14) and cystic fibrosis (clinical trials to start by year-end 2014).

AbbVie is also internally developing a JAK1 inhibitor, ABT-494, which is in Phase II studies with data expected early 2015.

ABBV Expands Role In Autoimmune Diseases With Licensing Of Anti-IL-6R Nanobody

In September 2013, AbbVie announced a global license agreement with Ablynx (a Belgium-based company focused on development of priority Nanobodies), to develop and commercialize its lead product, ALX-0061, an anti-IL-6R nanobody used to treat inflammatory diseases including RA and SLE. ALX-0061 targets the IL-6 receptor (key in inflammatory process) and its small size may enable better tissue penetration; it also has high specificity, binds to serum albumin which can extend its half-life, and like other nanobodies, has low immunogenicity. AbbVie paid Ablynx \$175MM upfront and will pay up to \$665MM in potential milestone payments. A Phase IIa study was completed in February 2013 showing good safety and efficacy data in patients with moderate-to-severe active RA treated with MTX. Ablynx will be responsible for completing the Phase II trials in RA and SLE (which will occur in 2014-15) and then,

based on pre-specified success criteria, AbbVie will in-license ALX-0061 and be responsible for Phase III studies and commercialization.

Shire Adds To GI Portfolio With UC Products

Shire will boost AbbVie's Humira presence in the GI market with Lialda/Mezavant and Pentasa, leading products in the ulcerative colitis area. Both products are reformulated mesalamine (5-aminosalicylic acid), with Lialda/Mezavent, a once-daily formulation. We estimate Lialda sales of \$650MM in 2015, \$675MM in 2106, \$720MM in 2018, and \$565MM in 2020.

HCV

Phase III Studies Successfully Completed; All-Oral, Interferon-Free Regimen Filed In U.S. And EU

In late January 2014, AbbVie announced that it had completed all six trials comprising its Phase III HCV program which evaluated regimens of ABT-450/r, ABT-267, and ABT-333 with and without ribavirin. The treatment duration was 12 weeks in non-cirrhotic patients, and 12 or 24 weeks in cirrhotic patients. The program enrolled more than 2,300 GT 1 patients in total. All studies showed SVR12 rates in a 90-100% range with acceptable tolerability. AbbVie filed the regimen, with Breakthrough Therapy designation, in the U.S. in April 2014, received priority review status in June and expects commercialization in 2014. AbbVie filed in the EU in May 2014 with an accelerated assessment, received MAA validation in June, and expects potential commercialization in early 2015. Pending AbbVie's ability to successfully reach its targeted populations, there is potential upside to our HCV franchise sales estimates of \$350MM in 2015, \$700MM in 2016, \$1,100MM in 2018, and \$1,300MM in 2020.

AbbVie Phase III Clinical Program Results

Study	Patients	Treatment Regimen*	SVR ₁₂
PEARL-II (12 weeks)	GT1b treatment-experienced (n=179)	3 DAA + RBV (n=88)	97%
		3 DAA only (n=91)	100%
PEARL-III (12 weeks)	GT1b treatment-naïve (n=419)	3 DAA + RBV (n=210)	99%
		3 DAA only (n=209)	99%
PEARL-IV (12 weeks)	GT1a treatment-naïve (n=305)	3 DAA + RBV (n=100)	97%
		3 DAA only (n=205)	90%
TURQUOISE-II (12 & 24 weeks)	GT1 treatment-naïve and treatment-experienced with compensated cirrhosis (n=380)	3 DAA + RBV, 12 weeks (n=208)	92%
		3 DAA + RBV, 24 weeks (n=172)	96%
SAPPHIRE-I (12 weeks)	GT1 treatment-naïve (n=631)	3 DAA + RBV (n=473)	96%
SAPPHIRE-II (12 weeks)	GT1 treatment-experienced (n=394)	3 DAA + RBV (n=297)	96%

*DAA = ABT-450/r, ABT-267, and ABT-333

Source: AbbVie

AbbVie To Target Difficult-To-Treat Patients, But Gilead Still Best Positioned Overall

The results from the Phase III program are very compelling, but the need for ribavirin and the 12-week treatment course (rather than 8 weeks) may be competitive disadvantages to the Gilead regimen. AbbVie has indicated they intend to target the more challenging patients, specifically those with fibrosis, cirrhosis, and treatment failures, as they believe these patients will be treated with a regimen that includes ribavirin and the Phase III trials demonstrated good success in this harder-to-treat population. However, the HCV treatment market will be crowded, and AbbVie's regimen still has the competitive disadvantage of the ritonavir boosting requirement.

AbbVie's 2 DAA +/- RBV HCV regimen reported solid data in a recently completed Phase II trial in Asia (PEARL-1 described below) and a Phase III program (2 DAA, no RBV) was recently initiated in Japan. AbbVie believes its regimen is well suited to the Japanese population and expects to file in Japan in 2015. AbbVie has also started PK studies to create a once-daily formulation of the current 3 pill DAA regimen.

Full Phase III Data At EASL 2014 Highlighted Success In Hard To Treat Patients

AbbVie presented full data on the Phase III SAPPHIRE I and II trials, which evaluated GT-1 treatment naïve (n=631) and treatment-experienced (n=394) patients with its 3DAA combo with RBV. The SVR12 for both studies was 96%, as previously announced. The breakdown by subtype showed GT-1a patients with an SVR12 of 95-96% and GT-1b patients at 97-98%. In SAPPHIRE-II (treatment-experienced), the SVR12 for the subgroups of null and relapsers was 95% and 100% for partial responders. These results were published in the NEJM.

AbbVie also presented new data for PEARL-1, a Phase IIb study in GT-4 patients (serotype prevalent in Middle East and Africa) with their HCV oral combo ABT-450/r + ABT-267 (ombitasvir). In the treatment naïve group, the SVR12 was 90.9% (40/44) and 100% (42/42) with RBV. In the treatment-experienced group, the SVR4 was 100% (37/37) with RBV.

Full data from the TURQUISE Phase III trial of AbbVie's 3DAA regimen + RBV (12 & 24 week treatments) in GT-1 patients with cirrhosis was presented. The SVR12s of 92% for 12 weeks and 96% for 24 weeks had been announced previously.

The full data showed very impressive SVRs for the subgroups of these cirrhotic patients (null, relapsers, and partial responders); the 24 week arms in particular were noteworthy, with reported SVRs of 100% in both GT-1a and GT-1b patients. These results may provide a competitive advantage in difficult-to-treat HCV patients such as cirrhotics.

Phase II PILOT Delivered Strong SVR24 Results In Treatment Naïves, But Late Relapse In SVR36 Data Raises Concerns

Abbott presented data from its Phase II PILOT and CO-PILOT studies of its all-oral antiviral HCV combinations at EASL 2012. The PILOT (M12-267) study showed that a regimen of ABT-450 (150mg/100mg QD) boosted with ritonavir plus non-nuc ABT-072 (400mg QD) plus ribavirin administered for 12 weeks achieved a sustained virologic response at 24 weeks (SVR24) in 91% (n=10/11) of treatment naïve genotype 1 patients. This was an impressive extension of the 90% SVR12 results (9/10 patients) reported at the interim look in October 2011. All 11 patients in the PILOT study maintained HCV RNA levels <25 IU/mL in weeks 4-12 and had undetectable HCV RNA from week 5 until the end of treatment. Common treatment related adverse events observed in the PILOT study included headache, fatigue, nausea, and dry skin, in-line with what was observed in the CO-PILOT study.

However, the SVR36 PILOT data showed that a relapse occurred between 24 and 36 weeks post treatment. Such a late relapse is relatively rare and has raised questions about the ability of a non-nuc based regimen to maintain efficacy over a longer period. This observation further opens the door to Gilead's '7977-based combinations to be viewed as superior to the AbbVie combinations.

The PILOT regimen achieved an SVR36 of 82% (n=9/11), which had slipped from the SVR24 data of 91% (n=10/11) in treatment naïve genotype 1 patients. The prior relapse was observed at 8 weeks post therapy. No additional relapses were observed in the 48-week post treatment data available. On the positive side, the longer-term safety profile of the PILOT regimen was maintained: the most common AEs observed in PILOT were headache (36%), fatigue (27%), nausea (27%), and dry skin (27%), which were all characterized as mild in severity.

The knocks on the AbbVie combinations have been: (1) the protease inhibitor component (ABT-450) requires boosting with ritonavir – adding a 4th component; and (2) the use of non-nucleoside polymerase inhibitors (ABT-072 in the PILOT regimen and ABT-333 in the CO-PILOT regimen) may lead to breakthrough resistance, particularly in prior treatment failure patients. 8 of the 17 (47%) treatment failure patients in the CO-PILOT study achieved an SVR12. That is a solid result, but the question of breakthrough resistance to the non-nucleoside polymerase inhibitor in prior treatment failures remains.

Our clinical experts have noted that while non-nucleoside polymerase inhibitors are good antiviral agents that provide a non-overlapping resistance profile with other agents, they believe non-nucs will be used in the third or fourth position in an effective regimen given the superior resistance profiles of the nucleoside/nucleotide polymerase inhibitors and NS5A inhibitors.

CO-PILOT (n=50) Also Delivered Strong Results In Treatment-Naïves

AbbVie's CO-PILOT (M12-746) study showed that a regimen of ABT-450 boosted with ritonavir (250mg/100mg) plus non-nuc ABT-333 (400mg BID) plus ribavirin administered for 12 weeks achieved sustained virologic response at 12 weeks post treatment (SVR12) in 95% (n=18/19 in arm 1) and 93% (n=13/14 in arm 2) of treatment-naïve genotype 1 patients. In the two treatment naïve arms, the response was independent of HCV subtype, host IL28B genotype, or dose of PI.

Co-Pilot Full Data Summary

Virologic Endpoint Measured	ABT-450/r 250mg/100mg QD + ABT-333 400mg BID + ribavirin	ABT-450/r 150mg/100mg QD + ABT-333 400mg BID + ribavirin	ABT-450/r 150mg/100mg QD + ABT-333 400mg BID + ribavirin
	<u>Treatment Naïve Arm 1</u> n=19	<u>Treatment Naïve Arm 2</u> n=14	<u>Non-Responder Arm</u> n=17*
RVR4 (HCV RNA<25 IU/mL at week 4)	n=19/19 (100%) ^A	n=13/14 (92.9%) ^B	n=15/17 (88.2%)
SVR4 (HCV RNA<25 IU/mL 4 weeks post treatment)	n=18/19 (94.7%)	n=13/14 (92.9%)	n=8/17** (47.1%) ^{C,D}
SVR12 (HCV RNA<25 IU/mL at 12 weeks post treatment)	n=18/19 (94.7%)	n=13/14 (92.9%)	n=8/17 (47.1%)

*6 patients were null responders, 12 patients were partial responders (failed to achieve undetectable HCV RNA at the end of treatment)

**3 were null responders, 5 were partial responders

A: one patient discontinued due to ALT and AST elevation

B: one patient discontinued due to noncompliance issue

C: 6 patients showed viral breakthrough

D: 3 patients showed relapse post treatment

Source: Abbott 2012 EASL Abstract; Cowen and Company

Baseline Demographics and Disease Characteristics

Male, n (%)	10 (52.6)	14 (100)	11 (64.7)
White, n (%)	15 (78.9)	12 (85.7)	13 (76.5)
Age, Years	53.6 ± 9.78	50.9 ± 10.45	52.3 ± 9.03
BMI, kg/m2	27.3 ± 3.84	24.6 ± 3.08	29.3 ± 5.11
HCV Genotype 1a, n (%)	17 (89.5)	11 (78.6)	16 (94.1)
IL28B CC Genotype 1a, n (%)	10 (52.6)	5 (35.7)	0
Baseline HCV RNA, log10 IU/mL, Mean +/- SD	6.25 ± 0.80	6.44 ± 1.15	6.93 ± 0.47
Virologic Results			
RVR	19 (100)	13 (92.9)	15 (88.2)
SVR4	18 (94.7)	13 (92.9)	8 (47.1)
SVR12	18 (94.7)	13 (92.9)	8 (47.1)

Source: Poordad et al, 2012 EASL abstract

In the non-responder arm of the CO-PILOT study, the regimen of ABT-450 boosted with ritonavir (150mg/100mg) plus non-nuc ABT-333 (400mg BID) plus ribavirin administered for 12 weeks achieved an SVR12 of 47% (n=8/17; 3 of the patients were null responders and 5 of the patients were partial responders). One patient in the 19-patient arm discontinued treatment due to asymptomatic ALT/AST elevation at week 2 and another patient in the 14-patient arm of the study discontinued due to a non-compliance issue in week 1. In the non-responder arm, six patients achieved viral breakthrough on treatment and three patients relapsed following treatment. While the patient numbers for this study were small, the SVR12 data is strong and will be

perceived as a sufficient HCV treatment regimen in using two direct acting antivirals. Common treatment related adverse events observed in the CO-PILOT study included fatigue (42%), nausea (22%), and headache (20%).

Aviator Phase II Data

Results from AbbVie's Phase IIB Aviator trial were presented at the AASLD meeting in November 2012. Aviator tested 8, 12, or 24 weeks of dosing of a regimen of ABT-450/r (dosed 100/100mg to 200/100mg QD), ABT-267 (25mg QD), ABT-333 (400mg BID) with and without ribavirin in non-cirrhotic naïve and null responder patients.

Highlights of the efficacy data for the 12 week arm include 97.5% SVR12 in treatment-naïve GT1 patients, and 93.3% SVR in GT1 null responders when ribavirin was included.

Aviator Efficacy Data

Duration	Treatment-Naïve					Null Responders	
	8 weeks	12 weeks			12 weeks	ABT-450/r, ABT-267, RBV	ABT-450/r, ABT-267, ABT-333, RBV
Regimen	ABT-450/r, ABT-267, ABT-333, RBV	ABT-450/r, ABT-333, RBV	ABT-450/r, ABT-267, RBV	ABT-450/r, ABT-267, ABT-333	ABT-450/r, ABT-267, ABT-333, RBV	ABT-450/r, ABT-267, RBV	ABT-450/r, ABT-267, ABT-333, RBV
Number dosed	80	41	79	79	79	45	45
Relapses	9	4	5	5	1	5	0
Breakthroughs	0	1	1	1	0	0	3
Lost to Follow up or withdrew consent	1	1	2	4	1	0	0
SVR (ITT)	87.5% (70/80)	85.4% (35/41)	89.9% (71/79)	87.3% (69/79)	97.5% (77/79)	88.9% (40/45)	93.3% (42/45)
SVR (OD)	88.6% (70/79)	87.5% (35/40)	92.2% (71/77)	92% (71/77)	98.7% (77/78)	88.9% (40/45)	93.3% (42/45)
SVR (ITT) GT 1a	84% (47/56)	79% (23/29)	85% (44/52)	83% (43/52)	96% (52/54)	81% (21/26)	89% (25/28)
SVR (ITT) GT 1b	96% (23/24)	100% (12/12)	100% (27/27)	96% (24/25)	100% (25/25)	100% (18/18)	100% (17/17)

Source: AbbVie

The regimen appeared generally well tolerated. 4 of 448 patients (1%) in the 8 and 12 week arms discontinued due to an adverse event. Of the five serious AEs (1%), one arthralgia (joint pain) was possibly study drug related. The most common adverse events were fatigue (28% in naïve and 27% in null responders) and headache (28% in naïve and 31% in null responders).

Moderate To Severe AEs Possibly Or Probably Related To Study Drug With >5% Incidence Of Any Arm

Regimen	Duration	Treatment-naïve Patients						Null Responders	
		8 wks			12 wks			12 wks	
		450/r 267 333 RBV	450/r 333 RBV	450/r 267 333 RBV	450/r 267 333 RBV	450/r 267 333 RBV	450/r 267 333 RBV	450/r 267 333 RBV	450/r 267 333 RBV
Number dosed		80	41	79	79	79	45	45	
Any AE, n (%)		20 (25.0)	12 (29.3)	14 (17.7)	10 (12.7)	19 (24.1)	7 (15.6)	11 (24.4)	
Fatigue		7 (8.8)	2 (4.9)	3 (3.8)	3 (3.8)	2 (2.5)	1 (2.2)	3 (6.7)	
Headache		3 (3.8)	4 (9.8)	3 (3.8)	0	1 (1.3)	0	1 (2.2)	
Insomnia		2 (2.5)	1 (2.4)	1 (1.3)	0	4 (5.1)	1 (2.2)	0	
Nausea		1 (1.3)	2 (4.9)	1 (1.3)	0	2 (2.5)	0	1 (2.2)	
Bilirubin increase		0	0	1 (1.3)	0	2 (2.5)	0	0	

Source: Cowen and Company

NexGen Program Targets Once-Daily, Ribavirin Free Regimen

AbbVie's next-gen oral HCV program has started Phase II trials. This regimen includes protease inhibitor ABT-493 and NS5A inhibitor ABT-530 and is RBV-free. Pre-clinical trials have shown pan-genotypic activity. Data on this regimen is expected later in 2014.

Renal

Atrasentan Targets Maintenance Treatment of CKD

AbbVie is developing a selective endothelin-A receptor antagonist (atrasentan) for the maintenance treatment of chronic kidney disease. Atrasentan targets patients earlier in the disease progression. Atrasentan blocks the effect of a protein that constricts blood vessels and raises blood pressure, which has an effect on kidney function. Phase II data demonstrated a reduction of albuminuria, an important biomarker of renal function. Atrasentan started global Phase III trials in Q2:13 and will evaluate impact on renal outcomes including onset of ESRD, transplant and death. Trial completion is expected in 2017 and AbbVie projects a potential launch for Atrasentan in 2018 in the U.S. and 2019 in foreign markets. We forecast Atrasentan sales of \$50MM in 2018 and \$300MM in 2020.

Our renal experts are encouraged by the Atrasentan Phase II data. They highlight that the patient population (Stage 2/3 CKD patients) with better kidney function is well suited for this drug and like its chances for success.

Atrasentan – Phase IIa Results Summary

Endpoint Measured	0.25 mg Atrasentan (n=22)	0.75 mg Atrasentan (n=22)	1.75 mg Atrasentan (n=22)	placebo (n=23)
Significant reduction in UACR achieved Reduction from baseline to final UACR	did not achieve significant reduction 21% p=0.291	p=0.001 42% p=0.023	p=0.011 35% p=0.073	11%
% of patients achieving >40% reduction in UACR	30% did not achieve significant reduction	50% p=0.029	38% did not achieve significant reduction	17%
Safety Data Summary				
Most common side effect observed	Peripheral Edema	14%	18%	46% p=0.007
AEs occurring in ≥5% patients at a rate of >5% vs PBO	dizziness urinary tract infection headache hypoglycemia			9%

Source: Company Data; Cowen and Company

Immunology

Zinbryta (Daclizumab) Could Be A Solid 2nd-/3rd-Line Therapy In MS

Zinbryta (daclizumab) is an anti-IL2R antibody being developed under a 50/50 collaboration between Biogen Idec and AbbVie (which acquired Facet Biotechnology) for MS. The drug is approved, but not marketed (for commercial reasons) for transplant rejection as Zenapax. Data from the Phase II CHOICE study and top-line data from the Phase II/III SELECT trial indicated that daclizumab dosed once monthly via subcutaneous injection is quite efficacious in MS. However, questions about the drug's longer-term safety persist.

In June 2014, top-line data from daclizumab's second pivotal study, DECIDE (daclizumab vs. Avonex, n=1,800+ patients with RRMS) showed Zinbryta (daclizumab high-yield process/DAC HYP) administered once-monthly SC was superior to weekly IM Avonex with a 45% reduction ($p<0.0001$) in annualized relapse rate (primary endpoint). DAC HYP was also superior on the first secondary endpoint, with a 54% reduction ($p<0.0001$) in new or newly enlarging T2-hyperintense lesions at week 96. On the other secondary endpoint of 3-month disability progression as measured by EDSS, the DAC HYP reduction of 16% over Avonex was not statistically significant. The safety profile was consistent with prior studies and the overall incidence of AEs was similar across the groups. However, the DAC HYP group showed an increased incidence of serious infections (4% vs 2%), serious cutaneous reactions (2% vs <1%), and increases in liver enzymes greater than 5x ULN (6% vs 3%). Four deaths in the Avonex group and 1 in the DAC HYP group were not considered treatment related. Overall the data suggests daclizumab effectiveness at reducing the annual relapse rate compared to INF beta-1a is on par with Gilenya (at 45% vs 50% respectively); however, safety issues (infections) suggest the drug may be best positioned as a second or third-line agent in refractory MS patients, possibly for JCV+ patients in place of Tysabri.

AbbVie and Biogen Idec anticipate filing the NDA for daclizumab in H1:15. We estimate Zinbryta sales of \$120MM in 2016, \$360MM in 2018, and \$600MM in 2020, assuming it gains approval as an alternative option to Tysabri in JCV (+) patients.

Daclizumab Demonstrates Strong Efficacy In SELECT Trial

In October 2011, Biogen and Abbott presented data at ECTRIMS from the SELECT Phase IIb registration study of daclizumab in 600 patients with relapsing-remitting

multiple sclerosis (RRMS). Patients in the study were randomized to daclizumab 150mg every four weeks ($n=201$), daclizumab 300 mg every four weeks ($n=203$), and placebo ($n=196$). The data showed that patients receiving daclizumab 150mg every four weeks achieved a 54% reduction in relapse rate ($p<0.0001$) and patients receiving daclizumab 300mg every four weeks achieved a 50% reduction in relapse rate ($p=0.0002$) at one year. Greater than 90% of patients receiving daclizumab therapy completed the study.

Relapsing patients on daclizumab showed a 55% reduction in relapses at the 150mg dose ($p<0.0001$) and a 51% reduction at the 300mg dose ($p=0.0003$). Patients receiving daclizumab 150mg showed a statistically significant improvement ($p=0.0007$) in quality of life as measured by the Multiple Sclerosis Impact Scale (MSIS-29), but not for the 300mg group ($p=0.1210$). Daclizumab-treated patients achieved statistically significant reductions in the number of new Gd+ lesions assessed by MRI at week 52 (79% at the 150mg dose and 86% at the 300mg dose; $p<0.0001$). Daclizumab-treated patients also achieved statistically significant disability risk reductions as measured by the Expanded Disability Status Scale (EDSS): 57% at the 150mg dose ($p=0.021$) and 43% at the 300mg dose ($p=0.091$).

Overall incidence of AEs and discontinuations were similar across treatment and placebo groups in the study. Serious adverse events were reported in 7% of patients receiving daclizumab 150mg, 9% of patients receiving daclizumab 300mg, and 6% of patients in the placebo group. Serious infections were reported in 2% of patients receiving daclizumab vs 0% in the placebo group; serious cutaneous events were reported in 1% of patients receiving daclizumab vs 0% in the placebo group; and liver enzyme elevations greater than 5x above the normal limit were recorded in 4% of patients on daclizumab therapy vs <1% in the placebo group. One death was recorded in the SELECT study from a patient who developed a psoas muscle abscess while recovering from a serious skin infection.

While the overall incidence of adverse events and treatment discontinuations were similar between daclizumab and placebo, serious infections (2% vs. 0%) and liver toxicity were more common in patients treated with daclizumab. Given that daclizumab is marketed as a transplant rejection drug in OUS geographies, it has the potential to be immunosuppressive. Therefore, long-term safety data will be critical for daclizumab to gain broad use in treating MS.

Daclizumab Demonstrated Very Good Efficacy In Select Trial

Daclizumab Phase II SELECT Data Summary

Efficacy Endpoint Measured	daclizumab 150mg q4w	daclizumab 300mg q4w	placebo
reduction in relapse rate @ 52 weeks - overall population	54% p<0.0001	50% p=0.0002	
reduction in relapse rate @ 52 weeks - relapsed population	55% p<0.0001	51% p=0.0003	
net improvement in QOL - MSIS-29 vs PBO	p=0.0007	p=0.1210	
reduction in # Gd+ lesions between 8-24 weeks	69% p<0.0001	78% p<0.0001	
reduction in # Gd+ lesions @ week 52	79% p<0.0001	86% p<0.0001	
reduction in newly enlarging T2 hyperintense lesions - 52 weeks	70% p<0.0001	79% p<0.0001	
reduction in 12-week sustained disability progression (EDSS) - 52 weeks	57% p=0.021	43% p=0.091	

Safety Summary	< 10%	9%	NM
discontinuation rate	7%		6%
serious AE rate		2%	0%
serious infections		1%	0%
serious cutaneous events		4%	< 1%
liver abnormalities/toxicity (>5xULN)		1	0
# deaths			

Source: Cowen and Company

AbbVie And Reata Strengthen Ties With AIMs Deal

In December 2011, Abbott and Reata announced a collaboration to develop next-generation antioxidant inflammation modulators (AIMs). These include Nrf2 activators, similar in mechanism to bardoxolone. The global deal includes a broad platform of modulators that will be developed for the treatment of respiratory, immunology, and CNS disorders. AbbVie and Reata will share the development costs and profits on any new candidates developed under the agreement. Product candidates are in early-stage preclinical. AbbVie is closely examining data from the Phase III study of bardoxolone to determine impact on development plans for other compounds. Abbott made a \$400MM upfront payment to Reata for the collaboration rights.

Women's Health

Elagolix Targets Injectable GnRHs For Endometriosis

Elagolix (NBI-56418) is a partial gonadotrophin-releasing hormone (GnRH) antagonist that is being developed for endometriosis, a condition that results when tissue lining of the uterus (endometrium) migrates outside of the uterus. There are currently few treatment options for endometriosis that offer a benign safety profile. Elagolix appears to lower serum estradiol levels sufficiently (to between 30 and 45 picograms) to relieve symptoms of endometriosis. Elagolix is believed to have efficacy similar to the GnRH super-agonists (including Lupron), while avoiding the side effects of these more powerful agents.

Our clinical consultants are optimistic that Elagolix could ultimately displace GnRH agonists, and take share from oral contraceptives in the endometriosis market. Although Lupron sells only about \$100MM in endometriosis today, about 15MM prescriptions are written annually for oral contraceptives for the treatment of endometriosis. An estimated 6.0-7.5MM women have endometriosis, of which 2.5MM are diagnosed by a physician. Our model assumes that Elagolix is able to expand the GnRH market, generating sales of \$150MM in 2017, \$300MM in 2018 and \$700MM in 2020.

Phase III Endometriosis Data Expected Around Year End

AbbVie and Neurocrine initiated the Phase III program for Elagolix in June 2012. The first of two Phase III trials (Violet Petal) is a double-blind, placebo-controlled study that will evaluate the safety and efficacy of Elagolix in 875 women age 18-49 with moderate-to-severe endometriosis over the course of 24 weeks.

The FDA agreed to similar endpoints in Phase III as in the successful Daisy PETAL Phase II trial, including co-primary endpoints of daily dysmenorrhea and non-menstrual pelvic pain. Endpoints will be measured by responder analysis (as opposed to a mean change from baseline), which AbbVie and Neurocrine believe will simplify explanation of efficacy results to physicians after commercial launch.

The study followed the women for two months to establish baseline values for dysmenorrhea and non-menstrual pelvic pain. The women were then randomized to either placebo, Elagolix 150M QD, or a higher Elagolix dose. The primary endpoints have already been assessed at the 3 month time point, although the trial's blind has not been broken. In order for the trial to be positive, both endpoints must be hit with statistical significance when evaluated independently. The women are being followed for another 3 months (through 6 months of treatment) to examine the secondary endpoints of persistence of efficacy, analgesic use, and dyspareunia. Neurocrine expects the last women to complete the 6 month blinded phase of the trial around November 15, and then all will enter a 6 month open-label phase during which the women randomized to Elagolix will remain on their dose, while placebo patients will be randomized to one of the two Elagolix doses. Top-line results will be released once the 6 month blinded phase has been completed, which is expected to be around year end 2014.

The partners continue to negotiate over the amount of detail about the results that will be provided. They will certainly disclose whether the primary endpoint of the trial was hit with statistical significance (meaning both dysmenorrhea and non-menstrual pelvic pain were independently hit). Neurocrine would also like AbbVie to disclose the trial's pvalue, Elagolix's effect size, and Elagolix's responder rates. However, it is unclear whether AbbVie will permit these details to be released, as ABBV thinks it could bias Elagolix's second Phase III trial. Neurocrine expects a general statement around safety to be made. Neurocrine does not anticipate any bone mineral density data will be in the initial release.

Second Phase III Solstice Trial To Complete Q4:2015

The second Phase III pivotal trial (Solstice) was initiated in August 2013. This 24-week multinational, randomized double-blind, placebo-controlled study was designed to evaluate the safety and efficacy of Elagolix in 788 women, age 18-49, with moderate-to-severe endometriosis-associated pain. This is an international trial, although two-thirds of the patients are expected to come from the U.S. Data is expected during Q4:15. Neurocrine anticipates that the bone mineral data from

both Violet Petal and Solstice studies will be released upon the completion of Solstice.

Neurocrine Is Confident That Violet Petal And Solstice Will Succeed

Management notes that dysmenorrhea responder rate and non-menstrual pain responder rate were hit with statistical significance in the Phase II Daisy Petal study which enrolled 137 women. With the Phase III trials enrolling 875 and 788 patients, Neurocrine thinks both are overpowered for efficacy. On safety, with the last patients exiting Violet Petal now, Neurocrine thinks that, had there been a safety issue fatal to the program, it would have already been disclosed. Therefore the company is confident that the safety profile will be similar to that seen in Phase II.

Phase IIb In Uterine Fibroids Expected To Complete Mid-2015

Elagolix is in a 520-patient Phase IIb trial in uterine fibroids. The trial tests 2 doses of Elagolix that are higher than those being tested in the endometriosis Phase III program. At each Elagolix dose level the trial tests regimens of no "add back" therapy, low dose "add back" therapy, and higher dose "add back" therapy. The primary endpoint of the trial is uterine blood flow. Data from the first dose cohort in the trial are expected to be in-house by year-end 2014, but results are not expected to be released until the second dose cohort completes, around mid-2015. AbbVie will make a "go/no go" decision about moving into Phase III at that time. It is unclear whether one or two Phase III trials will be needed, as it is possible that the Phase IIb is large enough and robust enough to serve as a supportive study. While AbbVie has yet to release data from the Phase IIa study, NBIX said it obtained some data on Elagolix's impact on uterine blood flow in its Phase II experience, and that the "results are dramatic."

Phase II DAISY PETAL Study Defines Successful Endpoints For Phase III Program

Previous Phase II trials (e.g. PETAL, LILAC PETAL) have demonstrated that Elagolix can statistically significantly improve daily dysmenorrhea, monthly non-menstrual pain scores, and Patient Global Impression of Change. The Daisy PETAL study enrolled 137 endometriosis subjects into one of two treatment groups: 150mg elagolix or placebo once daily for two months. Subjects subsequently continued for four months of open-label elagolix treatment and assessments. The top-line efficacy results are based on the ITT population of 132 women. Co-primary endpoints of dysmenorrheal and non-menstrual pelvic pain were evaluated to assess the improvements in endometriosis symptoms. Each utilized a daily scale (0 – 3) via daily electronic diary. Dyspareunia (painful intercourse) was also assessed using a daily scale (0 – 3) as an exploratory measure. Secondary endpoints included PGIC, EHP-5, and the CPSSS.

In the trial's co-primary endpoints, elagolix significantly improved both dysmenorrhea and non-menstrual pelvic pain.

Co-Primary And Exploratory Efficacy Endpoints

Mean Change, Baseline to Week 8	Baseline	Elagolix	Placebo	p-value
Dysmenorrhea	2.1	-1.13	-0.37	<0.001
Non-Menstrual Pelvic Pain	1.4	-0.47	-0.19	<0.01
Dyspareunia	1.4	-0.61	-0.23	<0.01

Source: Cowen and Company

At the recommendation of the FDA, a responder analysis was conducted of the proportion of patients demonstrating a 30% or greater improvement from baseline in each of the measures. Elagolix significantly improved the proportion of responders for each scale.

Efficacy Endpoints – Responder Analysis

Responder Analysis Wk 8	Elagolix	Placebo	p-value
Dysmenorrhea	63%	33%	<0.001
Non-Menstrual Pelvic Pain	63%	33%	<0.001
Dyspareunia	58%	34%	<0.05

Source: Cowen and Company

Elagolix was safe and well tolerated in the DAISY PETAL trial. Discontinuations due to adverse events were 4.4% for Elagolix compared to 1.4% for placebo. The most common adverse events were nausea (7.4% for elagolix, 2.9% for placebo), and there were no treatment-related serious adverse events.

Data from the 6-month open-label extension study of DAISY PETAL was reported in November 2010. Continued improvement in efficacy measures was seen in the ITT population. Non-menstrual pelvic pain, dysmenorrhea, and dyspareunia showed a further decrease in patients initially on Elagolix and continuing on the extension. These measures also improved for patients initially on placebo who switched to Elagolix for the remainder of the trial.

The extension provided additional safety data that will complement the experience from Elagolix's other trials. The extension also showed that the modified scales implemented for the first time in DAISY PETAL capture the durability of effect and perform out to six months of therapy.

Abbott Licensed Elagolix From Neurocrine Biosciences

Via the June 2010 collaboration with Neurocrine, Abbott licensed worldwide rights to develop and commercialize Elagolix and all next-generation GnRH antagonists for women's and men's health. Abbott made an upfront payment of \$75MM, and AbbVie will fund all ongoing development activities. Neurocrine could receive up to \$500MM in additional development, regulatory, and commercial milestones, as well as tiered double digit royalties on future sales. Neurocrine suggested the royalties approximate a 40-60 or 50-50 profit split, which implies a royalty rate of 15-20%.

Oncology

Elotuzumab In Phase III For Multiple Myeloma

AbbVie and Bristol-Myers Squibb are jointly developing elotuzumab, an antibody targeting CS1 glycoprotein in multiple myeloma cells. CS1 is a glycoprotein that resides on the cell surface and is highly expressed in myeloma cells compared to normal cells. In a Phase II study presented at ASCO 2011, elotuzumab demonstrated a 92% ORR and only a 1% incidence of infusion reactions. The Phase II data were a good demonstration of clinical activity supporting the anti-CS1 mechanism in multiple myeloma. Despite the approval of Velcade for the treatment of multiple myeloma, our

clinical consultants believe there is a need for multiple agents in the treatment armamentarium: 5-year survival rates for multiple myeloma patients are around 30% and 10-year survival rates are less than 5%.

Elotuzumab was also evaluated in combination with Velcade and Revlimid, which showed positive Phase I/II results: 82% of patients receiving elotuzumab achieved an objective response rate. Elotuzumab is also being studied in combination with Revlimid/low-dose dexamethasone.

Our consultants view the drug favorably, especially noting elotuzumab's ability to induce long median PFS when used in combination with Revlimid/dexamethasone. We estimate elotuzumab revenue recorded by AbbVie of \$110MM in 2016, \$330MM in 2018 and \$550MM in 2020. AbbVie records 30% of U.S. profits and a royalty ex U.S.

In May 2014, elotuzumab was granted Breakthrough Therapy designation for use in combination with lenalidomide and dexamethasone in multiple myeloma patients who have received one or more prior therapies. The designation was based on the Phase II data described below.

Phase II Study Of Elotuzumab + Revlimid/dexamethasone Promising

A Phase II study in relapsed/refractory multiple myeloma (1-3 prior therapies) was presented at ASH 2012 and updated at EHA 2013. This study randomized patients either to 10 mg/kg or 20 mg/kg elotuzumab weekly, each in combination with Rev/dex. In the 10 mg/kg arm (n=36), ORR was 92% and PFS was 33 months. In the 20 mg/kg arm (n=37), ORR was 76% and median PFS was 18.7 months. Regarding safety, 78% of patients experienced at least one treatment-emergent Grade 3 or higher event. The most common of these were lymphopenia (26% on the 10mg arm and 9% on the 20mg arm), neutropenia (21% and 22%), thrombocytopenia (21% and 17%), anemia (13% and 12%), leukopenia (8% and 7%), hyperglycemia (5% and 12%), pneumonia (8% and 5%), diarrhea (10% and 5%), fatigue (8% and 9%), and hypokalemia (8% and 5%). Infusion reactions were experienced by 14% of patients.

Phase III Trials In Progress; Data Expected Early 2015

Two Phase III trials have been initiated: ELOQUENT-1 is evaluating 10mg/kg once daily dose of elotuzumab+Rev/dex vs. Rev/dex alone in first-line, treatment-naive multiple myeloma patients; enrollment is estimated at 750 patients with a primary completion date of May 2016. The primary endpoint is PFS, with OS and ORR as secondary endpoints. Data is not expected until at least late 2016.

ELOQUENT-2 has fully enrolled 640 relapsed/refractory patients (1-3 prior lines of therapy). The study arms are also 10mg/kg once daily elotuzumab+ Rev/dex vs. Rev/dex alone. The trial has primary endpoints of PFS and ORR; OS is a secondary endpoint. Primary completion is expected August 2017. Internal data may be available H1:15.

ABT-199 Looks Promising; Phase III CLL Data In Late 2014

In September 2012, the FDA granted ABT-199, a selective Bcl-2 inhibitor, orphan drug status for the CLL indication. The drug is being developed in partnership with Roche/Genentech. AbbVie books sales globally. In the U.S. AbbVie and Roche share profits 50:50. Ex U.S., AbbVie pays Roche a royalty on net sales. A Phase II study in relapsed/refractory CLL patients with 17P chromosome depletion is in progress with data anticipated early 2015 and could be registrational. The primary endpoint of the

study is ORR. We estimate ABT-199 sales of \$250MM in 2016, \$800MM in 2018, and \$2B in 2020.

A Phase III study (n=370) in relapsed/ refractory CLL started in April 2014 comparing ABT-199 plus Rituxan versus Rituxan plus chemo (bendamustine). PFS is the primary endpoint. In early 2013, dosing/monitoring of ABT-199 was refined to minimize tumor lysis syndrome (TLS). Since the new protocol no clinically significant TLS events have been reported. Interim data presented at ASCO 2014 from the Phase Ib study (r/r CLL) of ABT-199 plus Rituxan reported an ORR of 84%. Another Phase III study of ABT-199 + Roche's GA101 in 1st line CLL is expected to start later in 2014. AbbVie is also evaluating ABT-199 in several other hematological malignancies including NHL, small lymphocytic leukemia, SLE, and multiple myeloma.

Physician Experts Impressed With Early Efficacy Data

Our consultants have been impressed by the high complete response (CR) rate produced by ABT-199, and expect it to be approved following its potential 2015 filing in the 17p population. They suspect that ABT-199 will produce durable responses, and that some patients may be able to come off therapy while in remission. They are hopeful that ABT-199 and Imbruvica (PCYC/JNJ) will be used in combination. In July 2014, Imbruvica received FDA approval for CLL patients with the 17p mutation. However, if not used in combo, they suggest that ABT-199's need for intensive tumor lysis syndrome monitoring may cause it to be sequenced behind Imbruvica in the treatment paradigm.

ABT-199 Generates An Impressive Response Rate

Early Phase Ib data presented at ASCO 2013 demonstrated solid efficacy data as monotherapy in patients with relapsed/refractory CLL.

ABT-199 Efficacy Data In CLL

ABT-199 Best Responses (n, %)	
Overall response rate	46 (84%)
Complete response (CR)	6 (11%)
CR/Incomplete marrow recovery	4 (7%)
Partial response	36 (65%)
Stable disease	4 (7%)
Disease progression	1 (2%)
ABT-199 Best Responses; del (17p) High Risk CLL (n, %)	
Overall response rate	13 (81%)
Complete response (CR)	1 (6%)
CR/Incomplete marrow recovery	1 (6%)
Partial response	11 (69%)
Stable disease	1 (6%)
Disease progression	1 (6%)
ABT-199 Best Responses; Floucitabine Refractory (n, %)	
Overall response rate	14 (78%)
Complete response (CR)	3 (17%)
CR/Incomplete marrow recovery	11 (61%)
Partial response	11 (69%)
Stable disease	1 (6%)

Source: ASCO 2013

PARP Inhibitor Veliparib Now In Phase III

Poly (ADP-ribose) polymerase, or PARP, is a protein that has several roles in cellular processes, most notably in DNA repair and programmed cell death (apoptosis). In some cases, a PARP inhibitor may be used alone, rather than in conjunction with chemo and radiation. PARP inhibitors appear to be safe, have demonstrated some efficacy in a broad subset of breast cancers (triple negative versus BRCA 1/2 for AstraZeneca's olaparib), and have demonstrated utility in combination with antineoplastic agents. Our clinical consultants remain encouraged about PARP inhibitors, despite the Phase III setbacks for the class. They believe the differences between current development candidates across the spectrum of safety, potency, effectiveness, drug interactions, and formulation could yield 1 or 2 approvable compounds.

AbbVie continues to develop its PARP-1/2 inhibitor veliparib (ABT-888) for the treatment of breast cancer (Phase III), NSCLC (Phase III initiated Q2:14, n=900), metastatic colorectal cancer, metastatic melanoma, ovarian cancer, and solid tumors. Veliparib demonstrated positive Phase II results in metastatic breast cancer, achieving an overall response rate (ORR) of 37.5% and median progression-free survival of 5.5 months in BRCA carriers enrolled in the study.

Interim Phase IIb data in treatment-naïve, advanced NSCLC was presented at ESMO 2014 which showed veliparib plus chemo resulted in a 35% improvement in PFS ($p=0.14$) for chemo alone and a 30% improvement ($p=0.21$) in OS. In those with squamous histology, median PFS improved to 5.8 months vs. 4.2 months and median OS of 11.7months vs. 9.1 months. AEs >20% included alopecia, anemia, neutropenia, nausea and peripheral neuropathy. Grade 3/4 AAEs included neutropenia and anemia. A Phase III study is ongoing to confirm these results. Phase IIb data in BRCA breast

cancer will be presented later this year. We forecast veliparib sales of \$100MM in 2017, \$200MM in 2018, and \$400MM in 2020.

I-SPY Trial Supports Potential In TNBC

The potential for veliparib was further supported by results from a unique trial that were presented in December 2013 at the San Antonio Breast Cancer Symposium. The trial showed veliparib to have the greatest benefit in women with triple-negative breast cancer. The I-SPY-2 trial is an adaptive, Phase II trial evaluating several drugs for breast cancer in the neoadjuvant setting. On a rolling basis, enrolled patients receive MRI screening which is later augmented by pathologic analysis. The adaptive randomization algorithm utilizes this data to then channel patients to the experimental arm that offers them the greatest potential benefit. This trial design not only helps steer patients to the settings with the most potential benefit, but also help drug companies identify appropriate patient subsets for larger Phase III trials. A drug “graduates” from this trial when an 85% likelihood of success in a Phase III trial is reached. Veliparib is the first “graduate” with a 300-patient Phase III trial of veliparib/carboplatin/paclitaxel in triple-negative patients predicted to have a 90% probability of success. Post these results, AbbVie announced they have started a Phase III trial for neoadjuvant treatment of triple-negative breast cancer.

Linifanib (ABT-869) Being Developed For NSCLC

Linifanib (ABT-869) is a potent dual inhibitor of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinases. AbbVie is developing linifanib for the treatment of advanced hepatocellular carcinoma (HCC) and metastatic non-small cell lung cancer (NSCLC). Linifanib was being evaluated in a 900-patient Phase III study in advanced hepatocellular carcinoma versus multi-kinase inhibitor Nexavar (sorafenib). However, investigators reported at ASCO-GI in January 2012 that the trial had failed.

Linifanib 0.25mg/kg QD demonstrated clinical activity in the Phase II study in advanced hepatocellular carcinoma. The study enrolled 44 patients with advanced hepatocellular carcinoma that had not received prior systemic therapy. Common treatment-related AEs in the study were fatigue (55%) and diarrhea (48%). Grade 3 or 4 treatment-related AEs included hypertension (18%) and fatigue (14%). There was one treatment-related death due to intracranial hemorrhage on day 111 of treatment in the CP-B subgroup. Approximately one-third of evaluable patients in the study showed a decrease in serum protein levels induced by vitamin K absence (PIVKA), which correlates to an improved overall survival (OS).

Linifanib Active In Phase II Trial

Linifanib Advanced Hepatocellular Carcinoma Phase II Data Summary

Key Endpoint Measured	Child-Pugh A (CPA) Subgroup n=38	Child-Pugh B (CPB) Subgroup n=6	Combined HCC Patients n=44
progression-free (PF) rate at 16 weeks (%)	34.2% [19.6%, 51.4%]	16.7% [0.4%, 64.1%]	31.8% [18.6%, 47.6%]
ORR* (%)	7.9% [1.7%, 21.4%]	0%	6.8% [1.4%, 18.7%]
time-to-progression** (TTP)	5.4 months [3.6, 14.1 months]	3.7 months [0.7, NR months]	3.7 months [3.6, 7.3 months]
time-to-radiographic progression** (TTPr)	5.4 months [3.6, NR months]	NR months [3.7, NR months]	5.4 months [3.6, NR months]
OS**	10.4 months [8.4, 14.9 months]	2.5 months [1.1, 4.5 months]	9.7 months [6.3, 12.2 months]

*Per RECIST - responses confirmed on 2 visits >4 weeks apart

** estimated median

NR = not reached

Source: Company data, Cowen and Company

The Phase II study of linifanib in non-small cell lung cancer (NSCLC) demonstrated linifanib's activity in this patient population, albeit modest. In the 139-patient open-label Phase II NSCLC study, patients receiving linifanib achieved: an objective response rate of 5.0%; progression-free rate at 16 weeks of 33.1%; median time to progression of 3.6 months; median progression-free survival of 3.6 months; and median overall survival of 9.0 months. Common AEs associated with linifanib treatment were fatigue (42%), decreased appetite (38%), hypertension (37%), diarrhea (32%), nausea (27%), palmar-plantar erythrodysesthesia (24%), and proteinuria (22%), mostly observed in patients receiving the high 0.25mg/kg QD dose. The most common grade 3/4 AE was hypertension (14%).

We currently do not have sales estimates for linifanib in any of the indications being pursued, pending greater visibility on its chances for success from the Phase II/III efficacy and safety data.

Navitoclax (ABT-263) Moving Ahead In CLL

In June 2011, Abbott reported data from its Phase II study of navitoclax (ABT-263) in patients with relapsed or refractory chronic lymphocytic leukemia (CLL). Navitoclax is a Bcl-2 inhibitor that restores apoptosis in tumor cells by blocking the function of prosurvival Bcl-2 proteins, and it also blocks the activity of Bcl-w, which causes a reduction in platelet counts.

Patients in the Phase II study received 1-6 other treatments (median of 2.6 treatments) prior to navitoclax. The primary endpoints of the study were objective tumor response rate and progression-free survival. The Phase II study evaluated a 7-day lead-in of navitoclax 100mg QD, followed by 250mg QD for 21 days until disease progression or intolerable toxicity was observed. In the Phase II study, navitoclax achieved an objective response rate of 33% (confirmed in 19% of patients) and 58% of patients with baseline nodal enlargement showed shrinkage of >50%.

The median progression-free survival for patients receiving navitoclax was 8.7 months based on preliminary data from 29 patients. For comparison, marketed drugs for the treatment of fludarabine-refractory CLL have demonstrated a progression-free survival of 6-9 months.

Safety data for the Phase II trial were as expected and showed 39% of patients recorded Grade 3 or 4 platelet count reductions, 58% experienced nausea, and 48% experienced diarrhea, characterized as mild and manageable. Grade 3/4 neutropenia were observed in 20% of patients, thrombocytopenia in 27% of patients, and tumor lysis syndrome and elevated liver enzymes were observed in a small number of patients. There were 5 patient discontinuations due to adverse events and 8 patients required dose reductions.

Collaboration With Infinity Expands Oncology Efforts To PI3K Inhibitors

In September 2014, AbbVie announced a collaboration with Infinity Pharmaceuticals to develop and commercialize duvelisib (IPI-145), a PI3K-delta and gamma inhibitor in hematological cancers. AbbVie paid \$275MM upfront and may pay an additional \$530MM to Infinity in milestone payments. Duvelisib is currently in Phase II (DYNAMO) in iNHL and Phase III (DUO) in CLL. A Phase III study (DYNAMO+R) with duvelisib plus Rituxan in r/r CLL is expected to start by year end. The two companies will jointly commercialize duvelisib in the U.S. and share equally in any profits; OUS,

AbbVie will be responsible for commercialization and will pay royalties of 23.5-30.5% of net sales to Infinity.

Metabolic

AndroGel Decline Already In Progress; FDA AdCom May Accelerate

In September 2014, the FDA Bone, Reproductive and Urologic Drugs and the Drug Safety and Risk Management AdComs jointly met to discuss testosterone replacement therapies. The panel voted 20-1 in favor of revising the current indication for testosterone therapies. When asked whether or not FDA should require sponsors of testosterone products to conduct a study to further assess potential cardiovascular risk with the use of testosterone replacement therapy, the FDA panel voted 16 yes, but only for certain indications for testosterone therapy; 4 yes, regardless of the indication for testosterone therapy; and 1 no. We already had assumed a decline in AndroGel sales: \$860MM (-17%) in 2014, \$660MM (-23%) in 2015, \$500MM (-24%) in 2016, and \$50MM in 2020. AndroGel is expected to contribute EPS of \$0.09 in 2014, \$0.05 in 2015, \$0.04 in 2016, and zero in 2020. Therefore, even if the decline in AndroGel becomes steeper than forecast, the impact on ABBV would be modest.

ALV003 Not A Huge Opportunity

In May 2013, AbbVie announced a collaboration with Alvine Pharmaceuticals to develop ALV003, a recombinant enzyme therapy composed of EPB2 and PEP, for the treatment of Celiac disease. Under the terms of the agreement, AbbVie made an upfront payment of \$70MM to Alvine with the exclusive option to acquire rights to ALV003 or equity in Alvine. Alvine will be responsible for Phase II development after which AbbVie may elect to take responsibility for Phase III development. ALV003 is currently in Phase II studies with a 2b study which started in 2013. Celiac disease is an autoimmune disease of the small intestine caused by an adverse reaction to gliadin, a gluten protein found in wheat, barley, and rye. Exposure to gliadin promotes immune system targeting of the small intestine resulting in an inflammatory reaction, villous atrophy, and the subsequent malabsorption of nutrients. A large multicenter trial in the U.S. suggests that 0.75% of the general population is diagnosed with celiac disease, yet historical data suggests the incidence is closer to 0.025-0.25%. 3% of primary care patients who report GI symptoms are ultimately diagnosed with the condition. Serological identification of antiendomysial (IgA) or tTG antibodies has increased the frequency of diagnosis in recent years. At present, the only treatment for Celiac disease is a lifelong gluten free diet. This diet is often difficult to comply with and gluten-free foods often contain trace amounts of gliadin that may adversely affect the most severe Celiac patients. However, U.S. studies suggest that quality of life in Celiac patients is comparable to the general population if a gluten-free diet is maintained. As such, an enzyme replacement therapy such as ALV003 may only be appropriate for a small minority of Celiac patients who are unable to adhere to or improve on a gluten-free diet.

CNS

Duopa A Niche Opportunity In Parkinson's

Duopa is an intestinal gel formulation of carbodopa/levodopa (5mg/20mg) for the treatment of advanced levodopa-responsive Parkinson's disease. Duopa is directly delivered to the duodenum via a portable pump to improve absorption of the combination therapy and achieve optimal steady-state plasma concentrations of the

levodopa component. The drug is administered three times a day. Duopa is marketed in the EU and other OUS markets and is under review in the U.S. with a PDUFA date in Q1:15. We estimate Duopa sales of \$230MM in 2014, \$300MM in 2015, \$370MM in 2016, \$510MM in 2018, and \$650MM in 2020.

Our consultants believe Duopa will get U.S. approval, although the waning pharmacodynamic response to levodopa as the disease advances provides a relatively narrow window of opportunity to use this formulation. They estimate Duopa may be used in 1,000+ patients/year in the U.S. who are either not good candidates for deep brain stimulation surgery or who want an alternative to the surgery.

Shire The Leader In ADHD

Vyvanse (lisdexamfetamine dimesylate) is approved for once-daily use in Attention Deficit Hyperactivity Disorder (ADHD). In June 2014, the U.S. District Court ruled in Shire's favor and granted summary judgment motion upholding 18 patent claims. The ruling prevents all five ANDA filers (Sandoz, Roxane, Amneal, Actavis, and Mylan) from launching generic versions of Vyvanse until either a successful federal court appeal or patent expiration in 2023. The 18 patent claims that were upheld cover the active ingredient and a method of use in ADHD. The summary judgment motion did not include every patent claim in the litigation so further litigation is possible. We estimate Vyvanse sales of \$1.6B in 2015, \$1.8B in 2016, \$2.15B in 2018, and \$2.45B in 2020.

In September 2014, the FDA accepted Shire's sNDA with priority review for use in adults with binge eating disorder (BED). It is estimated that 3MM adults (primarily women) suffer from BED and although more prevalent than anorexias, is largely under-diagnosed and untreated. There appears to be overlap with ADHD, so the added indication would be a positive for the franchise.

SHP465 Filed For Adult ADHD

Shire's SHP465 (mixed salts of a single entity amphetamine) is an extended release, once-daily amphetamine for adults with ADHD. Shire received feedback from the FDA in April 2014 and resubmitted the NDA in July 2014. SHP465 has the same active ingredient as Adderall XR but is designed to provide symptom control for up to 16 hours. Shire expects to launch in H1:2015.

Rare Diseases

Shire will further diversify AbbVie's line-up with products in the Rare Disease area. These include Elaprase in Hunters, Firazyr and Cinryze for HAE (hereditary angioedema), Replagel (Fabry disease OUS) and Vpriv (Gaucher disease) and a number of other products/new indications in the pipeline. Shire also acquired Lumena in June 2014 and its two lead compounds: SHP625 (in Phase II for four orphan indications), and SHP626 (will begin Phase II later in 2014), both inhibitors of apical sodium-dependent bile acid transporter (ABST). SHP625 is being studied in Alagille syndrome, progressive familial intrahepatic cholestasis, primary biliary cirrhosis, and primary sclerosing cholangitis. SHP626 is being evaluated in nonalcoholic steatohepatitis. We estimate sales from Rare Disease products to be \$2.415B in 2015, \$2.555B in 2016, \$2.76B in 2018, and \$2.835B in 2020.

AbbVie - Summary Annual Balance Sheet (\$MM)

	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Current Assets								
Cash/Equivalents	\$9,595	\$9,595	\$10,244	\$12,840	\$17,475	\$23,089	\$28,749	\$40,317
Investments	300	300	500	500	500	500	500	500
Accounts Receivable	3,854	3,755	5,140	5,600	5,955	6,030	6,180	6,290
Inventories	1,150	1,120	1,415	1,520	1,600	1,600	1,625	1,655
Other Current Assets	2,949	2,840	4,020	4,380	4,660	4,715	4,835	4,920
Total Current Assets	\$17,848	\$17,610	\$21,319	\$24,840	\$30,190	\$35,934	\$41,889	\$53,682
Property, Plant & Equipment	\$2,298	\$2,400	\$2,450	\$2,525	\$2,600	\$2,675	\$2,725	\$2,775
Goodwill	6,277	6,250	51,000	49,975	48,975	48,000	47,050	46,100
Intangible Assets	1,890	1,700	1,700	1,700	1,700	1,700	1,700	1,700
Long-Term Investments	118	100	100	100	100	100	100	100
Other	767	800	800	800	800	800	800	800
Total Assets	\$29,198	\$28,860	\$77,369	\$79,940	\$84,365	\$89,209	\$94,264	\$105,157
Liabilities & Equity								
Short-term borrowings	\$413	\$300	\$300	\$300	\$300	\$300	\$300	\$300
Current portion of long-term debt	18	0	0	0	0	0	0	0
Accounts payable & accrued liabilities	\$6,448	\$6,130	\$7,755	\$8,330	\$8,770	\$8,770	\$8,900	\$9,055
Due to Abbott	0	0	0	0	0	0	0	0
Total Current Liabilities	\$6,879	\$6,430	\$8,055	\$8,630	\$9,070	\$9,070	\$9,200	\$9,355
Long Term Debt	\$14,292	\$14,500	\$37,000	\$36,000	\$35,000	\$34,000	\$33,000	\$32,000
Other Liabilities	3,535	3,000	3,000	3,000	3,000	3,000	3,000	3,000
Net Equity	\$4,492	\$4,930	\$29,314	\$32,310	\$37,295	\$43,139	\$49,064	\$60,802

Source: Company data, Cowen and Company estimates

AbbVie - Summary Working Capital Buildup (\$MM)

	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Inventories								
Inventories	1,150	1,120	1,415	1,520	1,600	1,600	1,625	1,655
COGS	4,051	4,142	5,242	5,631	5,928	5,927	6,016	6,121
Inventory Turns	3.5	3.7	3.7	3.7	3.7	3.7	3.7	3.7
Months	3.4	3.2	3.2	3.2	3.2	3.2	3.2	3.2
Accounts Receivable	3,854	3,755	5,140	5,600	5,955	6,030	6,180	6,290
Sales	18,790	19,590	26,800	29,195	31,060	31,430	32,220	32,795
Receivable Days	75	70	70	70	70	70	70	70
Other Current Assets	2,949	2,840	4,020	4,380	4,660	4,715	4,835	4,920
% of Sales	16%	15%	15%	15%	15%	15%	15%	15%
Accounts Payable & Accrued	6,448	6,130	7,755	8,330	8,770	8,770	8,900	9,055
COGS	4,051	4,142	5,242	5,631	5,928	5,927	6,016	6,121
Payable Days	581	540	540	540	540	540	540	540
Net Working Capital (ex cash, debt)	1,505	1,585	2,820	3,170	3,445	3,575	3,740	3,810

Source: Company data, Cowen and Company estimates

AbbVie – Summary Annual Cash Flow Buildup (\$MM)

	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Operating Activities								
Net Income	\$5,066	\$5,031	\$8,024	\$9,391	\$10,468	\$10,577	\$10,892	\$11,100
Depreciation & Amortization	897	800	1,250	1,250	1,275	1,275	1,300	1,300
Other	(758)	0	0	0	0	0	0	0
Change In Working Capital	1,062	(80)	(1,235)	(350)	(275)	(130)	(165)	(70)
Net Operating Activities	\$6,267	\$5,751	\$8,039	\$10,291	\$11,468	\$11,722	\$12,027	\$12,330
Investing Activities								
Capital Expenditures	(\$491)	(\$500)	(\$675)	(\$700)	(\$700)	(\$700)	(\$700)	(\$700)
Acquisitions	(405)	0	(51,000)	0	0	0	0	0
(Purchase)/sale of securities	1,775	(1,200)	0	0	0	0	0	0
Other, Net	0	0	0	0	0	0	0	0
Net Investing Activities	\$879	(\$1,700)	(\$51,675)	(\$700)	(\$700)	(\$700)	(\$700)	(\$700)
Financing Activities								
Total Debt	(601)	(250)	22,500	(1,000)	(1,000)	(1,000)	(1,000)	(1,000)
Dividends	(2,555)	(2,702)	(3,768)	(3,956)	(4,154)	(4,362)	(4,580)	(4,809)
Other	(39)	(500)	27,500	0	0	0	0	0
Net transactions with Abbott Labs	(247)	50	0	0	0	0	0	0
Net Financing Activities	(\$3,442)	(\$3,402)	\$46,232	(\$4,956)	(\$5,154)	(\$5,362)	(\$5,580)	(\$5,809)
Net Change In Cash & Equivalents	3,694	650	2,596	4,635	5,614	5,660	5,747	5,821
Year-End Cash & Equivalents	\$9,595	\$10,244	\$12,840	\$17,475	\$23,089	\$28,749	\$34,496	\$40,317

Source: Company data, Cowen and Company estimates

DCF Analysis

9/26/14			
Assumptions:			
Share Price	\$59	Output Equity Value	\$138,124
		Estimated Share Price	\$65
Discount Rate	8.0%	Net Cash	(\$4,397)
Shares Outstanding (000)	2,136	Enterprise Value	\$142,521

ABBV DCF

	2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021P	2022P	2023P	2024P	2025P	Terminal
Total Revenues	\$18,790	\$19,590	\$26,800	\$29,195	\$31,060	\$31,430	\$32,220	\$32,795	\$33,779	\$34,792	\$35,836	\$36,911	\$38,166	
% Change	+4%	+4%	+37%	+9%	+6%	+1%	+3%	+2%	+3%	+3%	+3%	+3%	+3%	+3%
Cost of Goods	\$4,051	\$4,142	\$5,142	\$5,586	\$5,933	\$6,022	\$6,316	\$6,546	\$6,756	\$6,958	\$7,167	\$7,271	\$7,442	
Gross Profit	\$14,739	\$15,448	\$21,658	\$23,609	\$25,127	\$25,408	\$25,904	\$26,249	\$27,023	\$27,834	\$28,669	\$29,640	\$30,724	
Gross Margin - Total	78.4%	78.9%	80.8%	80.9%	80.9%	80.8%	80.4%	80.0%	80.0%	80.0%	80.0%	80.3%	80.5%	
SG&A	\$5,084	\$5,505	\$6,960	\$7,320	\$7,450	\$7,555	\$7,640	\$7,695	\$7,938	\$8,176	\$8,421	\$8,674	\$8,969	
% of Revs	27.1%	28.1%	26.0%	25.1%	24.0%	24.0%	23.7%	23.5%	23.5%	23.5%	23.5%	23.5%	23.5%	
R&D	\$2,831	\$3,200	\$4,275	\$4,320	\$4,495	\$4,570	\$4,645	\$4,720	\$4,898	\$5,045	\$5,196	\$5,352	\$5,534	
% of Revs	15.1%	16.3%	16.0%	14.8%	14.5%	14.5%	14.4%	14.4%	14.5%	14.5%	14.5%	14.5%	14.5%	
Operating Expenses	\$7,915	\$8,705	\$11,235	\$11,640	\$11,945	\$12,125	\$12,285	\$12,415	\$12,836	\$13,221	\$13,618	\$14,026	\$14,503	
% of Revenues	42.1%	44.4%	41.9%	39.9%	38.5%	38.6%	38.1%	37.9%	38.0%	38.0%	38.0%	38.0%	38.0%	
Operating Income	\$6,824	\$6,743	\$10,423	\$11,969	\$13,182	\$13,283	\$13,619	\$13,834	\$14,187	\$14,613	\$15,051	\$15,613	\$16,221	
% Operating Margin	36.3%	34.4%	38.9%	41.0%	42.4%	42.3%	42.3%	42.2%	42.0%	42.0%	42.0%	42.0%	42.3%	42.5%
Non-operating income	(31)	13	0	0	0	0	0	0	0	0	0	0	0	0
EBIT	\$6,793	\$6,756	\$10,423	\$11,969	\$13,182	\$13,283	\$13,619	\$13,834	\$14,187	\$14,613	\$15,051	\$15,613	\$16,221	
% of Revs	36.2%	34.5%	38.9%	41.0%	42.4%	42.3%	42.3%	42.2%	42.0%	42.0%	42.0%	42.3%	42.5%	
D&A	\$897	\$800	\$1,250	\$1,250	\$1,275	\$1,275	\$1,300	\$1,300	\$1,300	\$1,350	\$1,400	\$1,450	\$1,475	
EBITDA	\$7,690	\$7,556	\$11,673	\$13,219	\$14,457	\$14,558	\$14,919	\$15,134	\$15,487	\$15,963	\$16,451	\$17,063	\$17,696	
% of Revs	40.9%	38.6%	43.6%	45.3%	46.5%	46.3%	46.3%	46.1%	45.8%	45.9%	45.9%	46.2%	46.4%	
Net Interest Income (Expense)	(\$278)	(\$265)	(\$1,200)	(\$1,175)	(\$1,150)	(\$1,125)	(\$1,100)	(\$1,075)	(\$1,025)	(\$975)	(\$925)	(\$875)	(\$825)	
Pre-Tax Income	\$6,515	\$6,491	\$9,223	\$10,794	\$12,032	\$12,158	\$12,519	\$12,759	\$13,162	\$13,638	\$14,126	\$14,738	\$15,396	
Taxes	\$1,449	\$1,438	\$1,199	\$1,403	\$1,564	\$1,581	\$1,627	\$1,659	\$1,844	\$1,900	\$1,957	\$2,030	\$2,109	
Income Tax Rate	22.2%	22.1%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	
Net Income	\$5,066	\$5,053	\$8,024	\$9,391	\$10,468	\$10,577	\$10,892	\$11,100	\$11,318	\$11,738	\$12,169	\$12,709	\$13,287	
% of Revs	27.0%	25.8%	29.9%	32.2%	33.7%	33.7%	33.8%	33.8%	33.5%	33.7%	34.0%	34.4%	34.8%	
% Change	-3%	-0%	+59%	+17%	+11%	+1%	+3%	+2%	+2%	+4%	+4%	+4%	+5%	
NOPAT	\$5,344	\$5,318	\$9,224	\$10,566	\$11,618	\$11,702	\$11,992	\$12,175	\$12,343	\$12,713	\$13,094	\$13,584	\$14,112	
Adjustments:														
Capex	(\$491)	(\$500)	(\$675)	(\$700)	(\$700)	(\$700)	(\$700)	(\$700)	(\$725)	(\$750)	(\$775)			
Depreciation & Amortization	\$897	\$800	\$1,250	\$1,250	\$1,275	\$1,275	\$1,300	\$1,300	\$1,350	\$1,400	\$1,450	\$1,475		
Change In Working Capital	(\$1,062)	(\$80)	(\$1,235)	(\$350)	(\$275)	(\$130)	(\$165)	(\$70)	(\$150)	(\$150)	(\$150)	(\$150)	(\$100)	
Operating Free Cash Flow	\$4,410	\$5,278	\$7,984	\$9,591	\$10,768	\$11,022	\$11,327	\$11,680	\$11,768	\$12,213	\$12,669	\$13,234	\$13,887	\$174,678

Source: Cowen and Company

AbbVie Key Upcoming Events

Time Frame	Event Type	Event	Comments
2014	Clinical	ABT-888	Mid-stage studies read out
		ABT-199 + GA101	Initiation of Phase III study in first line CLL in 2014; Phase 1b study data at ASH
		ABT-199 + rituximab	Update of study in CLL at ASH
		ABT-199 + rituximab + bendamustine	First data on study in NHL/DLBCL (safety w/BR in dose escalation) at ASH
		ABT-199	Single-agent AML, multiple myeloma data at ASH
		ABT-199	Data from Phase I studies in other cancers
		Elagolix	Phase III data from first of two studies in endometriosis H2:14
		Elagolix	Data from Phase IIa POC UF study – presentation may await Phase IIb data
		GLPG-0634	Phase IIb data from partnered selective JAK-1 inhibitor Q4:14
		HCV regimen	Phase III readout - Japan
Regulatory		Next-gen HCV	3-day monotherapy at AASLD
		Veliparib	Phase IIb data in BRCA breast cancer
Corporate		HCV franchise	U.S. approval H2:14; Filing in Japan
		Humira	U.S. and E.U. submissions for hidradenitis suppurativa H2:14
Corporate		Shire acquisition	Closing Q4:14

Source: Company data

ABBVIE R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Arthritis/Inflammation							
Humira				.			Anti-TNF inhibitor; approved for pediatric Crohn's disease ; PIII for axial and peripheral spondyloarthritis, uveitis, hidradenitis suppurativa
ABT-981			.				Anti-IL-1a/anti-IL1B; osteoarthritis\
ABT-122		⇒	.				Anti-TNF/anti-IL-17; RA
ABT-494			.				Selective JAK-1 inhibitor; RA; combination with tofacitinib
ALV003			.				Celiac disease; oral; composed of two recombinant, gluten-specific enzymes; global collaboration with Alvive
ALX-0061			.				Anti-IL6 nanobody; RA, SLE; with Ablynx
BT-061			.				Tregalizumab; anti-CD4; RA, psoriasis; with Biotest
GLPG0634			.				Selective JAK-1 inhibitor; RA; with Galapagos
ABT-257			.				Rheumatoid arthritis
ABT-981/ABT-122		.					Anti-TNF/anti-IL-17 + Anti-IL-1a/anti-IL1B combination; rheumatoid arthritis
Cancer/Oncology/Hematology							
Elotuzumab			.				Anti-CS1; treatment of relapsed or refractory multiple myeloma; from Facet
ABT-199			.	.			Bcl-2 selective inhibitor; PIII initiated 1/14 in relapsed refractory CLL; PII AML, hematologic malignancies
Duvelisib			.	.			Dual PI3K inhibitor; PIII CLL; PII indolent non-Hodgkin lymphoma
Veliparib			.	.			ABT-888; PARP inhibitor; restores apoptosis; PIII for advanced breast cancer, early stage triple negative breast cancer, NSCLC, BRCA-deficient breast cancer; PII for brain metastasis, ovarian cancer; PI for treatment of various refractory tumors
ABT-165		.					Solid tumors
ABT-399		.					Solid tumors
ABT-414		.					Glioblastoma
ABT-700		.					Solid tumors
RTA-ABT 408		.					Solid tumors
Central Nervous System							
Duopa					Q2:13		Carbodopa/levodopa intestinal gel combination; advanced Parkinson's disease; received CRL regarding delivery system; approved EU/Canada
SHP-465					.		Single-entity mixed amphetamine sales (MAS); adult ADHD; from Shire
Daclizumab			.		H1:15		Treatment of relapsing-remitting or secondary multiple sclerosis; PIII results successful; working with regulators to determine the appropriate timelines for filings; with Biogen
Vyvanse			.				Binge eating disorder in adults; from Shire
ABT-126			.				a7 NNR agonist; cognitive deficits of schizophrenia
ABT-436		.					Alcohol use disorder
ABBV-672		.					Alzheimer's disease
ABT-354		.					Alzheimer's disease
ABT-957		.					Alzheimer's disease
Contraception/Women's Health							
Elagolix			.				GnRH antagonist; PIII endometriosis; PII uterine fibroids; with Neurocrine Bioscience
Gene Therapy							

ABBVIE R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Firazy				.			Icatibant; from Jerini acquisition; ACE-inhibitor-induced angioedema; from Shire
LUM001			.				Four rare hepatic diseases; from Shire
Maribavir			.				CMV in transplant patients; from Shire
SHP-609			.				HGT-2310; mucopolysaccharidosis; Hunter syndrome with CNS symptoms; from Shire
SHP-610			.				HGT-1410; mucopolysaccharidosis; Sanfilippo syndrome; from Shire
SHP-613			.				Acute vascular repair; from Shire
SHP-611		.	.				HGT-1110; treatment of metachromatic leukodystrophy (MLD), inherited genetic deficiency of lysosomal arylsulfatase A [ASA]; from Shire
Cinryze		.					HAE prophylaxis; IV and SC formulations; from Shire
FT-011							Renal impairment; from Shire
LUM002			.				NASH; from Shire
SHP-622		.					Friedreich's Ataxia; from Shire
Immunological							
GLPG0634		.					Selective JAK-1 inhibitor; Crohn's disease; with Galapagos
ABT-199							SLE
Infectious Disease							
HCV IFN-Free Combination					Q1:14		HCV genotype 1
ABT-530		.					NS5A inhibitor; 2nd generation pan-genotypic, HCV; active vs. resistant mutants; once-daily dosing
Ophthalmology							
Lifitegrast			.				SHP-606; dry eye disease; from Shire
ABT-RTA-408		.					Treatment and prevention of post-operative cataract inflammation
Premiplex		.					Prevention of retinopathy of prematurity (ROP); from Shire
Urology							
Atrasentan			.				Diabetic kidney disease
Total Drugs In Development	0	15	20	10	3		48

Progress since last update in bold; movement marked by arrow

Investor Relations Contact: Larry Peepo 847-935-6722

Liz Shea 847-935-2211

AstraZeneca PLC (ADR)

Price: \$71.44 (09/30/2014)
Price Target: \$75.00

MARKET PERFORM (2)

Steve Scala, R.Ph., CFA

617.946.3923
steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA

617.946.3857
kathy.miner@cowen.com

Jean Perreault

617.946.3967
jean.perreault@cowen.com

Key Data

Symbol **NYSE: AZN**

52-Week Range: **\$82.68 - 49.63**

Market Cap (MM): **\$90,209.0**

Net Debt (MM): **\$363.0**

Cash/Share: **NA**

Dil. Shares Out (MM): **1,262.7**

Enterprise Value (MM): **NA**

ROIC: **NA**

ROE (LTM): **NA**

BV/Share: **NA**

Dividend: **\$1.80**

Yield: **2.52%**

FY (Dec)	2013A	2014E	2015E
Earnings Per Share			
Q1	\$1.41	\$1.17A	\$0.98
Prior Q1	-	-	\$0.90
Q2	\$1.20	\$1.30A	\$0.89
Prior Q2	-	-	-
Q3	\$1.21	\$1.06	\$1.08
Prior Q3	-	\$0.96	\$1.07
Q4	\$1.23	\$0.87	\$1.15
Prior Q4	-	-	\$1.09
Year	\$5.05	\$4.40	\$4.10
Prior Year	-	\$4.30	\$3.95
P/E	14.1x	16.2x	17.4x
Reflects updated definition of core financial measures to exclude all intangible asset amortization charges and impairments, except those for IS-related intangibles.			
Consensus EPS	\$5.05	\$4.39	\$4.08
Consensus source: Thomson Reuters			

Revenue (MM)

Year	\$25,711.0	\$25,865.0	\$25,350.0
Prior Year	-	\$25,640.0	\$25,450.0

The Cowen Insight

Despite a sound long-term strategy, uncertainty surrounding existing products and the pipeline, as well as Pfizer's ultimate involvement, keeps us on the sidelines.

Astra's return to growth is dependent upon maximizing the value of existing products and delivering on the pipeline. Brilinta, diabetes franchise, and Crestor outlooks are unclear, Y/Y EPS prospects very inconsistent, the pipeline is improving but still of limited visibility, and management's 10-year forecasts appear aggressive. Core therapeutic areas will be strengthened through strategic partnering and bolt-on acquisitions, such as the purchase of BMY's diabetes assets, and management believes a large, transformative transaction is not required. Astra will reinvest cash flows into the business while maintaining its commitment to the dividend. Absent another bid from Pfizer, which would appear to have at least 50/50 probability, we prefer other stocks with more clear growth profiles and fewer risks.

EPS Down 13% In 2014 Mixed Outlook Through 2020

We forecast an EPS decline of 13%, to \$4.40 in 2014, due to generic pressures, primarily Nexium, followed by a 7% decline in 2015. After a rebound in 2016 to +6% EPS growth, Crestor's patent expiration in December 2016 (assuming pedi exclusivity) will likely pressure sales and EPS in 2017. 2014-20 EPS are forecast at +2%, with trough EPS in 2017E.

Pipeline Includes Many Large Potential Candidates

Astra has 35 NMEs in Phase I, 24 NMEs in Phase II, and 14 NMEs in Phase III/registrational development. While the late-stage pipeline is composed of 64% small molecules, compounds in earlier stages of development are well balanced between small and large molecules. Oncology, respiratory, and inflammation pipelines contain many interesting assets. Early stage assets appear weakest in the CV-metabolic therapeutic area.

Diabetes Acquisition Adds Visibility

The early 2014 buy-out of alliance partner Bristol's diabetes assets is a good strategic move providing Astra with a major foothold in a growing segment, and bolstering prospects while the pipeline matures.

Long Range Revenue Targets Sizable, But Visibility Needed

Astra's 10-year plan includes sizable revenue expectations including 2017 revenues "broadly in-line" with 2013 sales of \$25.7B, well above our \$23.76B forecast and consensus. Management also forecast annual revenue of \$45B+ by 2023. This top line growth is expected to be driven by a growing and accelerating mid-late stage pipeline (accounting for one-third of the 2023 total), with the remainder due to growth from Brilinta, diabetes, respiratory, emerging markets, and Japan.

Sizable EPS Decline In 2014E, Growth Returns In 2016E, Sustainable Recovery Not Forecast Until 2018E

EPS Estimated To Be Down 13% In 2014

We forecast a 13% decline in EPS in 2014 on +1% revenue growth, driven by continued generic pressures, particularly on Nexium, in tandem with infrastructure spending. R&D is expected to increase 12%, SG&A +9%, and other operating income up \$333MM. The tax rate is forecast to decline 1pp to 19.3% and the share count +1%.

Astra 2014 Guidance Versus Cowen Estimates

	AZN Guidance	Our Estimates
Revenue	In line with 2013 at CER (assuming Nexium generics on 10/1/14)	\$25.865B (+1%)
Gross Margin	NA	81.4%
Core Operating Costs	NA	\$14.725B (+10%)
Core Other Income	NA	\$1,085MM
Tax Rate	~23%	19.3%
Core EPS	Low double-digit decrease	\$4.40 (-13%)

Bold=revised

Source: Cowen and Company

EPS Down Again In 2015, Rebound In 2016

In 2015, revenue is forecast to decline 2% and EPS 7%, to \$4.10. Gross PM is forecast to decline 0.4pp to 81.0%, R&D could be up 2%, SG&A is expected to decline 5%, and other operating income may decline by \$235MM to \$850MM. The tax rate is forecast to jump 2.7pp to 22.0% and share count down 5MM to 1,255MM. We forecast 6% EPS growth on a 2% increase in revenue in 2016 with GM up 1pp and other P&L items broadly similar to 2015.

2017 Looks Like The Trough Year As Crestor Comes Off Patent; Growth To Return In 2018-20

Crestor loses exclusivity in January 2017. We expect 2017 Crestor sales to decline by 60% to \$2.015B (vs. \$5.075B in 2016E). We forecast the Crestor patent expiry leads to an 8% decline in total revenue, to \$23.76B, and a 14% decline in EPS, to \$3.75 in 2017. However, Astra has guided to 2017 revenue on par with 2013, or \$25.7B. This is \$1.9B above our estimate. EPS growth should resume in 2018 as new products grow the top-

line; top-line growth should range between 4-8% during 2018-20. We forecast EPS of \$4.10 (+9%) in 2018, \$4.50 (+10%) in 2019, and \$5.00 (+11%) in 2020.

Long Range Strategic Plan Portrays Lofty Growth Expectations

Post the acquisition interest from Pfizer, management reiterated its expectation of 2017 revenues “broadly in-line” with 2013 sales of \$25.7B. We estimate 2017 revenue at \$23.76B; consensus is just over \$23B. Management also forecast annual revenue of \$45B+ by 2023. This top line growth is expected to be driven by a growing and accelerating mid-late stage pipeline including: oncology agents MEDI4736 (PD-L1), AZD9291 (EGFR), olaparib (PARP); respiratory agents PT003 (LABA/LAMA), PT010 (LABA/LAMA/ICS) and benralizumab (asthma), and diabetes combo saxagliptin/dapagliflozin. Pipeline products are expected to account for one-third of the 2023 total, with the remainder due to growth from key platforms: Brilinta, diabetes, respiratory, emerging markets, and Japan.

Management estimates risk-adjusted peak year sales for pipeline products to be \$23B; non-risk adjusted estimated at \$63B. Probability of success for the overall portfolio is 36%, with some drugs (such as BACE) given a much lower probability.

Speculation On 2013-20E EPS Outcomes (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2013-16 CGR	2013-20 CGR	2014-20 CGR	Comments
Symbicort	\$0.79	\$0.85	\$0.87	\$0.82	\$0.74	\$0.67	\$0.59	\$0.51	1%	-6%	-8%	32.3% market share in U.S. 8/14; Teva generic filing 2014; BE guidelines another risk
Nexium	0.87	0.74	0.43	0.44	0.44	0.46	0.48	0.50	-21%	-8%	-6%	Assumes generic launch in October 2014
Brilinta	0.06	0.11	0.14	0.18	0.22	0.25	0.28	0.32	42%	26%	20%	Reversible ADP rec. antagonist; oral; arterial thrombosis; PEGASUS-TIMI 54 (ACS), EUCLID (PAD) underway
Crestor	1.27	1.25	1.22	1.18	0.47	0.36	0.30	0.26	-2%	-20%	-23%	Patent exp. 7/16 (without pedi exclusivity) US, 6/17 EU, LOE in Canada
Arimidex	0.08	0.06	0.05	0.04	0.03	0.02	0.01	0.00	-23%	-33%	-35%	Estrogen antagonist, breast cancer; generics eroding franchise
Seroquel	0.17	0.13	0.09	0.08	0.06	0.04	0.03	0.01	-24%	-32%	-34%	Substance patent expired 3/12 (with pedi exclusivity)
Other New Drugs	0.01	0.05	0.12	0.34	0.68	1.06	1.54	2.08	221%	114%	89%	PD-L1, AZN9291, Ekira, olaparib, PT003, many others
Diabetes Franchise	0.17	0.42	0.66	0.85	1.02	1.20	1.38	1.55	72%	37%	25%	Onglyza, Forxiga, Bydureon, Byetta; BMY's 50% stake purchased Q1:14
Other	1.63	0.79	0.51	0.44	0.09	0.06	-0.10	-0.23	-35%	-176%	NM	
EPS	\$5.05	\$4.40	\$4.10	\$4.35	\$3.75	\$4.10	\$4.50	\$5.00	-5%	0%	2%	Versus industry averages of +4%, +6% and +8%
% Change	-26%	-13%	-7%	6%	-14%	9%	10%	11%				

Source: Company data, Cowen and Company

AstraZeneca Quarterly Core EPS

	Total Sales	Gross P.M.	SG&A \$MM	R&D \$MM	Op. P.M.	Pretax P.M.	Tax Rate	Net Income	EPS (Dil.)	Y/Y % Chg.	Shares (MM)
	% Chg.	% Sls	% Sls	% Sls							
Q1	\$6,385	-13%	82.2%	\$2,055	32.2%	\$963	15.1%	36.4%	34.9%	21.3%	\$1,754
Q2	6,232	-6%	82.3%	2,173	34.9%	1,040	16.7%	33.0%	31.2%	22.2%	1,502
Q3	6,250	-6%	82.4%	2,154	34.5%	1,061	17.0%	32.4%	30.6%	20.3%	1,523
Q4	6,844	-6%	81.2%	2,483	36.3%	1,205	17.6%	29.0%	27.2%	16.9%	1,540
2013	\$25,711	-8%	82.0%	\$8,865	34.5%	\$4,269	16.6%	32.6%	30.9%	20.3%	\$6,320
Q1	\$6,416	0%	81.4%	\$2,317	36.1%	\$1,098	17.1%	30.4%	28.5%	19.3%	\$1,471
Q2	6,454	4%	82.1%	2,460	38.1%	1,208	18.7%	31.5%	29.3%	13.1%	1,642
Q3E	6,435	3%	82.1%	2,320	36.1%	1,200	18.6%	29.2%	26.9%	23.0%	1,335
Q4E	6,570	-4%	80.0%	2,558	38.9%	1,269	19.3%	23.7%	21.6%	23.0%	1,090
2014E	\$25,865	1%	81.4%	\$9,655	37.3%	\$4,775	18.5%	28.7%	26.5%	19.3%	\$5,538
Q1E	\$6,140	-4%	80.0%	\$2,200	35.8%	\$1,125	18.3%	28.0%	25.7%	22.0%	\$1,230
Q2E	6,060	-6%	80.0%	2,250	37.1%	1,200	19.8%	25.8%	23.6%	22.0%	1,114
Q3E	6,295	-2%	82.0%	2,200	34.9%	1,225	19.5%	29.7%	27.6%	22.0%	1,355
Q4E	6,855	4%	82.0%	2,490	36.3%	1,300	19.0%	28.8%	27.0%	22.0%	1,444
2015E	\$25,350	-2%	81.0%	\$9,140	36.1%	\$4,850	19.1%	28.1%	26.0%	22.0%	\$5,143
2016P	\$25,825	2%	82.0%	\$9,250	35.8%	\$5,000	19.4%	29.0%	27.0%	22.0%	\$5,442
2017P	\$23,760	-8%	81.0%	\$8,250	34.7%	\$5,100	21.5%	27.2%	25.2%	22.0%	\$4,669
2018P	\$24,675	4%	81.5%	\$8,520	34.5%	\$5,200	21.1%	28.2%	26.4%	22.0%	\$5,086
2019P	\$26,515	7%	82.0%	\$9,490	35.8%	\$5,300	20.0%	28.4%	26.9%	22.0%	\$5,555
2020P	\$28,670	8%	82.5%	\$10,580	36.9%	\$5,400	18.8%	28.8%	27.5%	22.0%	\$6,149

Source: Cowen and Company

AstraZeneca Quarterly Product Line Buildup (\$MM)

	2012A	Q1:13A	Q2:13A	Q3:13A	Q4:13A	2013A	Q1:14A	Q2:14A	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Change in Euro per \$ (as of 9/16/14)									1.0022	0.9535		0.9474	0.9466	0.9776	1.0000	
Nexium - U.S.	\$2,272	\$523	\$555	\$500	\$545	\$2,123	\$484	\$455	\$400	\$75	\$1,415	\$20	\$10	\$10	\$10	\$50
Nexium - EU. (lc, ex fx)									80	75		70	65	60	55	
Nexium - E.U.	447	93	89	86	92	360	94	100	80	70	345	65	60	60	55	240
Nexium - Estab. ROW	476	130	157	145	165	597	151	184	165	185	685	160	195	175	195	725
Nexium - Emerging ROW	749	194	222	187	189	792	201	232	190	210	835	210	240	200	220	870
Nexium - Worldwide	3,944	940	1,023	918	991	3,872	930	971	835	540	3,275	455	505	445	480	1,885
Losec - U.S.	\$30	\$7	\$9	\$7	\$7	\$30	\$8	\$6	\$0	\$0	\$15	\$5	\$0	\$0	\$0	\$5
Losec - EU. (lc, ex fx)									30	30		25	25	20	20	
Losec - E.U.	191	34	32	30	35	131	34	33	30	30	125	25	25	20	20	90
Losec - Estab. ROW	316	41	45	38	41	165	26	28	25	25	105	20	20	20	20	80
Losec - Emerging ROW	173	43	35	43	39	160	42	38	40	35	155	35	35	30	30	135
Losec - Worldwide	710	125	121	118	122	486	110	105	95	90	400	85	80	75	70	310
Other - U.S.	\$144	\$36	\$37	\$53	\$42	\$168	\$35	\$45	\$55	\$45	\$180	\$35	\$45	\$55	\$50	\$185
Other - EU. (lc, ex fx)									10	10		10	20	10	10	
Other - E.U.	44	15	15	10	10	50	10	20	10	10	50	10	20	10	10	50
Other - Estab. ROW	6	1	3	1	2	7	5	5	0	0	10	5	5	5	0	15
Other - Emerging ROW	3	0	1	1	1	3	0	0	0	0	5	0	0	0	5	5
Other - Worldwide	197	52	56	65	55	228	50	70	65	60	245	50	70	70	65	255
Movantik												10	10	10	20	50
Axanum	1	1	1	1	0	3	5	5	5	5	20	10	10	10	10	40
Gastrointestinal	\$4,852	\$1,118	\$1,201	\$1,102	\$1,168	\$4,589	\$1,095	\$1,151	\$1,000	\$695	\$3,940	\$810	\$675	\$810	\$645	\$2,540
% Change	-12%	-5%	1%	-11%	-7%	0%	-2%	-4%	-9%	-40%	-14%	-44%	-41%	-39%	-7%	-36%
Crestor - U.S.	\$3,164	\$652	\$762	\$719	\$779	\$2,912	\$705	\$771	\$725	\$770	\$2,970	\$675	\$750	\$700	\$750	\$2,875
Crestor - EU. (lc, ex fx)									290	300		315	300	290	295	
Crestor - E.U.	1,229	316	302	296	311	1,225	301	310	290	285	1,185	300	285	285	295	1,165
Crestor - Estab. ROW	1,269	199	234	170	204	807	156	182	150	150	640	125	150	125	125	525
Crestor - Emerging ROW	591	156	182	171	169	678	170	187	180	180	715	180	200	190	190	760
Crestor - Worldwide	6,253	1,323	1,480	1,356	1,463	5,622	1,332	1,450	1,345	1,385	5,510	1,280	1,385	1,300	1,360	5,325
Seloken/Toprol XL - U.S.	\$320	\$56	\$31	\$25	\$19	\$131	\$24	\$29	\$20	\$20	\$95	\$10	\$10	\$10	\$10	\$40
Seloken/Toprol XL - EU. (lc, ex fx)									30	25		25	25	25	25	
Seloken/Toprol XL - E.U.	133	32	34	31	33	130	31	32	30	25	120	25	25	25	25	100
Seloken/Toprol XL - Estab. ROW	30	6	7	4	7	24	5	5	5	5	20	5	5	5	0	15
Seloken/Toprol XL - Emerging ROW	435	130	111	113	111	465	133	127	120	115	495	140	130	125	120	515
Seloken/Toprol XL - Worldwide	918	224	183	173	170	750	193	193	175	185	725	180	170	165	155	670
Atacand - U.S.	\$150	\$27	\$24	\$11	\$10	\$72	\$11	\$9	\$10	\$10	\$40	\$10	\$10	\$5	\$5	\$30
Atacand - EU. (lc, ex fx)									40	35		30	25	20	15	
Atacand - E.U.	461	61	56	54	54	225	49	47	40	35	170	30	25	20	15	90
Atacand - Estab. ROW	142	23	21	14	13	71	11	11	10	10	40	10	10	5	5	30
Atacand - Emerging ROW	256	57	65	64	57	243	51	72	65	55	245	55	75	60	50	240
Atacand - Worldwide	1,009	168	166	143	134	611	122	139	125	110	495	105	120	90	75	390
Tenormin - U.S.	\$10	\$2	\$5	\$5	\$3	\$15	\$2	\$2	\$0	\$0	\$5	\$5	\$0	\$0	\$0	\$5
Tenormin - EU. (lc, ex fx)									10	10		10	10	5	5	
Tenormin - E.U.	53	13	12	13	13	51	12	13	10	10	45	10	10	5	5	30
Tenormin - Estab. ROW	106	19	20	19	19	77	13	16	15	15	60	10	10	10	10	40
Tenormin - Emerging ROW	60	12	17	14	11	54	12	11	10	10	45	10	15	5	5	35
Tenormin - Worldwide	229	46	54	51	46	197	39	42	35	35	150	35	35	20	20	110

Source: Company data, Cowen and Company

AstraZeneca Quarterly Product Line Buildup (\$MM) (continued)

	2012A	Q1:13A	Q2:13A	Q3:13A	Q4:13A	2013A	Q1:14A	Q2:14A	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E	
Zestril - U.S.	\$8	\$2	\$2	\$2	\$2	\$8	\$5	\$2	\$0	\$0	\$5	\$5	\$0	\$0	\$0	\$5	
Zestril - E.U. (lc, ex fx)									10	10	10	10	10	5	5	5	
Zestril - E.U.	56	13	13	13	13	52	10	12	10	10	40	10	10	5	5	30	
Zestril - Estab. ROW	10	1	3	2	2	8	0	2	5	5	10	0	0	5	5	10	
Zestril - Emerging ROW	41	5	12	11	10	38	10	9	5	5	30	10	5	5	5	25	
Zestril - Worldwide	115	21	30	28	27	106	25	25	20	20	90	25	15	15	15	70	
Plendil - U.S.	\$4	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	
Plendil - E.U. (lc, ex fx)									5	0	5	5	0	0	0	0	
Plendil - E.U.	24	5	5	5	6	21	5	5	0	0	15	5	5	0	0	10	
Plendil - Estab. ROW	12	2	4	1	3	10	2	2	0	0	5	5	5	0	0	10	
Plendil - Emerging ROW	212	59	55	58	57	229	62	46	60	60	230	60	50	65	65	240	
Plendil - Worldwide	252	66	64	64	66	260	69	53	65	60	245	70	60	65	65	260	
Onglyza - U.S.	\$237	\$64	\$75	\$63	\$63	\$265	\$106	\$144	\$155	\$165	\$570	\$180	\$195	\$210	\$225	\$810	
Onglyza - E.U. (lc, ex fx)									55	60	65	70	75	80			
Onglyza - E.U.	50	13	14	14	15	56	26	43	55	55	180	60	65	75	80	280	
Onglyza - Estab. ROW	13	5	4	5	6	20	11	16	15	20	60	20	20	20	20	80	
Onglyza - Emerging ROW	23	8	9	11	9	37	19	35	40	45	140	50	55	60	65	230	
Onglyza - Worldwide	323	90	102	93	93	378	162	238	265	285	950	310	335	365	390	1,400	
Brilinta - U.S.	\$19	\$15	\$16	\$18	\$24	\$73	\$28	\$35	\$40	\$45	\$150	\$50	\$55	\$60	\$65	\$230	
Brilinta - E.U. (lc, ex fx)									60	60	65	65	70	70			
Brilinta - E.U.	57	30	38	44	51	163	52	58	60	55	225	60	60	70	70	260	
Brilinta - Estab. ROW	3	2	4	5	6	17	6	8	10	10	35	15	15	15	15	60	
Brilinta - Emerging ROW	10	4	7	8	11	30	13	16	15	15	60	20	20	20	20	80	
Brilinta - Worldwide	89	51	65	75	92	283	99	117	125	125	465	145	150	165	170	630	
Bydureon - U.S.	\$37	\$27	\$27	\$37	\$40	\$131	\$69	\$95	\$110	\$120	\$395	\$140	\$160	\$180	\$200	\$680	
Bydureon - E.U. (lc, ex fx)									20	25	35	45	55	65			
Bydureon - E.U.		5	6	6	7	17	9	15	20	25	70	35	45	55	65	200	
Bydureon - Estab. ROW			1	1	1	1	1	2	5	5	15	5	5	10	10	30	
Bydureon - Emerging ROW			2	2	1	1	0	5	5	5	10	5	5	10	10	30	
Bydureon - Worldwide	37	27	32	43	49	151	80	112	140	155	485	185	215	255	285	940	
Byetta - U.S.	\$74	\$42	\$36	\$38	\$36	\$152	\$52	\$53	\$55	\$55	\$215	\$60	\$60	\$60	\$60	\$240	
Byetta - E.U. (lc, ex fx)									25	25	30	30	35	35	35		
Byetta - E.U.		13	12	11	36	17	17	23	25	25	90	30	30	35	35	130	
Byetta - Estab. ROW		4	3	4	11	5	7	5	5	5	20	5	5	10	10	30	
Byetta - Emerging ROW		4	3	2	14	4	5	5	5	5	20	5	5	10	10	30	
Byetta - Worldwide	74	42	53	57	54	206	78	88	90	90	345	100	100	115	115	430	
Others - U.S.	\$17	\$9	\$10	\$12	\$13	\$44	\$9	\$14	\$15	\$15	\$55	\$20	\$20	\$20	\$20	\$80	
Others - E.U. (lc, ex fx)									25	25	20	25	25	25	25		
Others - E.U.	112	29	19	38	23	109	25	25	25	25	100	20	20	25	25	90	
Others - Estab. ROW	22	4	4	2	4	14	5	5	5	5	20	0	5	5	0	10	
Others - Emerging ROW	81	4	3	2	5	14	5	5	5	5	20	5	5	5	5	20	
Others - Worldwide	232	46	36	54	45	181	44	49	50	50	195	45	55	55	45	200	
Forxiga		1	3	3	3	10	10	10	15	20	55	25	30	35	40	130	
Epanova									5	10	15	15	20	25	30	90	
Metreleptin									10	10	20	10	10	10	10	40	
Symlin						75	15	15	25	25	80	20	20	25	25	90	
Cardiovascular	\$9,531	15	20	20	20	20	\$2,288	\$2,288	\$2,581	\$2,485	\$2,585	\$9,810	\$2,585	\$2,700	\$2,880	\$2,770	\$10,885
% Change	-7%	-9%	-3%	-8%	-9%	0%	7%	11%	15%	12%	11%	12%	7%	8%	9%	9%	

Source: Company data, Cowen and Company

AstraZeneca Quarterly Product Line Buildup (\$MM) (continued)

	2012A	Q1:13A	Q2:13A	Q3:13A	Q4:13A	2013A	Q1:14A	Q2:14A	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Symbicort - U.S.	\$1,003	\$287	\$289	\$307	\$350	\$1,233	\$344	\$377	\$375	\$390	\$1,485	\$360	\$390	\$390	\$405	\$1,545
Symbicort - E.U. (lc, ex fx)									345	390		375	360	335	360	
Symbicort - E.U.	1,465	384	374	349	395	1,502	386	371	345	370	1,470	355	340	330	360	1,385
Symbicort - Estab. ROW	443	83	101	110	129	423	115	96	110	130	450	120	100	115	135	470
Symbicort - Emerging ROW	283	72	78	73	102	325	83	84	85	110	360	90	95	95	120	400
Symbicort - Worldwide	3,194	826	842	839	976	3,483	928	928	915	1,000	3,770	925	925	930	1,020	3,800
Pulmicort - U.S.	\$233	\$62	\$56	\$47	\$59	\$224	\$52	\$52	\$45	\$55	\$205	\$40	\$40	\$40	\$50	\$170
Pulmicort - E.U. (lc, ex fx)									30	35		40	35	25	25	
Pulmicort - E.U.	191	53	41	33	44	171	46	43	30	35	155	40	35	25	25	125
Pulmicort - Estab. ROW	127	26	28	24	34	112	25	22	25	30	100	25	20	20	25	90
Pulmicort - Emerging ROW	315	92	88	72	108	360	140	92	90	110	430	145	100	100	120	465
Pulmicort - Worldwide	866	233	213	176	245	867	263	209	190	230	890	250	195	185	220	850
Rhinocort - U.S.	\$55	\$12	\$13	\$13	\$14	\$52	\$10	\$3	\$10	\$10	\$35	\$10	\$10	\$5	\$5	\$30
Rhinocort - E.U. (lc, ex fx)									5	5		5	5	0		
Rhinocort - E.U.	28	8	9	6	7	30	10	9	5	5	30	5	5	5	0	15
Rhinocort - Estab. ROW	17	2	3	5	4	14	3	3	5	5	15	0	0	5	5	10
Rhinocort - Emerging ROW	22	17	16	17	21	71	15	20	15	20	70	15	10	15	15	55
Rhinocort - Worldwide	177	39	41	41	46	167	38	35	35	40	150	30	25	30	25	110
Others - U.S.	\$10	\$2	\$1	\$4	\$2	\$9	\$2	\$5	\$0	\$5	\$10	\$0	\$0	\$0	\$5	\$5
Others - E.U. (lc, ex fx)									20	20		15	15	20	20	
Others - E.U.	101	23	22	24	21	90	18	20	20	20	80	15	15	20	20	70
Others - Estab. ROW	23	4	3	2	5	14	3	5	0	5	15	0	0	5	5	10
Others - Emerging ROW	44	13	11	12	11	47	9	10	15	15	50	10	15	15	15	55
Others - Worldwide	178	42	37	42	39	160	32	40	35	45	150	25	30	40	45	140
Eklira												\$60	\$65	\$70	\$75	\$270
PT003 GFF																
Brodalumab																
AZD 2115																
Abediterol																
PT010																
MEDI9929																
AZN9412 (SNG001)																
PT001 GP																
Benralizumab																
Tralokinumab																
Respiratory	\$4,415	\$1,140	\$1,133	\$1,098	\$1,306	\$4,877	\$1,261	\$1,212	\$1,175	\$1,315	\$4,980	\$1,280	\$1,240	\$1,255	\$1,385	\$5,170
% Change	-1%	9%	4%	4%	6%	0%	11%	7%	7%	1%	6%	2%	2%	7%	5%	4%
Arimidex - U.S.	\$21	\$3	\$5	\$4	\$4	\$6	\$5	\$4	\$0	\$0	\$10	\$0	\$0	\$5	\$0	\$5
Arimidex - E.U. (lc, ex fx)									15	15		15	15	10	10	
Arimidex - E.U.	138	25	23	23	22	93	21	20	15	15	70	15	15	10	10	50
Arimidex - Estab. ROW	279	39	40	37	38	154	27	28	25	25	105	20	20	20	20	80
Arimidex - Emerging ROW	105	25	25	26	22	98	25	26	20	20	90	20	20	15	15	70
Arimidex - Worldwide	543	92	83	90	86	351	78	78	60	60	275	55	55	50	45	205
Casodex - U.S.	\$3	\$0	\$1	\$2	\$2	\$5	\$1	\$2	\$0	\$0	\$5	\$0	\$0	\$0	\$0	\$0
Casodex - E.U. (lc, ex fx)									10	10		10	10	5	5	
Casodex - E.U.	60	14	13	13	13	53	11	11	10	10	40	10	10	5	5	30
Casodex - Estab. ROW	301	55	58	55	57	225	43	45	45	45	180	40	40	40	40	160
Casodex - Emerging ROW	96	23	24	23	23	93	28	25	25	25	105	30	25	25	30	110
Casodex - Worldwide	454	92	96	93	95	376	83	83	80	80	325	80	75	70	75	300

Source: Company data, Cowen and Company

AstraZeneca Quarterly Product Line Buildup (\$MM) (continued)

	2012A	Q1:13A	Q2:13A	Q3:13A	Q4:13A	2013A	Q1:14A	Q2:14A	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Zoledex - U.S.	\$24	\$6	\$6	\$6	\$5	\$23	\$6	\$5	\$5	\$0	\$15	\$5	\$5	\$0	\$0	\$10
Zoledex - E.U. (lc, ex fx)									55	55		50	50	50	50	
Zoledex - E.U.	271	66	65	61	60	252	58	59	55	50	220	45	45	50	50	190
Zoledex - Estab. ROW	448	90	96	90	96	372	75	81	80	90	325	70	75	70	80	295
Zoledex - Emerging ROW	350	78	96	89	86	349	82	91	85	80	340	80	90	80	80	330
Zoledex - Worldwide	1,093	240	263	246	247	996	221	236	225	220	900	200	215	200	210	825
Iressa - U.S.	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$5	\$0	\$0	\$0	\$5
Iressa - E.U. (lc, ex fx)									45	50		45	45	50	55	
Iressa - E.U.	155	45	44	43	45	177	43	41	45	50	180	45	45	50	55	195
Iressa - Estab. ROW	222	47	51	51	53	202	50	39	40	60	190	55	45	45	65	210
Iressa - Emerging ROW	234	76	61	71	60	268	76	67	75	65	285	80	70	80	70	300
Iressa - Worldwide	611	168	156	165	158	647	169	147	160	175	650	185	160	175	190	710
Faslodex - U.S.	\$310	\$73	\$81	\$83	\$87	\$324	\$76	\$85	\$85	\$90	\$335	\$80	\$90	\$90	\$95	\$355
Faslodex - E.U. (lc, ex fx)									60	60		65	65	65	65	
Faslodex - E.U.	219	54	55	54	58	221	63	60	60	55	240	60	60	65	65	250
Faslodex - Estab. ROW	62	14	15	16	17	62	15	13	15	20	65	15	15	20	20	70
Faslodex - Emerging ROW	63	16	22	16	20	74	18	21	20	20	80	20	25	20	25	90
Faslodex - Worldwide	654	157	173	169	182	681	172	179	180	185	715	175	190	195	205	765
Caprelsa - U.S.	\$19	\$6	\$5	\$4	\$6	\$21	\$6	\$6	\$10	\$10	\$30	\$10	\$10	\$15	\$15	\$50
Caprelsa - E.U. (lc, ex fx)									5	10		10	10	10	10	
Caprelsa - E.U.	8	4	4	5	5	18	4	6	5	10	25	10	10	10	10	40
Caprelsa - Estab. ROW	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Caprelsa - Emerging ROW	0	0	0	1	1	2	1	1	0	0	0	0	0	0	0	0
Caprelsa - Worldwide	27	10	9	10	12	41	11	13	15	20	60	20	20	25	25	90
Others - U.S.	\$6	\$1	\$1	\$0	\$1	\$3	\$0	\$0	\$0	\$5	\$5	\$0	\$0	\$0	\$5	\$5
Others - E.U. (lc, ex fx)									0	0		0	0	0	5	
Others - E.U.	11	2	3	2	4	11	4	5	0	0	10	0	0	0	5	5
Others - Estab. ROW	63	14	14	14	18	60	9	10	15	15	50	10	10	10	15	45
Others - Emerging ROW	22	2	2	8	5	27	2	8	10	5	30	5	10	10	10	35
Others - Worldwide	107	24	25	24	28	101	20	23	25	25	95	15	20	20	35	90
MEDI 4736																
AZN9291																
Olaparib																
Tremelimumab																
Moxatumomab																
Selumetinib																
AZD 2014																
AZD 5363																
AZD 4547																
MEDI 551																
MEDI 573																
MK-1775																
Volitinib																
Oncology	\$3,489	\$783	\$805	\$797	\$808	\$3,193	\$754	\$759	\$745	\$765	\$3,020	\$740	\$750	\$755	\$815	\$3,080
% Change	-6%	-8%	-10%	-8%	-8%	0%	-4%	-6%	-7%	-5%	-5%	-2%	-1%	7%	1%	

Source: Company data, Cowen and Company

AstraZeneca Quarterly Product Line Buildup (\$MM) (continued)

	2012A	Q1:13A	Q2:13A	Q3:13A	Q4:13A	2013A	Q1:14A	Q2:14A	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Seroquel IR - U.S.	\$697	\$7	\$3	\$2	\$19	\$17	\$7	\$19	\$0	\$0	\$25	\$0	\$0	\$0	\$0	\$0
Seroquel IR - E.U. (lc, ex fx)									15	10		10	10	5	5	5
Seroquel IR - E.U.	235	29	27	25	24	105	24	23	15	10	70	10	10	5	5	30
Seroquel IR - Estab. ROW	202	41	39	28	-2	106	7	14	10	10	40	5	5	5	0	15
Seroquel IR - Emerging ROW	160	50	36	33	32	151	28	33	30	30	120	25	25	25	25	100
Seroquel IR - Worldwide	1,294	127	99	84	35	345	66	89	55	50	260	40	40	35	30	145
Seroquel XR - U.S.	\$811	\$170	\$185	\$194	\$194	\$743	\$166	\$181	\$190	\$190	\$725	\$160	\$175	\$185	\$185	\$705
Seroquel XR - E.U. (lc, ex fx)									80	75		70	70	65	65	65
Seroquel XR - E.U.	500	101	107	104	104	416	93	88	80	70	330	65	65	65	65	260
Seroquel XR - Estab. ROW	97	23	23	14	11	71	9	11	15	20	55	10	10	10	10	40
Seroquel XR - Emerging ROW	101	28	24	27	28	107	24	24	30	30	110	30	30	30	30	120
Seroquel XR - Worldwide	1,509	322	339	339	337	1,337	292	304	315	310	1,220	265	280	290	290	1,125
Local Anesthetics - U.S.	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Local Anesthetics - E.U. (lc, ex fx)									45	45		50	50	45	45	45
Local Anesthetics - E.U.	212	53	52	48	53	206	53	53	45	45	195	45	45	45	45	180
Local Anesthetics - Estab. ROW	206	43	47	43	49	182	40	40	40	40	160	40	40	35	35	150
Local Anesthetics - Emerging ROW	122	29	31	32	30	122	29	34	30	25	120	25	30	30	25	110
Local Anesthetics - Worldwide	540	125	130	123	132	510	122	127	115	110	475	110	115	110	105	440
Zomig - U.S.	\$12	\$2	\$2	\$1	\$2	\$7	\$0	\$3	\$0	\$3	\$0	\$0	\$0	\$0	\$0	\$0
Zomig - E.U. (lc, ex fx)									10	10		10	10	10	10	10
Zomig - E.U. (lc, ex fx)	103	18	18	18	19	73	15	19	10	10	55	10	10	10	10	40
Zomig - Estab. ROW	55	10	10	12	12	44	10	10	5	2	25	5	5	5	5	20
Zomig - Emerging ROW	12	3	3	2	3	11	5	2	5	5	15	5	5	5	5	20
Zomig - Worldwide	182	33	33	33	36	135	30	28	20	20	100	20	20	20	20	80
Diprivan - U.S.	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Diprivan - E.U. (lc, ex fx)									5	5		5	5	5	5	0
Diprivan - E.U.	32	9	7	7	7	30	5	7	5	5	20	5	5	5	0	15
Diprivan - Estab. ROW	78	15	12	13	13	53	15	11	15	15	55	15	15	15	20	65
Diprivan - Emerging ROW	181	45	41	48	45	179	45	50	45	45	185	45	45	45	50	185
Diprivan - Worldwide	291	69	60	68	65	262	65	68	65	65	265	65	65	65	70	265
Others - U.S.	\$16	\$6	\$7	\$9	\$7	\$29	\$5	\$5	\$5	\$5	\$20	\$5	\$5	\$5	\$5	\$20
Others - E.U. (lc, ex fx)									0	5		5	5	5	5	5
Others - E.U.	11	3	3	3	1	10	5	5	0	5	15	5	5	5	5	20
Others - Estab. ROW	1	0	1	0	0	1	0	0	0	5	5	0	0	0	5	5
Others - Emerging ROW	14	2	4	4	5	15	5	5	5	5	20	5	5	5	5	20
Others - Worldwide	42	11	15	16	13	55	15	15	10	20	60	15	15	15	20	65
AZD 3293																
AZD 3241																
AZD 5213																
Neuroscience	\$3,858	\$687	\$676	\$663	\$618	\$2,644	\$590	\$631	\$580	\$575	\$2,380	\$515	\$535	\$535	\$535	\$2,120
% Change	-46%	-51%	-27%	-17%	-16%	0%	-14%	-7%	-13%	-7%	-10%	-13%	-15%	-8%	-7%	-11%

Source: Company data, Cowen and Company

AstraZeneca Quarterly Product Line Buildup (\$MM) (continued)

	2012A	Q1:13A	Q2:13A	Q3:13A	Q4:13A	2013A	Q1:14A	Q2:14A	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Symagis - U.S.	\$611	\$313	\$2	\$6	\$300	\$617	\$266	\$3	\$5	\$300	\$665	\$255	\$5	\$5	\$300	\$665
Symagis - E.U. (lc, ex fx)									125	215		75	35	135	220	
Symagis - E.U.	427	91	13	124	215	443	72	44	125	205	445	70	35	130	220	455
Symagis - Estab. ROW	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Symagis - Emerging ROW	0	0	0	0	0	0	0	0	0	5	5	0	0	0	5	5
Symagis - Worldwide	1,038	404	11	130	515	1,060	328	47	130	510	1,015	325	40	135	525	1,025
Merrem - U.S.	\$38	\$2	\$6	\$5	\$2	\$11	\$4	\$2	\$0	\$5	\$10	\$5	\$0	\$0	\$5	\$10
Merrem - E.U. (lc, ex fx)									10	10		10	10	5	5	
Merrem - E.U.	83	15	12	11	11	49	9	7	10	10	35	10	10	5	5	30
Merrem - Estab. ROW	18	2	1	2	0	5	1	1	0	0	0	5	0	0	0	5
Merrem - Emerging ROW	257	53	62	49	64	228	51	55	50	50	205	45	50	45	45	185
Merrem - Worldwide	396	68	81	67	77	293	65	65	60	65	255	65	60	50	55	230
FluMist/Fluenz - U.S.	\$174	\$5	\$2	\$170	\$22	\$199	\$5	\$6	\$175	\$25	\$210	\$0	\$0	\$180	\$30	\$210
FluMist/Fluenz - E.U. (lc, ex fx)									15	15		0	0	15	15	
FluMist/Fluenz - E.U.	3	0	0	16	26	42	0	0	15	15	30	0	0	15	15	30
FluMist/Fluenz - Estab. ROW	3	0	0	2	2	4	2	0	5	0	5	0	0	5	0	5
FluMist/Fluenz - Emerging ROW	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FluMist/Fluenz - Worldwide	181	5	2	188	50	245	7	5	195	40	245	0	0	200	45	245
Others - U.S.	\$58	\$19	\$7	\$18	\$10	\$54	\$10	\$10	\$15	\$15	\$50	\$10	\$10	\$15	\$15	\$50
Others - E.U. (lc, ex fx)									5	5		0	0	5	5	
Others - E.U.	5	5	0	2	0	7	3	5	5	5	20	0	0	5	5	10
Others - Estab. ROW	16	5	2	1	5	13	5	5	0	5	15	5	5	0	5	15
Others - Emerging ROW	21	11	2	0	1	14	0	5	5	5	15	5	5	5	5	20
Others - Worldwide	100	40	11	21	16	88	18	25	25	30	100	20	20	25	30	95
Vimovo	65	20	24	23	24	91	25	25	30	30	110	30	30	35	35	130
CAZ AVI (CAZ104)						1	0	1	5	3	10	10	10	15	15	50
Zinforo (Ceftaroline)																
Lesinurad																
Mavilimumab																
Anifrolumab																
Sifalimumab																
Tenapanor																
MEDI-2070																
MEDI-7183																
RDEA3170																
AZN4901																
CXL																
Roxadustat																
AZD5847																
Other	\$1,780	\$537	\$129	\$430	\$682	\$1,778	\$448	\$170	\$450	\$685	\$1,755	\$450	\$160	\$460	\$705	\$1,775
% Change	-6%	4%	-33%	13%	-1%	0%	-17%	32%	5%	0%	-1%	0%	-6%	2%	3%	1%
TOTAL PHARMA	\$27,973	\$6,385	\$6,232	\$6,250	\$6,844	\$25,711	\$6,416	\$6,454	\$6,435	\$6,570	\$25,865	\$6,140	\$6,060	\$6,295	\$6,855	\$25,350
% Change	-17%	-13%	-6%	-6%	-6%	0%	0%	4%	3%	-4%	1%	-4%	-6%	-2%	4%	-2%

Source: Company data, Cowen and Company

AstraZeneca Annual Product Line Buildup (\$MM)

	2012A	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CGR 2014-20	CGR 2013-20	Comment
Change in Euro per \$ (as of 9/16/14)												
Nexium - U.S.	\$2,272	\$2,123	\$1,415	\$50	\$40	\$30	\$20	\$10	\$5	-61%	-58%	Assumes generic launch in October 2014
Nexium - EU. (lc, ex fx)												
Nexium - E.U.	447	360	345	240	150	75	50	25	10	-45%	-40%	Available generically in major markets
Nexium - Etab. ROW	476	597	685	725	775	825	875	925	975	6%	7%	Patent expires 7/20/20 in Japan; Japan, Canada, Australia, New Zealand
Nexium - Emerging ROW	749	732	835	870	910	950	990	1030	1070	4%	4%	
Nexium - Worldwide	3,944	3,872	3,275	1,885	1875	1880	1935	1990	2060	-7%	-9%	Generics/OTC products pressure market
Losec - U.S.	\$30	\$30	\$15	\$5	\$5	\$5	\$5	\$5	\$5	-17%	-23%	
Losec - EU. (lc, ex fx)												
Losec - E.U.	191	131	125	90	70	50	30	20	10	-34%	-31%	
Losec - Etab. ROW	316	165	105	80	60	40	20	10	5	-40%	-39%	Japan, Canada, Australia, New Zealand
Losec - Emerging ROW	173	160	155	135	115	100	85	70	55	-16%	-14%	
Losec - Worldwide	710	486	400	310	250	195	140	105	75	-24%	-23%	Off patent in many markets
Other - U.S.	\$144	\$168	\$180	\$185	\$190	\$195	\$200	\$205	\$210	3%	3%	
Other - EU. (lc, ex fx)												
Other - E.U.	44	50	50	50	50	50	50	50	50	0%	0%	
Other - Etab. ROW	6	7	10	15	20	25	30	35	40	26%	28%	Japan, Canada, Australia, New Zealand
Other - Emerging ROW	3	3	5	5	5	5	5	5	5	0%	8%	
Other - Worldwide	197	228	245	255	265	275	285	295	305	4%	4%	Off patent in many markets
Movantik			50	100	150	200	250	300	NM	NM	NM	Naloxegol; oral peripherally-acting opioid antag.; opioid-induced constipation; U.S. launch H1:15, filed E.U.
Axanum	1	3	20	40	60	80	100	120	140	38%	NM	Nexium/low-dose aspirin combination; launched in E.U., withdrawn in U.S., Japan filing H1:13
Gastrointestinal	\$4,852	\$4,589	\$3,940	\$2,540	\$2,550	\$2,580	\$2,680	\$2,780	\$2,880	-5%	-6%	
% Change	-12%	0%	-14%	-36%	0%	1%	3%	4%	4%			
Crestor - U.S.	\$3,164	\$2,912	\$2,970	\$2,875	\$2,675	\$250	\$100	\$50	\$25	-55%	-49%	9.5% market share in U.S. 8/14; patent expiration July 2016 (without pedi exclusivity)
Crestor - EU. (lc, ex fx)												
Crestor - E.U.	1,229	1,225	1,185	1,165	1,175	600	300	150	25	-47%	-43%	Patent expiration June 2017
Crestor - Etab. ROW	1,269	807	640	525	425	325	225	125	50	-35%	-33%	LOE in Canada pressures; Japan, Canada, Australia, New Zealand
Crestor - Emerging ROW	591	678	715	760	800	840	880	920	960	5%	5%	
Crestor - Worldwide	6,253	5,622	5,510	5,325	5,075	2,015	1,505	1,245	1,060	-24%	-21%	
Seloken/Toprol XL - U.S.	\$320	\$131	\$95	\$40	\$20	\$15	\$10	\$5	\$5	-39%	-37%	
Seloken/Toprol XL - E.U. (lc, ex fx)												
Seloken/Toprol XL - E.U.	133	130	120	100	85	70	55	40	25	-23%	-21%	
Seloken/Toprol XL - Etab. ROW	30	24	20	15	10	5	5	5	5	-21%	-20%	Japan, Canada, Australia, New Zealand
Seloken/Toprol XL - Emerging ROW	435	465	495	515	535	555	575	595	615	4%	4%	
Seloken/Toprol XL - Worldwide	918	750	725	670	650	645	645	645	650	-2%	-2%	AZN brand, Par authorized generic, and Watson on market; Sandoz a threat
Atacand - U.S.	\$150	\$72	\$40	\$30	\$20	\$10	\$5	\$5	\$5	-29%	-32%	0.1% market share in U.S. 8/14; U.S. patent expired 6/12
Atacand - EU. (lc, ex fx)												
Atacand - E.U.	461	225	170	90	70	50	30	20	10	-38%	-36%	E.U. patent expired 6/12
Atacand - Etab. ROW	142	71	40	30	20	10	5	5	5	-29%	-32%	Japan, Canada, Australia, New Zealand
Atacand - Emerging ROW	256	243	245	240	220	200	180	160	140	-9%	-8%	
Atacand - Worldwide	1,009	611	495	390	330	270	220	190	160	-17%	-17%	A2 antagonist
Tenormin - U.S.	\$10	\$15	\$5	\$5	\$5	\$5	\$5	\$5	\$5	NM	-15%	
Tenormin - EU. (lc, ex fx)												
Tenormin - E.U.	53	51	45	30	20	10	5	5	5	-31%	-28%	
Tenormin - Etab. ROW	106	77	60	40	20	10	5	5	5	-34%	-32%	Japan, Canada, Australia, New Zealand
Tenormin - Emerging ROW	60	54	45	35	25	15	10	5	5	-31%	-29%	
Tenormin - Worldwide	229	197	150	110	70	40	25	20	20	-29%	-28%	Old beta blocker

Source: Company data, Cowen and Company

AstraZeneca Annual Product Line Buildup (\$MM)

	2012A	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CGR 2014-20	CGR 2013-20	Comment
Zestril - U.S.	\$8	\$8	\$5	\$5	\$5	\$5	\$5	\$5	\$5	0%	-6%	
Zestril - E.U. (lc, ex fx)												
Zestril - E.U.	56	52	40	30	20	10	5	5	5	-29%	-28%	
Zestril - Estab. ROW	10	8	10	10	10	10	10	10	10	0%	3%	Japan, Canada, Australia, New Zealand
Zestril - Emerging ROW	41	38	30	25	20	15	10	5	5	-26%	-25%	
Zestril - Worldwide	115	106	90	70	55	40	30	25	25	-19%	-19%	Old ACE inhibitor
Plendil - U.S.	\$4	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	NM	NM	
Plendil - E.U. (lc, ex fx)												
Plendil - E.U.	24	21	15	10	5	5	5	5	5	-17%	-19%	
Plendil - Estab. ROW	12	10	5	10	10	10	10	10	10	12%	0%	Japan, Canada, Australia, New Zealand
Plendil - Emerging ROW	212	229	230	240	250	260	270	280	290	4%	3%	
Plendil - Worldwide	252	260	245	260	265	275	285	295	305	4%	2%	Old calcium channel blocker
Onglyza - U.S.	\$237	\$265	\$570	\$810	\$900	\$975	\$1,060	\$1,140	\$1,220	14%	24%	1% market share in U.S. 8/14; Komboglyze (Onglyza/metformin combo) launched as QD
Onglyza - E.U. (lc, ex fx)												
Onglyza - E.U.	50	56	180	280	340	385	420	460	500	19%	37%	Komboglyze (Onglyza/metformin combination) launched as BID
Onglyza - Estab. ROW	13	20	60	80	100	120	140	160	180	20%	37%	Japan, Canada, Australia, New Zealand
Onglyza - Emerging ROW	23	32	140	230	300	350	400	450	500	24%	45%	
Onglyza - Worldwide	323	378	950	1,400	1,640	1,830	2,020	2,210	2,400	17%	30%	Saxagliptin; DPP-IV inhib.; SAVOR-TIMI 54 showed no CV benefit
Brilinta - U.S.	\$19	\$73	\$150	\$230	\$300	\$350	\$400	\$450	\$500	22%	32%	Approved in U.S. in July 2011; 2.8% market share in U.S. 8/14
Brilinta - E.U. (lc, ex fx)												
Brilinta - E.U.	57	163	225	260	310	350	390	430	470	13%	16%	Approved in E.U. December 2010; launched in H2:11
Brilinta - Estab. ROW	3	17	35	60	80	100	120	140	160	29%	38%	Japan, Canada, Australia, New Zealand
Brilinta - Emerging ROW	10	30	60	80	100	120	140	160	180	20%	NM	
Brilinta - Worldwide	89	283	465	630	790	920	1,050	1,180	1,310	19%	24%	Reversible ADP rec. antagonist; oral; arterial thrombosis; PEGASUS-TIMI 54 (ACS), EUCLID (PAD) underway
Bydureon - U.S.	\$37	\$131	\$395	\$680	\$850	\$950	\$1,050	\$1,150	\$1,200	20%	37%	Once-weekly GLP1; dual chamber pen device launch in H2:14 0.5% share 8/14
Bydureon - E.U. (lc, ex fx)												
Bydureon - E.U.	17	70	200	400	600	800	1,000	1,200	1,600	61%	NM	
Bydureon - Estab. ROW	1	15	30	40	50	60	70	80	80	NM	NM	Japan, Canada, Australia, New Zealand
Bydureon - Emerging ROW	2	10	30	40	50	60	70	80	80	NM	NM	
Bydureon - Worldwide	37	151	485	940	1,330	1,650	1,970	2,290	2,560	32%	NM	Synthetic exendin-4; BMY's 50% stake acquired Q1:14
Byetta - U.S.	\$74	\$152	\$215	\$240	\$260	\$280	\$300	\$320	\$340	8%	NM	Twice daily GLP1; 0.4% share 8/14
Byetta - E.U. (lc, ex fx)												
Byetta - E.U.	36	90	130	160	190	220	250	280	280	21%	NM	
Byetta - Estab. ROW	11	20	30	40	50	60	70	80	80	NM	NM	Japan, Canada, Australia, New Zealand
Byetta - Emerging ROW	2	20	30	40	50	60	70	80	80	NM	NM	
Byetta - Worldwide	74	206	345	430	500	570	640	710	780	15%	NM	Synthetic exendin-4; BMY's 50% stake acquired Q1:14
Others - U.S.	\$17	\$44	\$55	\$80	\$100	\$120	\$140	\$160	\$180	22%	NM	
Others - E.U. (lc, ex fx)												
Others - E.U.	112	109	100	90	80	70	60	50	40	-14%	-13%	
Others - Estab. ROW	22	14	20	10	5	5	5	5	5	-21%	-14%	Japan, Canada, Australia, New Zealand
Others - Emerging ROW	81	14	20	20	20	20	20	20	20	0%	5%	
Others - Worldwide	232	181	195	200	205	215	225	235	245	4%	4%	
Forxiga	10	55	130	200	300	400	500	600	490	NM	Dapagliflozin; SGLT2 inhibitor; diabetes; approved in E.U. and U.S.	
Epanova		15	90	150	200	250	300	350	350	NM	NM	Hypertriglyceridemia; omega-3 free fatty acid composition; approved; Omthera acquired 7/8/13
Metreleptin		20	40	60	80	100	120	140	140	NM	NM	Lipodystrophy
Symtlin	75	80	90	100	110	120	130	140	140	10%	NM	Pramlintide
Cardiovascular	\$9,531	\$8,830	\$9,810	\$10,685	\$11,270	\$8,980	\$9,235	\$8,795	\$10,395	1%	2%	
% Change	-7%	0%	11%	9%	5%	-20%	3%	6%	6%			

Source: Company data, Cowen and Company

AstraZeneca Annual Product Line Buildup (\$MM) (continued)

	2012A	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CGR	CGR	Comment
										2014-20	2013-20	
Symbicort - U.S.	\$1,003	\$1,233	\$1,485	\$1,545	\$1,400	\$1,200	\$1,000	\$800	\$600	-14%	-10%	32.3% market share in U.S. 8/14; Teva generic filing 2014; BE guidelines another risk
Symbicort - E.U. (lc, ex fx)												
Symbicort - E.U.	1,465	1,502	1,470	1,385	1,200	1,000	800	600	400	-20%	-17%	Teva generic filing 2013
Symbicort - Estab. ROW	443	423	450	470	490	510	530	550	570	4%	4%	Japan, Canada, Australia, New Zealand
Symbicort - Emerging ROW	283	325	360	400	425	450	475	500	525	6%	7%	
Symbicort - Worldwide	3,194	3,483	3,770	3,800	3,515	3,160	2,805	2,450	2,095	-9%	-7%	
Pulmicort - U.S.	\$233	\$224	\$205	\$170	\$140	\$110	\$80	\$50	\$20	-32%	-29%	Respules for nebulizer (infants) patent ruled invalid, TRO issued, appeal argument heard 8/13
Pulmicort - E.U. (lc, ex fx)												
Pulmicort - E.U.	191	171	155	125	80	60	40	20	10	-37%	-33%	
Pulmicort - Estab. ROW	127	112	100	90	80	70	60	50	40	-14%	-14%	Japan, Canada, Australia, New Zealand
Pulmicort - Emerging ROW	315	360	430	465	500	535	570	600	635	7%	8%	
Pulmicort - Worldwide	866	867	890	850	800	775	750	720	705	-4%	-3%	
Rhinocort - U.S.	\$55	\$52	\$35	\$30	\$20	\$15	\$10	\$5	\$5	-28%	-28%	
Rhinocort - E.U. (lc, ex fx)												
Rhinocort - E.U.	28	30	30	15	10	5	5	5	5	-26%	-23%	
Rhinocort - Estab. ROW	17	14	15	10	5	5	5	5	5	-17%	-14%	Japan, Canada, Australia, New Zealand
Rhinocort - Emerging ROW	22	21	20	55	45	35	25	15	5	-36%	-32%	
Rhinocort - Worldwide	177	167	150	110	80	60	45	30	20	-29%	-26%	Nasal steroid
Others - U.S.	\$10	\$9	\$10	\$5	\$5	\$5	\$5	\$5	\$5	-11%	-8%	
Others - E.U. (lc, ex fx)												
Others - E.U.	101	90	80	70	60	50	40	30	20	-21%	-19%	
Others - Estab. ROW	23	14	15	10	10	10	10	10	10	-7%	-5%	Japan, Canada, Australia, New Zealand
Others - Emerging ROW	44	47	50	55	60	65	70	75	80	8%	8%	
Others - Worldwide	178	160	150	140	135	130	125	120	115	-4%	-5%	Accolate, Oxis (OUS)
Eklira			\$270	\$350	\$400	\$450	\$500	\$550	NM	NM	NM	Acidinium (LAMA); LAS40464 (LAMA/LABA in 2015); via Almirall resp acq for \$875MM and \$1.22B in milestones
PT003 GFF				50	100	200	300	400	NM	NM	NM	LABA/LAMA, formoterol/glycopyrrolate; COPD; filing 2015 (US), 2016 (EU); Pearl acquired 6/27/13
Brodalumab				50	75	100	125	150	NM	NM	NM	Anti-IL17R MAb; psoriasis Phase III, NDA 2015; PA Phase III, asthma Phase II
AZD 2115					25	50	75	100	NM	NM	NM	MABA (LABA/LAMA), linker key; COPD; Phase II; combo with AZN 5423 for triple combo; 2nd cmpd via Almirall
Abediterol					25	50	75	100	NM	NM	NM	QD LABA; via Almirall
PT010					25	50	75	100	NM	NM	NM	LABA/LAMA/ICS, COPD; Phase II
MEDI9929					25	50	75	100	NM	NM	NM	Anti-TSLP MAb, asthma; Phase II
AZN9412 (SNG001)					25	50	75	100	NM	NM	NM	Inhaled interferon beta, asthma/COPD; Phase II
PT001 GP					25	50	75	100	NM	NM	NM	LAMA; COPD; Phase III; NDA 2015 (US), 2016 (EU)
Benralizumab					25	50	75	100	NM	NM	NM	Anti-IL-5R MAb; severe asthma Phase III, NDA 2016 US and EU; COPD Phase III, NDA 2018 US and EU
Tratokinumab					25	50	75	100	NM	NM	NM	Anti-IL-13 antibody; severe asthma, IPF, UC; Phase II; asthma PIII to initiate Q3:14
Respiratory	\$4,415	\$4,677	\$4,980	\$5,170	\$4,980	\$4,800	\$4,875	\$4,845	\$4,835	0%	0%	
% Change	-1%	0%	6%	4%	-4%	-2%	-1%	-1%	0%	0%	0%	
Arimidex - U.S.	\$21	\$6	\$10	\$5	\$5	\$5	\$5	\$5	\$5	-11%	-3%	Generics launched 6/10
Arimidex - E.U. (lc, ex fx)												
Arimidex - E.U.	138	93	70	50	40	30	20	10	5	-36%	-34%	Patent expired 8/10 but exclusivity extended until 2/11
Arimidex - Estab. ROW	279	154	105	80	60	40	20	10	5	-40%	-39%	Japan, Canada, Australia, New Zealand
Arimidex - Emerging ROW	105	98	90	70	50	35	20	5	5	-38%	-35%	
Arimidex - Worldwide	543	351	275	205	155	110	65	30	20	-35%	-34%	Aromatase inhibitor (AI); breast cancer
Casodex - U.S.	\$3	\$5	\$5	\$0	\$0	\$0	\$0	\$0	\$0	NM	NM	Patent expired 10/08
Casodex - E.U. (lc, ex fx)												
Casodex - E.U.	60	53	40	30	20	10	5	5	5	-29%	-29%	
Casodex - Estab. ROW	301	225	180	160	140	120	100	75	50	-19%	-19%	Japan, Canada, Australia, New Zealand
Casodex - Emerging ROW	96	93	105	110	115	120	125	130	135	4%	5%	
Casodex - Worldwide	454	376	325	300	275	250	230	210	190	-9%	-9%	Non-steroidal anti-androgen; prostate cancer

Source: Company data, Cowen and Company

AstraZeneca Annual Product Line Buildup (\$MM) (continued)

	2012A	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CGR 2014-20	CGR 2013-20	Comment		
Zoledex - U.S.	\$24	\$23	\$15	\$10	\$5	\$5	\$5	\$5	\$5	-17%	-20%			
Zoledex - E.U. (lc, ex fx)														
Zoledex - E.U.	271	252	220	190	170	140	110	80	50	-22%	-21%			
Zoledex - Estab. ROW	448	372	325	295	255	215	175	135	100	-18%	-17%	Japan, Canada, Australia, New Zealand		
Zoledex - Emerging ROW	350	249	340	330	320	310	300	290	280	-3%	-3%			
Zoledex - Worldwide	1,093	996	900	825	750	670	590	510	435	-11%	-11%	LHRH agonist; prostate cancer, gyn/fertility disorders; 70% of use is 3 month release where no generics; no generics for one month depot		
Iressa - U.S.	\$0	\$0	\$0	\$5	\$5	\$5	\$5	\$5	\$5	NM	NM			
Iressa - E.U. (lc, ex fx)														
Iressa - E.U.	155	177	180	195	210	225	240	255	270	7%	6%	E.U. rollout underway		
Iressa - Estab. ROW	222	202	190	210	230	250	270	290	310	9%	6%	Japan, Canada, Australia, New Zealand		
Iressa - Emerging ROW	234	268	285	300	315	330	345	360	375	5%	5%			
Iressa - Worldwide	611	647	650	710	760	810	860	910	960	7%	6%	EGFR positive NSCLC		
Faslodex - U.S.	\$310	\$324	\$335	\$355	\$375	\$395	\$415	\$435	\$455	5%	5%			
Faslodex - E.U. (lc, ex fx)														
Faslodex - E.U.	219	221	240	250	260	270	280	290	300	4%	4%	E.U. rollout underway		
Faslodex - Estab. ROW	62	62	65	70	75	80	85	90	95	7%	6%	Japan, Canada, Australia, New Zealand		
Faslodex - Emerging ROW	63	74	80	90	100	110	120	130	140	10%	10%			
Faslodex - Worldwide	654	681	715	765	810	855	900	945	990	6%	5%	EGFR positive NSCLC		
Caprelsa - U.S.	\$19	\$21	\$30	\$50	\$70	\$90	\$110	\$130	\$150	31%	32%	Phase III in differentiated thyroid cancer; 20 investigator-sponsored trials underway		
Caprelsa - E.U. (lc, ex fx)														
Caprelsa - E.U.	8	18	25	40	60	80	100	120	140	33%	34%			
Caprelsa - Estab. ROW	0	0	0	0	0	0	0	0	0	NM	NM	Japan (Q3:14 filing), Canada, Australia, New Zealand		
Caprelsa - Emerging ROW	1	2	1	1	1	1	1	1	1	NM	NM			
Caprelsa - Worldwide	27	41	60	90	130	170	210	250	290	30%	NM	Vandetanib; dual RTK inhibitor (VEGF/EGFR); approved for medullary thyroid cancer		
Others - U.S.	\$6	\$3	\$5	\$5	\$5	\$5	\$5	\$5	\$5	0%	8%			
Others - E.U. (lc, ex fx)														
Others - E.U.	11	11	10	5	5	5	5	5	5	-11%	-11%			
Others - Estab. ROW	63	60	50	45	40	35	30	25	20	-14%	-15%	Japan, Canada, Australia, New Zealand		
Others - Emerging ROW	27	22	30	35	40	45	50	55	60	12%	12%			
Others - Worldwide	107	101	95	90	90	90	90	90	90	-1%	-2%	Faslodex, Novadex, Tomudex		
MEDI 4736							100	300	600	NM	NM	PD-L1; 3rd line NSCLC NDA 2016 (US), 2017 (EU, J); stage 3 NSCLC NDA 2017 (US), 2020 (EU, J)		
AZN9291							50	100	200	400	600	NM	EGFRm+; Phase III T790M+ NSCLC, US, EU, J filing H2:15 but could be Q1:16; solid tumors in Phase I	
Olaparib							50	100	200	300	400	500	NM	Oral PARP-BRCA; ovarian CHMP decision Q4:14, priority review in U.S., PDUFA 1/3/15; gastric, breast Phase III
Tremelimumab							50	100	200	400	400	NM	Anti-CTLA4 Mab; mesothelioma, combo with PD-L1; Phase III; NDA 2017 (US, EU, J)	
Moxetumomab							25	50	75	100	125	150	NM	CD22 recombinant immunotoxin; hairy cell leukemia Phase III; NDA 2018
Selumetinib							50	75	100	125	125	NM	MEK inhib, shorter t1/2; 2nd line NSCLC, diff. thyroid (NDA 2017), melanoma (NDA 2015), other solid tumors	
AZD 2014							25	50	75	100	100	NM	mTOR; solid tumors; Phase II	
AZD 5363							25	50	75	100	100	NM	AKT kinase inhibitor; breast cancer; Phase II	
AZD 4547							25	50	75	100	100	NM	FGFR tyrosine kinase inhibitor; gastric, breast, NSCLC; Phase II	
MEDI 551							25	50	75	100	100	NM	Anti-CD19 Mab; CLL, DLBCL; Phase II; head-to-head vs rituxan data in 2014	
MEDI 573							25	50	75	100	100	NM	Anti-IGF MAb; metastatic breast cancer; Phase II	
MK-1775							25	50	75	100	100	NM	WEE1 kinase; oral small molecule; ovarian; Phase II	
Volitinib							25	50	75	100	100	NM	Papillary renal cell carcinoma; Phase II	
Oncology	\$3,489	\$3,193	\$3,020	\$3,080	\$3,170	\$3,605	\$4,170	\$4,985	\$6,050	12%	10%			
% Change	-6%	0%	-5%	1%	4%	14%	16%	20%	21%					

Source: Company data, Cowen and Company

AstraZeneca Annual Product Line Buildup (\$MM) (continued)

	2012A	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CGR 2014-20	CGR 2013-20	Comment	
Seroquel IR - U.S.	\$697	\$17	\$25	\$0	\$0	\$0	\$0	\$0	\$0	NM	NM	Substance patent expired 3/12 (with pedi exclusivity)	
Seroquel IR - E.U. (lc, ex fx)													
Seroquel IR - E.U.	235	105	70	30	15	10	5	5	5	-36%	-35%	Patent expired 3/12	
Seroquel IR - Estab. ROW	202	106	40	15	10	5	5	5	5	-29%	-35%	Japan, Canada, Australia, New Zealand	
Seroquel IR - Emerging ROW	160	151	120	100	80	60	40	20	10	-34%	-32%		
Seroquel IR - Worldwide	1,294	345	260	145	105	75	50	30	20	-35%	-33%		
Seroquel XR - U.S.	\$811	\$743	\$725	\$705	\$685	\$300	\$50	\$25	\$5	-56%	-51%	4.2% share for SR in the U.S. 8/14; patent expires 2017	
Seroquel XR - E.U. (lc, ex fx)													
Seroquel XR - E.U.	500	416	330	260	225	175	125	75	25	-35%	-33%	Patent expires 2017	
Seroquel XR - Estab. ROW	97	71	55	40	30	20	15	10	5	-33%	-32%	Japan, Canada, Australia, New Zealand	
Seroquel XR - Emerging ROW	101	107	110	120	130	140	150	160	170	8%	7%		
Seroquel XR - Worldwide	1,509	1,337	1,220	1,125	1,070	635	340	270	205	-26%	-24%		
Local Anesthetics - U.S.	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	NM	NM		
Local Anesthetics - E.U. (lc, ex fx)													
Local Anesthetics - E.U.	212	206	195	180	165	150	135	120	105	-10%	-9%		
Local Anesthetics - Estab. ROW	206	182	160	150	140	130	120	110	100	-8%	-8%	Japan, Canada, Australia, New Zealand	
Local Anesthetics - Emerging ROW	122	122	120	110	100	90	80	70	60	-11%	-10%		
Local Anesthetics - Worldwide	540	510	475	440	405	370	335	300	265	-9%	-9%	Xylocaine + Marcaine in E.U.; Abraxis records sales in U.S.	
Zomig - U.S.	\$12	\$7	\$0	\$0	\$0	\$0	\$0	\$0	\$0	NM	NM	1% market share in the U.S. 8/14; patent exp 5/13	
Zomig - E.U. (lc, ex fx)													
Zomig - E.U. (lc, ex fx)	103	73	55	40	30	20	10	5	5	-33%	-32%		
Zomig - Estab. ROW	55	44	25	20	10	5	5	5	5	-24%	-27%	Japan, Canada, Australia, New Zealand	
Zomig - Emerging ROW	12	11	15	20	20	20	20	20	20	5%	9%		
Zomig - Worldwide	182	135	100	80	60	45	35	30	30	-18%	-19%	Undifferentiated triptan for migraine	
Diprivan - U.S.	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	NM	NM	Abraxis records sales in U.S.	
Diprivan - E.U. (lc, ex fx)													
Diprivan - E.U.	32	30	20	15	10	5	5	5	5	-21%	-23%		
Diprivan - Estab. ROW	78	53	55	65	70	75	80	85	90	9%	8%	Japan, Canada, Australia, New Zealand	
Diprivan - Emerging ROW	181	179	185	185	190	195	200	205	210	2%	2%		
Diprivan - Worldwide	291	262	265	265	270	275	285	295	305	2%	2%		
Others - U.S.	\$16	\$29	\$20	\$20	\$20	\$20	\$20	\$20	\$5	-21%	-22%		
Others - E.U. (lc, ex fx)													
Others - E.U.	11	10	15	20	25	30	35	40	45	20%	24%		
Others - Estab. ROW	1	1	5	5	5	5	5	5	5	0%	26%	Japan, Canada, Australia, New Zealand	
Others - Emerging ROW	14	15	20	20	20	20	20	20	20	0%	4%		
Others - Worldwide	42	55	60	65	70	75	80	85	75	4%	5%		
AZD 3293								100	200	NM	NM	BACE inhibitor; Alzheimer's disease; Phase III in 2014; collaboration with LLY	
AZD 3241								25	75	NM	NM	Myeloperoxidase (MPO) inhibitor; multiple system atrophy; Phase II	
AZD 5213								25	50	75	100	NM	Histamine 3 receptor antagonist; Tourette's/neuropathic pain; Phase II
Neuroscience	\$3,858	\$2,844	\$2,380	\$2,120	\$1,980	\$1,525	\$1,225	\$1,280	\$1,300	-10%	-10%		
% Change	-46%	0%	-10%	-11%	-7%	-23%	-20%	3%	3%				

Source: Company data, Cowen and Company

AstraZeneca Annual Product Line Buildup (\$MM) (continued)

	2012A	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CGR 2014-20	CGR 2013-20	Comment
Synagis - U.S.	\$611	\$617	\$565	\$565	\$565	\$565	\$565	\$565	\$565	0%	-1%	
Synagis - E.U. (lc, ex fx)												
Synagis - E.U.	427	443	445	455	465	475	485	495	505	2%	2%	
Synagis - Estab. ROW	0	0	0	0	0	0	0	0	NM	NM		Japan, Canada, Australia, New Zealand
Synagis - Emerging ROW	0	0	5	5	5	5	5	5	5	0%	NM	
Synagis - Worldwide	1,038	1,060	1,015	1,025	1,035	1,045	1,055	1,065	1,075	1%	0%	Humanized Mab binds to F-protein of RSV
Merrem - U.S.	\$38	\$11	\$10	\$10	\$5	\$5	\$5	\$5	\$5	-11%	-11%	
Merrem - E.U. (lc, ex fx)												
Merrem - E.U.	83	49	35	30	20	10	5	5	5	-28%	-28%	
Merrem - Estab. ROW	18	5	0	5	5	5	5	5	NM	0%		Japan, Canada, Australia, New Zealand
Merrem - Emerging ROW	257	228	205	185	165	145	125	105	85	-14%	-13%	
Merrem - Worldwide	396	293	255	230	195	165	140	120	100	-14%	-14%	Carbopenem antibiotic; patent expired 9/09 in E.U., 6/10 in U.S.
FluMist/Fluenz - U.S.	\$174	\$199	\$210	\$210	\$220	\$230	\$240	\$250	\$260	4%	4%	
FluMist/Fluenz - E.U. (lc, ex fx)												
FluMist/Fluenz - E.U.	3	42	30	30	30	30	30	30	30	NM	NM	
FluMist/Fluenz - Estab. ROW	3	4	5	5	5	5	5	5	5	NM	NM	
FluMist/Fluenz - Emerging ROW	1	0	0	0	0	0	0	0	0	NM	NM	
FluMist/Fluenz - Worldwide	181	245	245	245	255	265	275	285	295	3%	3%	Intranasal influenza vaccine for healthy patients age 2-49 years
Others - U.S.	\$58	\$54	\$50	\$50	\$50	\$50	\$50	\$50	\$50	0%	-1%	
Others - E.U. (lc, ex fx)												
Others - E.U.	5	7	20	10	10	10	10	10	10	-11%	5%	
Others - Estab. ROW	16	13	15	15	15	15	15	15	15	0%	2%	Japan, Canada, Australia, New Zealand
Others - Emerging ROW	21	14	15	20	20	20	20	20	20	5%	5%	
Others - Worldwide	100	88	100	95	95	95	95	95	95	-1%	1%	
Vimovo	65	91	110	130	150	170	190	210	230	13%	NM	Naproxen + esomeprazole; OA, RA and AS symptoms; OUS only, divested U.S. rights; with Pozen
CAZ AVI (CAZ104)					50	75	100	125	150	NM	NM	Beta lactamase inhibitor/cephalosporin; serious infections; Phase III; NDA Q4:14 in E.U., 2015 Japan, EM; not in U.S.; hosp acquired pneumonia NDA 2017
Zinforo (Ceftazidime)	1	30	50	70	90	110	130	150	150	31%	NM	Extended spectrum cephalosporin; pneumonia/skin infectious; approved in E.U.; filed in China
Lesinurad					25	50	75	100	125	NM	NM	URAT1; chronic tx of patients with gout; NDA Q4:14 in U.S. and E.U.
Mavilimumab					25	50	75	100	100	NM	NM	Anti-GM-CSFR MAb; rheumatoid arthritis; Phase III in 2014
Aniflumab					25	50	75	100	100	NM	NM	MEDI-546; anti-IFN-alphaR MAb; systemic lupus erythematosus; Phase II
Sifalimumab					25	50	75	100	100	NM	NM	Anti-IFN-alpha MAb; systemic lupus erythematosus; Phase II
Tenapanor					25	50	75	100	100	NM	NM	NHE3 inhibitor; complications of ESRD-Pi and CKD with T2DM; Phase II; from Ardelyx
MEDI-2070					25	50	75	100	100	NM	NM	IL-23 MAb; Crohn's disease, Phase II
MEDI-7183					25	50	75	100	100	NM	NM	Anti-A4b7 Mab; Crohn's disease, ulcerative colitis; Phase II
RDEA3170					25	50	75	100	100	NM	NM	URAT1; chronic mgmt of hyperuricemia in gout; Phase II
AZN4901					25	50	75	100	100	NM	NM	Hormone modulator; polycystic ovarian syndrome; Phase II
CXL					25	50	75	100	100	NM	NM	Beta lactamase inhib/cephalosporin; MRSA; Phase II; partnered
Roxadustat							25	50	50	NM	NM	AZD9941; inhibits hypoxia-induced factor; anemia in CKD/ESRD; NDA US (2018), China
AZD5847							20	30	40	NM	NM	Oxazolinone antibacterial inhibitor; tuberculosis; Phase II
Other	\$1,780	\$1,778	\$1,755	\$1,775	\$1,875	\$2,190	\$2,510	\$2,860	\$3,210	11%	9%	
% Change	-6%	0%	-1%	1%	6%	17%	15%	14%	12%			
TOTAL PHARMA	\$27,973	\$25,711	\$25,865	\$25,350	\$25,825	\$23,760	\$24,675	\$26,515	\$28,670	2%	2%	
% Change	-17%	0%	1%	-2%	2%	-8%	4%	7%	8%			

Source: Company data, Cowen and Company

Oncology

Oncology Pipeline Well Balanced Between Small Molecules And Biologics

AZN's current pipeline includes: Phase I – 10 NMEs; Phase II – 7NMEs; and Phase III/Reg – 6 NMEs. In 2015, it expects 9 NMEs in Phase III/Registration. AZN is well positioned to combine agents within and between specific mechanisms given that its portfolio includes four key MOAs: Tumor drivers/resistance (FGFR, MEK, AZD9291, Pi3K, C-Met, others), DNA damage response (olaparib, Wee-1, ATR), ADCs (moxetumomab, others), and IO (PD-L1, Treme, OX40, PD-1, others). AZN believes combos are key. It is currently evaluating a PD-L1 plus PD-1 combo because it anticipates synergistic activity/clinical benefit to be gained by completely blocking the PD-1 pathway. AZN is also looking at PD-L1 + CTLA4, PD-L1 + OX40, and PD-L1 plus small molecules (AZD9291, Iressa, BRAF/MEK). A summary of Astra's oncology portfolio is below:

Summary Of Oncology Portfolio

Phase I		Phase II		Phase III	
Small Molecule	Large Molecule	Small Molecule	Large Molecule	Small Molecule	Large Molecule
AZD1208 (PIM)	MEDI-565 (CEA BITE)	AZD4547 (FGFR)	MEDI-551 (CD19)	olaparib (PARP)	moxetumomab (CD22)
AZD8186 (PI3)	MEDI0639 (DLL-4)	AZD2014 (TOR)	MEDI-573 (IGF)	AZD9291(EGFR)	MEDI4736 (PD-L1)
AZD9150 (STAT3)	MEDI3617 (ANG2)	AZD5363 (AKT)		selumetinib (MEK)	tremelimumab (CTLA-4)
AZD6738 (ATR)	MEDI6469 (mOX40)	volitinib (MET)			
AZD5312 (androgen)	MEDI0680 (PD-1)	AZD1775 (Wee 1)			

Source: Company data

Emerging Anti-PD-L1 Data Continues To Encourage

MEDI4736 is an anti-PD-L1 mAb in Phase I studies across a variety of solid tumors with multiple Phase I to Phase III opportunities. The drug appears well tolerated and has demonstrated tumor regression during the dose escalation phase. A monotherapy trial (PACIFIC) in NSCLC (as sequential therapy following chemoradiation in patients with locally advanced, unresectable NSCLC) started in May 2014 and a Phase III trial in combination with tremelimumab in NSCLC was expected to start in Q4:14. In May 2014, Astra entered into a non-exclusive collaboration with Incyte to evaluate MEDI4736 with Incyte's IDO1 inhibitor (INCB24360) in multiple solid tumors including melanoma, NSCLC, SCCHN, and pancreatic cancer. MEDI4736 is also in combo studies with Iressa, MEDI0680 (anti-PD-1), AZD9291 (Phase IIb started Q3:14) and others. We estimate MEDI4736 sales of \$100MM in 2018 and \$600MM in 2020.

At ASCO 2014, data of MEDI4736 (PD-1) was presented which demonstrated clinical activity and tolerability across a range of tumor types in analyses looking at dose-escalation, dose expansion, and pharmacokinetics. In a Phase I study of 27 patients with NSCLC, melanoma, CRC and RCC, a reduction of tumor burden was seen at multiple doses in as early as six weeks, and activity was maintained for at least one year, with 19% of patients achieving a partial response and 39% of patients achieving disease control. Serious adverse events were infrequent, and no dose-limiting toxicities were observed. Dose-dependent PK was seen with MEDI4736. The waterfall plots of MEDI4736 did not look as impressive as that with other agents, but likely is due to inclusion of tumor types for which immune-based therapies may or may not be useful.

At ESMO 2014, preliminary data from a Phase I expansion study reported an ORR of 10% across 8 tumor types at 10mg/kg q2weeks. Approximately 4-fold higher ORR was reported in PD-L1+ patients compared to PD-L1- patients. Responses are continuing in 88% of patients.

Pivotal Trials In Head & Neck Cancer To Be Initiated

In addition, results from a Phase I study in Head and Neck (H&N) cancer were presented which demonstrated at a 10mg/kg dose, a 12 week ORR of 14%, with 50% in PD-L1+ patients and 6% in PD-L1-. At ESMO, data from a study in 53 patients (both PD-L1 + and -) reported a DCR at 12 weeks of 28% and ORR of 11%. All 6 responses are ongoing. 53% of patients had drug-related AE's; 7% were Grade 3 or greater, but none were pulmonary. Astra plans to initiate Phase III pivotal trials for MEDI4736 as monotherapy and in combination with tremelimumab in H&N cancer in 2014.

Data In NSCLC Encouraging

At ESMO 2014, Astra presented data which showed a 16% ORR at 12 weeks in 162 patients having both squamous and non-squamous histology. An ORR of 25% was reported in PD-L1+ patients and 10% in PD-L1- patients. Responses are ongoing in 88% of patients with duration of 0.1-32.4 weeks.

Also presented were results from a Phase I trial of MEDI4736 plus tremelumab which showed the combo was administered safely at full monotherapy doses of MEDI4736. 75% of AE's were low grade. A 30% ORR was reported in a PD-L1- cohort.

Collaboration With Advaxis

In July 2014, Astra announced a collaboration with Advaxis to evaluate MEDI4736 + ADXS-HPV, Advaxis' lead cancer immunotherapy vaccine, as treatment for advanced, recurrent, or refractory HPV-associated cervical cancer and HPV-associated squamous cell carcinoma of the head and neck. Pre-clinical work has suggested that ADX-HPV combined with a checkpoint inhibitor can enhance anti-tumor response. The Phase I (dose) and Phase II (safety) portions of the trial will be funded and conducted by Advaxis. Results will inform further efforts. The collaboration is non-exclusive for HPV-driven tumors, with Astra having first right of negotiation for future development combos involving MEDI4736.

Collaboration With Kyowa Hakko Kirin

Announced in July 2014, the collaboration will evaluate MEDI4736 + mogamulizumab (anti-CCR4) and also mogamulizumab + tremelimumab. The studies will be co-funded and Kyowa will conduct the trials.

Olaparib Approved For Ovarian Cancer In E.U., But Nixed By AdCom Panel

Olaparib (AZD2281) is an oral inhibitor of the enzyme poly-ADP-ribose polymerase (PARP). Patients with BRCA1/2 mutations may be genetically predisposed to developing some forms of cancer, and are often resistant to other forms of cancer treatment, but this also sometimes gives their cancers a unique vulnerability, as the cancer cells have increased reliance on PARP to repair their DNA and enable them to continue dividing. Drugs that selectively inhibit PARP may be of significant benefit in patients whose cancers are susceptible to this treatment.

In September 2013, olaparib was approved in the EU for the maintenance treatment of patients with BRCA mutated platinum-sensitive relapsed serious ovarian cancer.

In May 2014, the FDA granted olaparib Priority Review for monotherapy maintenance treatment in platinum-sensitive relapsed ovarian cancer. However, in June 2014, an FDA Adcom panel voted down an accelerated approval, preferring to wait for full data from the Phase III SOLO-2 trials. The Phase III SOLO trials were initiated in September 2013 with PFS as the primary endpoint. SOLO-2 is evaluating olaparib as maintenance monotherapy in BRCA mutated ovarian cancer patients who are in complete or partial remission following platinum-based chemo; SOLO-1 looks at the same population but in the first line setting. Data for SOLO-1 is expected H1:17 and H1:16 for SOLO-2. Astra submitted an amendment to the NDA in July, and the PDUFA data was subsequently extended from October 3rd to January 3rd, 2015 to allow time to review this data.

We estimate olaparib sales of \$50MM in 2015, \$100MM in 2016, \$300MM in 2018, and \$500MM in 2020.

Olaparib Accelerated Approval Voted Down 11-2 By AdCom Panel

In late June 2014, an FDA Adcom meeting was held to discuss the proposed accelerated approval for olaparib as monotherapy maintenance treatment in platinum-sensitive relapsed ovarian cancer. By a vote of 11-2, the panel voted against accelerated approval citing concerns surrounding the reliability of data from the small study, side effects (both frequency of less severe ones as well as potential for a few rare blood toxicities), lack of support for PFS as endpoint in maintenance setting by some panel members, and concerns that early approval may hinder finalization/reliability of ongoing confirmatory study.

Data presented (Study 19) represented a subgroup analysis of 96 patients with gBRCAm platinum-sensitive ovarian cancer. PFS for the olaparib arm was 11.2 months versus 4.1 months for placebo. There was no significant difference in OS. On SEs, grade 1-2 events were frequent (nausea, fatigue, abdominal pain), but grade 3-4 SEs were rare, although concerns for the possible risk of blood cancers AML and MDS (<1%) were discussed.

Phase II Data In Ovarian Cancer Encouraging

Results from a Phase II trial comparing olaparib maintenance therapy to placebo in 256 women with platinum-sensitive, relapsed ovarian cancer were presented at ASCO 2011. Olaparib met the primary PFS endpoint when compared to placebo (8.4 months for olaparib vs. 4.8 months for placebo, HR=0.35, p<0.00001). Differences in PFS were maintained across all pre-defined subgroups (age, performance status, BRCA mutation status) and were consistent whether measured by CA-125 or RECIST criteria. 12.3% of the olaparib group exhibited a PR compared to 4.2% of patients on placebo. No differences were observed between treatment groups in end-of-study quality of life (QoL) scores or in time to worsening of QoL scores. OS data were too premature for analysis at the time of the presentation. The most frequently reported ADRs that were reported in greater frequency for olaparib compared to placebo were nausea, fatigue, vomiting, and anemia. The majority of ADRs were grade 1 and 2. 23% of olaparib patients required a dose reduction compared to 7% of patients on placebo.

Olaparib+Cediranib Combo Also Demonstrates Positive Data In Ovarian Cancer

At ASCO 2014, Astra reported positive data from a Phase II study (conducted by NCI) of olaparib + cediranib (AZD 2171, anti-VEGF) in women with recurrent, platinum-sensitive high-grade serous ovarian cancer. This is the first study with two investigational oral drugs in ovarian cancer. The olaparib+cediranib combo nearly

doubled the PFS compared to olaparib alone (17.7 months vs. 9 months). The NCI is planning two Phase III trials of the combo.

Olaparib Being Evaluated In Gastric And Breast Cancer

In September 2013, Astra advanced olaparib into the Phase III GOLD trial which is evaluating OS benefit of olaparib + paclitaxel in second-line gastric cancer in Asian patients (data expected H2:17). This follows a Phase III study in Korean patients with relapsed gastric cancer which showed olaparib + paclitaxel significantly improved OS vs. paclitaxel alone.

In Q2:14 Astra initiated a second Phase III study of olaparib in mBRCA breast cancer. The OlympiAD trial will evaluate olaparib vs. placebo for a maximum of 12 months as adjuvant therapy in mBRCA high-risk HER2- patients. The primary endpoint is PFS. Astra anticipates filing for this indication in the U.S. and EU in 2016.

Selumetinib Inferior In Metastatic Melanoma, But Potential In Other Areas

Selumetinib (AZD6244) is a potent, selective, ATP uncompetitive inhibitor of MEK1/2, licensed from Array. Phase II studies in melanoma, second- and third-line NSCLC, and third-line CRC have been underwhelming. In a Phase III trial in metastatic melanoma, selumetinib plus DTIC demonstrated superior PFS versus DTIC alone (5.6 months for selumetinib vs. 3.0 months for DTIC; HR=0.63, p=0.21), but failed to demonstrate an overall survival benefit (13.5 months for selumetinib vs. 10.5 months for DTIC; HR=0.93, p=0.3873). Several adverse events occurred more frequently in selumetinib treated patients, including acneiform dermatitis, diarrhea, vomiting, and peripheral edema. The lack of an OS benefit in this setting suggests selumetinib is significantly less effective than GSK's tremetinib. In June 2009, Astra and Merck entered a collaboration combining selumetinib and MK 2206 as a new regimen for the treatment of colorectal cancer and in 2012 initiated a study in pancreatic cancer Astra is targeting a 2015 submission.

In October 2013, Astra decided to move selumetinib into Phase III trials for NSCLC. The SELECT-1 study (n=634) will evaluate the safety and efficacy (PFS and OS) of selumetinib + docetaxel as second-line therapy in advanced or metastatic NSCLC with KRAS+ tumors. Study completion is Q3:16. Selumetinib is also in Phase II studies in metastatic uveal melanoma (SUMIT) and thyroid cancer (ASTRA). We estimate selumetinib sales of \$50MM in 2017, \$75MM in 2018, and \$125MM in 2020.

Selumetinib First to Demonstrate Benefit In Uveal Melanoma, Although Commercial Opportunity Limited

Uveal melanoma is an orphan disease that affects 2-3K people in the U.S. and a similar number in the E.U. The biology of uveal melanoma is distinct from its cutaneous counterpart. While half of cutaneous melanomas are driven by BRAF mutations, uveal melanoma is driven by Gnaq/Gna11 mutations resulting in the activation of the MAPK pathway. There are currently no effective systemic therapies.

In results from a Phase II trial presented at ASCO 2013, 98 uveal melanoma patients were randomized 1:1 to selumetinib or temozolomide/DTIC with a primary endpoint of PFS and a secondary OS endpoint. 50% of patients on selumetinib demonstrated tumor regression compared to 11% of patients on DTIC. PFS for selumetinib was 15.9 weeks compared to 7.0 weeks on DTIC (p=0.0005); however this modest PFS benefit failed to translate into an OS benefit (10.8 months for selumetinib vs. 9.4 months for DTIC; HR=0.78, p=0.4). Several adverse effects occurred more frequently in the

selumetinib arm, including rash, anemia, fatigue, CPK elevation, edema, and muscle weakness (see summary below).

Adverse Events On Selumetinib – Uveal Melanoma

	TMZ/DTIC (n=49)	Selumetinib(n=47)
Anemia	7 (14%)	14 (30%)
Leukopenia	8 (16%)	6 (13%)
Lymphopenia	5 (10%)	4 (8%)
Neutropenia	5 (10%)	4 (8%)
Thrombocytopenia	8 (16%)	8 (17%)
Rash	3 (6%)	40 (85%)
Fatigue	24 (49%)	28 (60%)
CPK elevation	--	17 (36%)
AST/ALT	4 (8%)	19 (40%)
Edema	1 (2%)	18 (38%)
Nausea	19 (39%)	18 (38%)
Vomiting	11 (22%)	11 (23%)
Pain	5 (10%)	10 (21%)
Mucositis	1 (2%)	6 (13%)
Dyspnea	--	8 (10%)
Muscle weakness	--	7 (8%)

Source: ASCO 2012

Iressa Marketed In Europe In Activating EGFR Mutations In NSCLC; Potential For First Line In Asia

Iressa (gefitinib) inhibits the tyrosine kinase enzyme in the EGFR, thus blocking the transmission of signals involved in the growth and spread of tumors. A mutation in the EGFR is a characteristic occurring in 10-15% of lung cancers in Europe. There are approximately 106,000 new cases of advanced lung cancer in Europe (top 5 countries) per year. In July 2009 the European Commission granted marketing authorization for Iressa for the treatment of adults with locally advanced or metastatic NSCLC (non-small cell lung cancer) with activating mutations of EGFR-TK across all lines of therapy. The authorization is based on two pivotal Phase III studies comparing Iressa with chemotherapy, IPASS and INTEREST. Iressa is approved for pre-treated NSCLC in the Asia-Pacific region and AstraZeneca is in consultation with regulatory authorities to discuss the potential use of Iressa in first-line therapy. Data published in September 2009 from a study of 654 East-Asian patients demonstrated that Iressa is superior to carboplatin-paclitaxel as an initial treatment for pulmonary adenocarcinoma among nonsmokers or former light smokers in East Asia. The presence of a mutation of the EGFR gene was a strong predictor of a better outcome with Iressa. In October 2011, Astra announced a \$200MM investment in a new manufacturing facility in the Taizhou, Jiangsu province to produce a number of intravenous and oral solid medicines, including Iressa, for the local populations. In July, Astra announced a collaboration with Qiagen to develop a circulating tumor DNA test to identify NSCLC patients suitable for treatment with Iressa. We estimate Iressa sales of \$650MM (flat) in 2014, \$710MM in 2015, \$760MM in 2016, \$860MM in 2018, and \$960MM in 2020.

IPASS demonstrated superior progression-free survival, greater objective response rate, improved tolerability and significant quality of life benefits for Iressa compared to carboplatin/paclitaxel doublet chemotherapy in clinically selected first-line patients in Asia. However, the treatment effect was not constant over time, with the probability of being progression-free in favor of carboplatin/paclitaxel in the first six months and in favor of Iressa in the following 16 months. This was likely due to the different effect of

Iressa in subgroups defined by EGFR tumor mutation status. PFS was significantly longer for Iressa than doublet chemotherapy in patients with EGFR mutation positive tumors, and significantly longer for doublet chemotherapy than Iressa in patients with EGFR mutation negative tumors.

The INTEREST study met its primary objective, demonstrating equivalent overall survival (OS) and significant quality of life benefits for Iressa compared to standard chemotherapy (docetaxel) in the pre-treated setting. Pre-planned sub-group analyses showed a significant improvement in PFS and ORR for Iressa over docetaxel in patients with EGFR mutation positive tumors.

Iressa was approved in the U.S. in 2003 for NSCLC but in June 2005, post the ISEL study failure, AstraZeneca in consultation with FDA announced that Iressa would be restricted to only those patients who were benefiting or had benefited from Iressa. In 2005, AstraZeneca also withdrew its E.U. marketing authorization application for Iressa following data from the ISEL study. The analysis of the primary endpoint of the ISEL study showed that Iressa did not significantly prolong survival in the overall population (HR 0.89, p=0.11, Median 5.6 versus 5.1 months for IRESSA and placebo respectively), or in patients with adenocarcinoma (HR 0.83, p=0.07, Median 6.3 vs. 5.4 months for Iressa and placebo respectively). In April 2012, the FDA revoked accelerated approval of Iressa for the treatment of NSCLC.

Arimidex Clipped By Generics

Arimidex (anastrozole) is an oral aromatase inhibitor (AI) used primarily in post-menopausal women with ER-positive breast cancer. Arimidex dominated the U.S. AI market due to it being first to market; however, its efficacy and safety profile are undifferentiated from Aromasin (Pfizer) and Femara (Novartis). Our physician consultants believe that these drugs can be used interchangeably despite the fact that Femara demonstrated superior aromatase inhibition in a pharmacodynamic study and superiority over tamoxifen in advanced diseases where Arimidex demonstrated non-inferiority. In the past, AIs were most commonly used by women who failed other anti-estrogen therapies. However, the ATAC (Arimidex vs. tamoxifen) and the BIG 1-98 (Femara vs. tamoxifen) studies demonstrated that aromatase inhibitors can be used as adjuvant therapies instead of tamoxifen for early breast cancer and the IES, ARNO-95 and ITA studies demonstrated a benefit in early switching from tamoxifen to aromatase inhibitors after 2-3 years. Arimidex's patent expired on December 27, 2009, and pediatric exclusivity expired on June 27, 2010. We forecast Arimidex sales of \$275MM (-22%) in 2014, \$205MM in 2015, \$155MM in 2016, \$65MM in 2018, and \$20MM in 2020.

Several Other Assets In The Oncology Pipeline Hold Promise

AZD9291 – a second-generation EGFR TKI.. At ASCO 2014, data from a Phase I study (part of larger Phase II/III AURA trial) in EGFRm+ NSCLC patients who failed on previous TKIs, showed AZD9291 achieved a 94% disease control rate. The ORR in 205 evaluable patients was 53%, and 64% in patients who were T790M+. Grade 3-4 AEs were reported in 24% with 2% requiring dose reduction and 4% (10 patients) discontinuing treatment. Six interstitial lung disease-like cases were reported. Astra expects to begin the Phase III trial in 1st-line EGFR+ NSCLC in Q4:14. Astra also plans to evaluate AZD9291 in combo with MEDI4736, selumetinib and volitinib in EGFR+ NSCLC with trials expected to have started in Q3:14. In July 2014, Astra announced that it will be collaborating with Roche Diagnostics to develop a plasma-based companion diagnostic test to support AZD9291 which will identify EGFR mutations in

both tumor tissue and plasma in NSCLC patients. AstraZeneca anticipates filing in H2:15. We estimate AZD9291 sales of \$50MM in 2016, \$200MM in 2018, and \$600MM in 2020.

At ESMO 2014, results from an updated Phase I study of AZD9291 in EGFR-TKI-resistant NSCLC were presented which showed an overall ORR of 51% and 70% in patients with confirmed T790M+ disease. Current median PFS in patients with T790M+ EGFR-TKI-resistant NSCLC is 9.6 months. The most common AE's at 80mg were diarrhea and rash. Drug-related Grade 3 AE's occurred in 10 patients (11%), with no patients requiring dose reductions and one patient discontinuing drug.

Also presented was a dose-escalation and expansion study in EGFR-TKI resistant NSCLC patients with brain metastases, AZD9291 treated patients showed extracranial ORR at all doses (20–240mg). Clear evidence of brain mets shrinkage was seen in some patients (at doses 40–160mg).

Moxetumomab Pasudotox- is a novel CD22-protein synthesis inhibitor combination product targeting the ~6K patients with relapsed acute lymphoblastic leukemia and hairy cell leukemia. Moxetumomab Pasudotox demonstrated robust responses in Phase I trials for pediatric ALL and an 88% ORR and 55% CR in a Phase I trial in hairy cell leukemia (durability of response >2 years). Astra has accelerated the development of moxetumomab pasudotox and initiated a Phase III trial in hairy cell leukemia in March 2013.

AZD4547- is a first in class FGFR inhibitor that has demonstrated clinical activity in various FGFR-amplified tumors. AZD4547's initial opportunity appears to be in FGFR-amplified gastric cancer (~6K patients). Phase II trials are ongoing in gastric cancer and breast cancer and Phase I in solid tumors.

MEDI-551- is a high-affinity mAb against CD19 with enhanced antibody-dependent cell-mediated cytotoxicity. Given that CD19 is more widely expressed than CD20, Astra believes MEDI-551 has the potential to be more effective than Rituxan in B cell lymphomas. MEDI-551's initial opportunity appears to be in the 40K patients with 2nd-line DLBCL and CLL. An active head-to-head Phase II study with Rituxan in relapsed/refractory DCBCL and CLL is ongoing.

Tremelimumab- is an anti-CTLA4 mAb in Phase II studies across solid tumors with safety and efficacy data in >1,000 patients with a focus on novel combinations.

MEDI6469- is a first-in-class murine mAb against OX40 in Phase I trials across a variety of solid tumors. MEDI6469 has shown clinical activity with a single cycle in treatment refractory patients. MEDI6469 is in Phase I/II trials in prostate and breast cancer. AZN has two other OX40 agents in development: MEDI6383 (a humanized fusion protein) and MEDI0562.

AMP-514 is an anti- PD-1 mab acquired as part of the October 2013 Amplimmune acquisition (\$225MM upfront cash and \$275MM on potential milestones). An IND for AMP-514 was filed in Q4:13. Other assets acquired with Amplimmune include molecules in pre-clinicals that target the B-7 pathways. AMP-514 is in a Phase Ia study in cancer (all comers).

ADCs were acquired with the October 2013 acquisition of privately-held Spirogen. Astra has also entered into an agreement with ADC Therapeutic to jointly develop two of its ADC currently in pre-clinicals.

A summary of anticipated 2014 oncology news flow is below:

H2:14 Oncology News Flow

Timeline	Asset	Indication	Clinical Data and Potential Milestones
H2:14	AZD 9291	T790M+ NSCLC	Initiate Phase III
	Olaparib	Ovarian	EU approval
	Iressa	EGFRm+NSCLC	U.S. re-filing
	MEDI-4736 w/tremelimumab	Solid tumors	Initiate Phase III

Source: Company data

Cardiovascular

Brilinta Gaining A Foothold In U.S. Slowly

Brilinta (AZD6140; tigcagrelor) is a twice-a-day reversible adenosine diphosphate (ADP is responsible for platelet aggregation) receptor blocker. Astra priced Brilinta at a premium (\$7.24/day). In August 2009, the full results of its pivotal PLATO study presented at ESC confirmed Brilinta's superior effectiveness over Plavix and a bleeding profile in line, although possibly better than Effient (Lilly/Daiichi). Brilinta appears less potent than Effient given the lower event reduction in the primary endpoint (superiority to Plavix in the composite endpoint) and in stent thrombosis. The group that stands out most is CABG patients among whom all-cause mortality was reduced 51%; in the STEMI group of PLATO mortality was reduced 18%; patients with planned invasive treatment had a 19% reduction. Brilinta's increasing benefit beyond 30 days (versus no benefit for Plavix) was viewed as not critical. On July 20, 2011 the FDA approved Brilinta to reduce cardiovascular death and myocardial infarction in patients with acute coronary syndrome (ACS). The label reflects the North American experience in the PLATO trial via a boxed warning against the concomitant use of aspirin and Brilinta at doses above 100mg per day. We estimate worldwide Brilinta sales of \$465MM (+64%) in 2014, \$630MM in 2015, \$790MM in 2016, \$1,050MM in 2018, and \$1,310MM in 2020.

Brilinta Growth Accelerating In 2014

Astra believes the rate of Brilinta uptake will be driven by ACS prevalence, ACS incidence, and formulary/protocol access. To facilitate uptake, Astra focuses its marketing efforts on core prescribers (interventionalists) to make sure they understand the benefit of Brilinta in combination with low dose aspirin. Additionally, Astra will market extensively to cardiologists to ensure that patients continue on Brilinta post-discharge from the hospital. In May 2012, Astra began a global collaboration to co-promote Brilinta with The Medicines Company. Under the agreement, Astra will also promote The Medicines Company's Angiomax (bivalirudin) and cangrelor (in development as an acute IV antiplatelet agent). Under the four-year agreement, Astra will pay The Medicines Company \$15MM per year with an additional \$5MM per year paid if performance thresholds are met.

Astra believes Brilinta's 21% RRR in CV deaths vs. clopidogrel in ACS would save 100,000 lives each year should Brilinta be prescribed to every heart attack patient worldwide; however, these data alone have not been sufficient to make Brilinta a commercial success. In 2013, Astra concentrated on securing preferred unrestricted access, focusing on the mortality benefit, and deploying superior reps to customer facing roles. Brilinta growth may be accelerated through retail pharmacy promotion, the launch of the "My BRILINTA" access program, implementing a more broad

approach to contracting (commercial and Medicare Part D), and expanding preferred unrestricted access to 80%. Astra will increase its CV specialty sales team by 20%, increase the number of primary care reps selling Brilinta by 3-fold, increase field based scientific staff by 30%, offering 3-times more medical education programs, increase investigator-initiated studies by 20x, and expand its call list to include emergency room physicians and discharge nurses. Ensuring access to Brilinta throughout the continuum of care is critical to ensuring Brilinta remains the OAP of choice outside of the hospital setting. Astra believes increased investment behind Brilinta is expected to translate into a meaningful improvement in financial performance beginning in Q1:14. As of August 2014, Brilinta held 2.8% market share, with new Rx+53% y/y.

Expanding into indications beyond incident ACS is key to maximizing the potential of Brilinta. A summary of the OAP opportunity for Brilinta is below:

Brilinta Opportunity Beyond Incident ACS

	Incident ACS		Post ACS 1-3yrs	PAD	Stroke	T2DM + CAD *
	Invasive	Medical				
Brilinta	Label (PLATO)	Label (PLATO)	PEGASUS (Submit 2015)	EUCLID (Submit 2016)	SOCRATES (submit 2015-16)	THEMIS (submit 2017)
Plavix	Label	Label	No Label	Label	Label (non-acute)	
Effient	Label (TRITON)	Label (TRILOGY)				

* no MI/stroke history

Source: Company data

Brilinta Could Be Used In Broad Patient Population

AstraZeneca has initiated a large cardiovascular outcomes trial, PEGASUS-TIMI 54, in patients who have experienced a MI from one to three years prior to enrollment. The current standard of care is dual antiplatelet therapy for up to twelve months post-MI followed by longer-term treatment with aspirin alone. The PEGASUS-TIMI 54 trial will evaluate the risk for secondary cardiovascular events in patients treated with ticagrelor and aspirin to those receiving aspirin alone. Patient enrollment began in Q4:10 and is expected to finish in Q4:14 with data presentation in Q1:15 and U.S. filing in 2015.

Two New Global Studies Initiated In High Risk Patients

In November 2013, Astra announced the initiation of two global studies evaluating the use of Brilinta in additional high risk populations. These will be part of the PARTHENON program which also includes PEGASUS (Brilinta in secondary MI prevention in patients with previous MI), and EUCLID (use of Brilinta in patients with peripheral artery disease).

The first, SOCRATES, will enroll 9,600 patients who have had an acute ischemic stroke or a transient ischemic attack (TIA). The trial is a randomized, parallel group study evaluating Brilinta compared to aspirin in reducing major vascular events (composite of all-cause mortality, MI, and stroke). The second trial is THEMIS, which will enroll 17,000 patients with Type 2 diabetes at high risk of CV events (no previous MI or stroke, but with documented atherosclerosis). It is an event-driven, randomized, parallel group study evaluating long term treatment with Brilinta vs. placebo in the prevention of MACE (composite of CV death, MI, or stroke).

ATLANTIC Study Supports Use In STEMI Patients Undergoing PCI

In September 2014, AstraZeneca released results from the Phase IV ATLANTIC study which demonstrated that Brilinta could be safely administered in a pre-hospital or in-hospital setting to patients with ST segment elevation myocardial infarction. Results showed there was no statistically significant difference between pre-hospital and in-hospital arms in the composite primary endpoints of 1) pre-PCI (percutaneous coronary intervention) procedural effectiveness; 2) percentage of patients not achieving ST segment elevation resolution $\geq 70\%$ before PCI; and 3) percentage of patients not reaching thrombolysis in myocardial infarction flow grade 3 in the infarct-related artery. While not powered to look at outcomes, the pre-hospital administration of Brilinta indicated a risk reduction of post-PCI stent thrombosis.

The ATLANTIC results are also in line with new ESC/EACTS 2014 Guidelines on Myocardial Revascularisation that were presented at ESC 2014 which gave a class I recommendation to start dual antiplatelet therapy in STEMI patients at first medical contact.

Brilinta Bleeding Profile In Line To Better Compared To Effient

Brilinta's non-CABG major bleeding risk is similar to Effient's. These spontaneous bleeds are potentially more concerning than CABG-related bleeds that may be easier to control. The calculation of PLATO's reported TIMI major CABG-related bleeds was not the same as in TIMI 38 (PLATO used the ITT as the denominator while TIMI 38 used only the patients going to CABG as the denominator). However, when compared on equal footing, while extremely high (50%+) in PLATO, the trend still favors Brilinta. Nonetheless, Brilinta's reversibility will allow doctors to stop it up to two days before CABG and major surgeries (vs. 5-7 days for Plavix and Effient).

PLATO demonstrated an increase in dyspnea, ventricular pauses, and brady-arrhythmia in the Brilinta arm. There was no cancer signal. Dyspnea resulted in a dropout rate of <1%. The higher rate of ventricular pauses may be an issue, especially given the increased incidence of syncope. The laboratory findings of raised plasma uric acid and creatinine levels require further understanding but were not viewed as particularly concerning by our physician consultants.

The PLATO design included a broader population than Effient's TIMI 38 and allowed for Brilinta to be given to patients whose coronary anatomy is not defined, upstream from where Effient is indicated. Our cardiology consultants believe that Brilinta will be used in patients at risk for bleeding or those who might go to surgery. Effient is best suited for patients requiring more potent therapy and/or those unlikely to be compliant (10-15% patients are non-compliant). Based on PLATO, 85% of patients would be eligible for Brilinta; those with severe COPD/asthma and at risk for brady-arrhythmias total the remaining 15%.

Label Warns Against Concomitant Use of High-Dose Aspirin

The FDA confirmed that Brilinta was more effective than Plavix in preventing heart attacks and death, but that this advantage was only seen with daily aspirin doses of 75 to 100 milligrams. The Brilinta label contains a boxed warning stating that concomitant use of aspirin at doses above 100mg per day decreases the efficacy of Brilinta. An additional boxed warning stating that, "like other blood-thinning agents, Brilinta increases the rate of bleeding and can cause significant, sometimes fatal, bleeding." The most common adverse reactions reported by people taking Brilinta in clinical trials were bleeding and difficulty breathing (dyspnea) and this is also included in the labeling. Brilinta was approved with a REMS to ensure that the drug's benefits

outweigh its risks. As part of the REMS, Astra must conduct educational outreach to physicians to alert them about the risk of using higher doses of aspirin. Additionally, Brilinta will be dispensed with a medication guide that informs patients of the most important information about the medication.

In June 2011, Health Canada approved Brilinta for the secondary prevention of atherothrombotic events in patients with Acute Coronary Syndrome. The label warns against the concomitant use of high-dose aspirin maintenance therapy.

In December 2010, the European Commission granted marketing authorization for prevention of atherothrombotic events post-ACS. The European Society for Cardio-thoracic Surgery (ESCTS) has granted a class 1B recommendation to Brilique in revised guidelines for myocardial revascularization.

ACC Guidelines For PCI Management

In November 2011, the American College of Cardiology Foundation, American Heart Association, and Society for Cardiovascular Angiography and Interventions updated their guidelines for the management of PCI patients to provide a Class I recommendation for the use of Brilinta. In February 2012, the ACC guidelines were updated to reflect the preferred use of Brilinta compared to Plavix in the post-ACS setting. The guidelines are as follows:

For patients in the first year after an ACS who have not undergone percutaneous coronary intervention (PCI):

- ACC recommends dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low-dose aspirin 75-100 mg daily or clopidogrel 75 mg daily plus low-dose aspirin 75-100 mg daily) over single antiplatelet therapy (Grade 1B).
- ACC suggests ticagrelor plus low-dose aspirin over clopidogrel plus low-dose aspirin (Grade 2B).
- For patients in the first year after an ACS who have undergone PCI with stent placement:
 - ACC recommends dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low-dose aspirin 75-100 mg daily, clopidogrel 75 mg daily plus low-dose aspirin, or prasugrel 10 mg daily plus low-dose aspirin over single antiplatelet therapy) (Grade 1B);
 - ACC suggests ticagrelor 90 mg twice daily plus low-dose aspirin over clopidogrel 75 mg daily plus low-dose aspirin (Grade 2B).

Efficacy: Comparison Of AZN's PLATO Versus Lilly's TIMI 38

	PLATO				TIMI 38			
	Brilinta N=9,333 %	Plavix N=9,291 %	Odds Ratio (95% CI)	p-value	Effient N=6,813 %	Plavix N=6,795 %	Odds Ratio (95% CI)	p-value
	CV Death, Non fatal MI, Non fatal stroke	9.8	11.7	0.84 (0.77–0.92)	<0.001	9.9	12.1	0.82 (0.73–0.90)
CV death			0.79 (0.69–0.91)	0.001	2.1	2.4	0.89 (0.70–1.12)	0.31
Nonfatal MI			0.84 (0.75–0.95)	0.005	7.3	9.5	0.76 (0.67–0.85)	<0.001
Nonfatal stroke			1.17 (0.91–1.52)	0.22	1.0	1.0	1.02 (0.71–1.45)	0.93
Death from any cause			0.78 (0.69–0.89)	<0.001	3.0	3.2	0.95 (0.78–1.16)	0.64
Death from any cause, nonfatal MI, nonfatal stroke	10.2	12.3	0.84 (0.77–0.92)	<0.001	10.7	12.7	0.83 (0.75–0.92)	<0.001
Probable or definite stent thrombosis	2.2	2.9	0.75 (0.59–0.95)	0.009	1.1	2.4	0.48 (0.36–0.64)	<0.001

Dashed border = either PLATO or TIMI 38 appears favorable

Source: Cowen and Company

Safety: Comparison Of AZN's PLATO Versus Lilly's TIMI 38

	PLATO				TIMI 38			
			Hazard Ratio for				Hazard Ratio for	
	Brilinta N=9,333	Plavix N=9,291	Brilinta (95% CI)	p-value	Effient N = 6,741	Plavix N = 6,716	Prasugrel (95% CI)	p-value
Non-CABG-related TIMI major bleeding	% 2.8	% 2.2	1.25 (1.03, 1.53)	0.03	% 2.4	% 1.8	1.32 (1.03–1.68)	0.03
CABG-related TIMI major bleeding†	48	49			13.4	3.2	4.73 (1.90–11.82)	<0.001
Life-threatening	5.8	5.8	1.03 (0.90–1.16)	0.7	1.4	0.9	1.52 (1.08–2.13)	0.01
Fatal	0.3	0.3	0.87 (0.48–1.59)	0.66	0.4	0.1	4.19 (1.58–11.11)	0.002
Intracranial	0.3	0.2	1.87 (0.98–3.58)	0.06	0.3	0.3	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	11.4	10.9	1.05 (0.96–1.15)	0.33	5.0	3.8	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion	8.9	8.9	1.00 (0.91–1.11)	0.96	4.0	3.0	1.34 (1.11–1.63)	<0.001
Neoplasms	1.4	1.7		0.17	2.27	1.83		
Dyspnea*					NA	NA		
Any	13.8	7.8	1.84 (1.68–2.02)	<0.001				
Requiring discontinuation	0.9	0.1	6.12 (3.41–11.01)	<0.002				
Other Cardiovascular*								
Bradycardia	4.4	4.0		0.21	NA	NA		
Syncope	1.1	0.8		0.08	NA	NA		
Ventricular pauses								
Week 1: ≥3 sec	5.8	3.6		0.01	NA	NA		
At 30 days: ≥3 sec	2.1	1.7		0.52				
Uric acid (increase from baseline %)*								
At 1 month	14±46	7±44		<0.001	NA	NA		
At 12 months	15±52	7±31		<0.001				
1 Months after end of treatment	7±43	8±48		0.56				
Creatinine (increase from baseline %)*					NA	NA		
At 1 month	10±22	8±21		<0.001				
At 12 months	11±22	9±22		<0.001				
1 Months after end of treatment	10±22	10±22		0.59				

† In order to compare PLATO and TIMI 38 CABG bleeds, the number of TIMI major bleeds in patients that went to CABG was divided by the number of CABG surgeries

* For Effient these were not highlighted in FDA briefing documents, nor in any publications

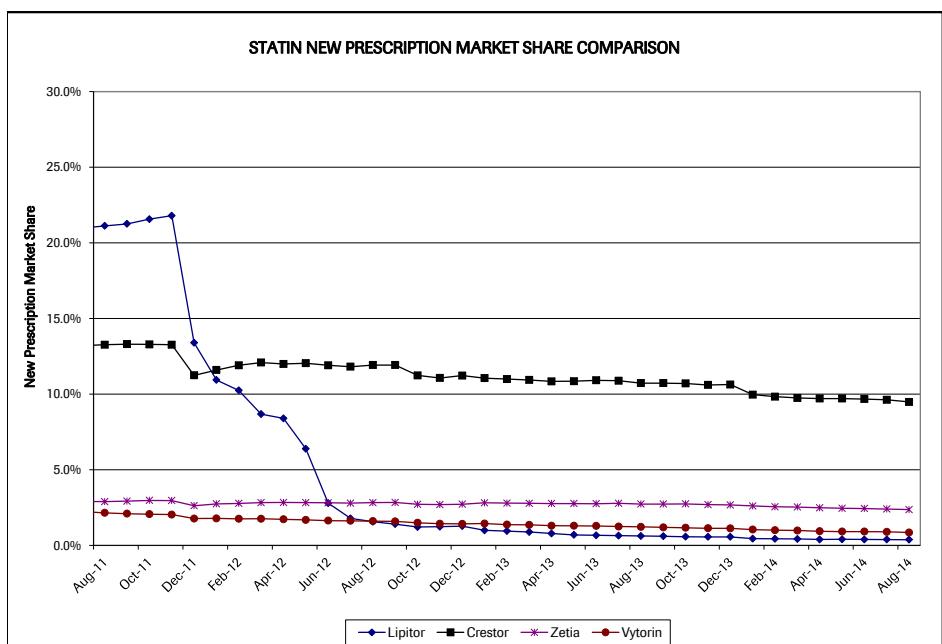
Dashed border = either PLATO or TIMI 38 appears favorable

Source: NEJM.org; Cowen and Company; FDA documents

Crestor Continues To Be Pressured By Generic Statins; Modest Decline Anticipated Through 2016

In November 2011, Crestor had 13.3% of the cholesterol market, which rapidly decreased to 11.2% in December 2011, with the introduction of generic Lipitor. As of August 2014, Crestor maintained 9.5% (-2%) share of the cholesterol market. We estimate Crestor sales of \$5.51B (-2%) in 2014, \$5.325B in 2015, \$5.075B in 2016, \$1.505B in 2018, and \$1.06B in 2020 post the 2017 patent expiry.

Statin New Prescription Market Share Comparison



Source: IMS America

In late December 2013, AZN announced that it settled arbitration with Shinogi over Crestor royalties and extended the period of royalty payments to Shionogi from 2016 to 2023. Under the revised terms, the payment structure has been modified to reduce the royalty rate in 2014-15 by low-single digits. There will be a fixed minimum annual royalty payment from 2014 to 2020 ("low hundreds of millions of dollars") and a maximum total payment for the 2016-2020 timeframe.

Composition Of Matter Patent Upheld In U.S.; Settlement Agreement With Generics

On November 1, 2007, AstraZeneca received notice from eight generic manufacturers that each had filed an ANDA with the FDA alleging that one or more of the three Orange Book-listed U.S. patents ('314 expiring 01/16; '450 expiring 08/20; and '618 expiring 12/21) referencing Crestor was not infringed or otherwise invalid or unenforceable. On November 11, 2007, AstraZeneca filed infringement suits against six of the companies alleging infringement of the '314 composition of matter patent which it had licensed from Shionogi. A ruling upholding the validity of the patent was made in June 2010. The decision was appealed with arguments heard on October 5, 2011, by the U.S. Court of Appeals for the Federal Circuit. In December 2012, the Court of Appeals upheld the decision of the District Court, finding that the U.S. substance patent is valid and enforceable. In January 2013, defendants filed petitions for rehearing. The Court denied these petitions and in March 2013, AZN entered into a settlement agreement with Watson, Actavis, and EGIS which permits Watson to begin

selling generics on May 2, 2016 at a fee to Astra of 39% of net sales, until July 8, 2016 when pediatric exclusivity ends. A patent trial was held in Australia in October 2012; on March 5, 2013, all three patents were invalidated. Astra has appealed the decision. Crestor sales in Australia were \$350MM in 2012.

New Cholesterol Guidelines A Plus For Crestor

The new 2013 ACC/AHA blood cholesterol treatment guidelines, released in November 2013, no longer target specific LDL levels. Rather, the new guidelines recommend categorizing patients by CV risk, then treating with an appropriate intensity of statin dose that has been shown to improve outcomes in a randomized clinical trial. The guidelines do not recommend the use of non-statin drugs as adjuncts to statins in most patients, as these have not been shown to improve outcomes. Familial hypercholesterolemia is an exception and treatment remains targeted to LDL level goals.

Our physician consultants believe an optimal LDL level still exists and note the guidelines emphasize moderate to high dose statin, either atorvastatin 40-80 or Crestor 20-40. Crestor has an advantage in that it raises HDL-C more. Zetia will still be used in patients who can't tolerate high dose daily statin (we note about one-third of Zetia use is monotherapy) but will likely be stopped if they do tolerate atorvastatin or Crestor and their LDL is close to 100. Niacin will not be used to raise HDL but solely to lower LDL more in patients who can't tolerate a potent statin or cannot get close to an LDL-C of 100. Our consultants still believe that there is an optimal level of LDL-C which is likely between 40-60 and predict the guidelines will be much different in 4 years.

Crestor Atherosclerosis And Endpoint Studies

Study	Full Name	Dosing/ Results	Date Of Presentation/ Expected Year Of Completion
ORION	Outcome of Rosuvastatin treatment on carotid artery atheroma: a magnetic Resonance Imaging ObservatioN	The 24-month study to assess the progression of carotid artery atheroma using MRI and ultrasound, in hypercholesterolemic subjects with asymptomatic carotid disease following treatment with low or high dose Crestor demonstrated that Crestor 5mg and 40mg reduced the proportion of lipid-rich necrotic core (LRNC) in the most diseased area of atherosclerotic plaques by 17.6% (p=NS) and 35.5% (p=0.006), respectively. LDL-C was reduced 39 percent and 58 percent, respectively (p<0.001). In terms of individual responses to Crestor 5mg and 40mg, regression of plaques from baseline at the most diseased sites occurred in 75% and 90% of patients, respectively. No significant median (mean) percent change in carotid artery wall volume was observed versus baseline from baseline: 0.5% (-1.2%) and -1.4% (1.1%) at 5 mg and 40 mg respectively (p=NS).	Presented 2005
ASTEROID	A Study To evaluate the Effect of Rosuvastatin On Intravascular ultrasound-Derived Coronary Atheroma Burden	Open label, 26-month, non-comparative study using intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) showed Crestor 40mg led to a 0.79% (median) reduction in percent atheroma volume in the entire target vessel in patients with coronary artery disease who required angiography.	Presented 3/06
METEOR	Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin	The 24-month intima media thickness (IMT) study in low risk, asymptomatic, hypercholesterolemic subjects (mean LDL-C 154 mg/dL) with sub-clinical evidence of atherosclerosis, demonstrated that patients on Crestor 40mg experienced a 0.0014 mm/yr decrease in the mean max-IMT compared to a progression of 0.0131 mm/yr for those on placebo (p<0.0001). Crestor 40mg was associated with a 48.8 percent reduction in LDL-C and an 8.0 percent increase in HDL-C (both p<0.0001 vs placebo).	Presented 3/07
CORONA	COntrolled ROsuvarstatin multiNAtional trial in heart failure	Crestor 10mg did not significantly improve the prognosis for patients with advanced heart failure. Patients on Crestor 10mg experienced an 8% reduction (p=0.12) in the combined primary endpoint of cardiovascular death or myocardial infarction or stroke, which was not statistically significant. This reduction was primarily driven by a decrease in atherosclerotic events, i.e. stroke and myocardial infarctions (post hoc analysis p=0.05). The majority of deaths were due to sudden death, or non-ischemic cause. In addition, significantly fewer hospitalizations occurred in patients on CRESTOR compared to placebo, whether due to any cause (p=0.007), cardiovascular causes (p<0.001), or for worsening heart failure (p=0.01).	Presented 11/07
AURORA	A study evaluating the Use of Rosuvastatin in patients requiring Ongoing Renal dialysis: an Assessment of survival and cardiovascular events	Study to evaluate the effects of Crestor 10mg on survival and major cardiovascular events in subjects with end stage renal disease on chronic hemodialysis.	2008+
JUPITER	Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin	15,000 patient study to assess Crestor 20mg in the primary prevention of cardiovascular events in subjects with low LDL-C levels and elevated levels of C-reactive protein (CRP). After a median of 1.9 years (versus the planned 4 year follow-up) Crestor significantly reduced the primary composite end point (1.6% vs. 2.8% in the placebo arm; 0.77 versus 1.36 per 100 person years follow-up) by 44% (HR 95% CI 0.46-0.69; p<0.00001). Reductions in the components included: 65% in nonfatal MI, 48% in the risk of nonfatal stroke and 47% in the risk of hard cardiac events (a composite of MI, stroke, and death from cardiovascular causes). At 24-months LDLs in the Crestor arm were 54 versus 108mg/dL (50% reduction) in the placebo arm; CRP levels were 2.2 versus 3.5mg/L, respectively (37% reduction).	Presented 2008
GRAVITY	Gauging the lipid effects of Rosuvastatin plus ezetimibe Versus simvastatin plus ezetimibe Therapy	12-week, open-label, randomised, parallel-group, multicentre, Phase IIIb study of 800 patients to compare the efficacy and safety of CRESTOR 10mg and 20mg in combination with ezetimibe 10mg and simvastatin 40mg and 80mg in combination with ezetimibe 10mg in patients with hypercholesterolemia and coronary heart disease (CHD) or a CHD risk equivalent, atherosclerosis or a 10-year CHD Risk of >20%. Crestor 20mg combination achieved a statistical significant reduction in LDL-c relative to both simvastatin groups.	Results available on line
SATURN	Study of Coronary Atheroma by InTravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin	104-week, parallel-group, multicentre, double-blind, Phase IIIb intravascular ultrasound (IVUS) imaging study of approximately 1,300 patients at 170 centres worldwide designed to measure the impact of Crestor 40mg and Lipitor 80mg on the progression of atherosclerosis in high risk patients.	Missed primary endpoint; reductions in PAV primary endpoint, modest changes in TAV.

Source: AstraZeneca, reuters.com, medicalnewstoday.com, clinicaltrials.gov

Epanova Approved For Severe Hypertriglyceridemia

Epanova is an ultra-pure mixture of the free fatty acid forms of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), derived from fish oils. It is given as a once daily dose (2 or 4 capsules) to treat patients with severe hypertriglyceridemia (triglycerides > or = to 500mg/dL). Epanova was approved in the U.S. in May 2014 based on data from the Phase III EVOLVE and ESPRIT trials (both conducted under an SPA) which demonstrated the effectiveness of Epanova in lowering very high triglycerides and in lowering non-HDL cholesterol in combo with a statin. Astra is also initiating a CV outcomes study (STRENGTH) which will evaluate patients (n=38,576) with a TG level of 200-500 mg/dl, on statin therapy, and who are at increased risk of CV disease, treated with either Epanova +statin or corn oil + statin. The study has not yet commenced but is expected to complete May 2019. The primary endpoint is time to MACE. Astra plans to develop a fixed dose combination of Epanova plus a statin.

We estimate Epanova sales of \$15MM in 2014, \$90MM in 2015, \$150MM in 2016, \$250MM in 2018, and \$350MM in 2020.

Toprol XL Clipped By Re-Entry Of Generics

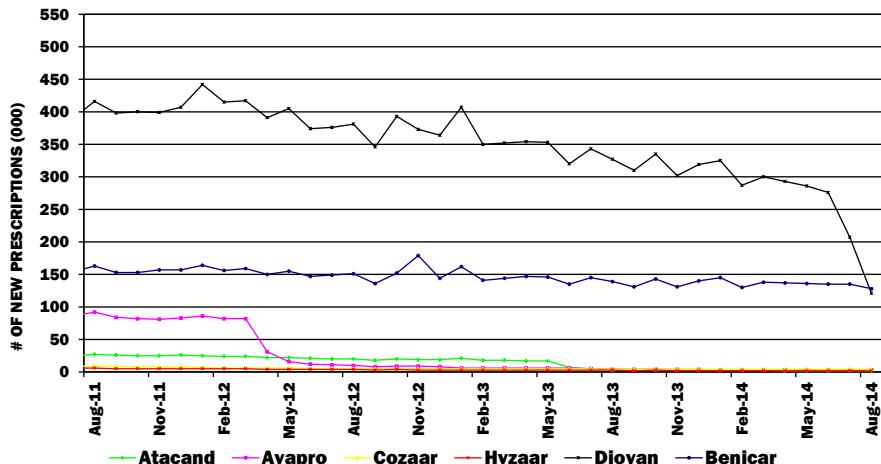
Toprol XL, a once-daily version of metropolol, enjoyed great success, driven by broad use as a once-daily antihypertensive, use in CHF, and its attractive pricing. In January 2006, Judge Sippel of the U.S. District Court for the Eastern District of Missouri ruled in favor of Andrx, KV, and Eon (Novartis) that patents 5,081,154 and 5,001,161, which cover Toprol XL and were set to expire in September 2007, were invalid and unenforceable based on anticipation, obviousness-based double patenting, and inequitable conduct. In November 2006, Par began shipment of the authorized generic Toprol XL 25mg for AstraZeneca simultaneous with Novartis' true generic launch. In April 2009, AstraZeneca ramped up production of Toprol-XL and removed certain restrictions it established for purchases of the drug because demand for the brand increased after recalls by generic competitors facing quality issues. However, generics have reentered the market. We forecast Toprol XL sales of \$725MM (-3%) in 2014, \$670MM in 2015, \$650MM in 2016, \$645MM in 2018, and \$650MM in 2020.

Atacand In Decline Post June 2012 E.U. Patent Expiry

Atacand, a prodrug that is hydrolyzed to candesartan, is an angiotensin II receptor blocker (ARB) indicated for the treatment of hypertension and heart failure. Atacand/HCT, the fixed-dose combination with a hydrochlorothiazide diuretic, is only indicated in patients requiring more than a monotherapy. Candesartan was discovered and originally synthesized by Takeda, and it was jointly developed with AstraZeneca. Atacand was unable to a garner significant share in the U.S. reflecting a tempered commercial effort due to unfavorable economics because of royalties paid to Merck and Takeda, and strong competition from Novartis' Diovan. Atacand achieved a 1.0% NRx share in the U.S. in May 2013, but share slipped to 0.2% in January 2014 with NRxs down year on year by 86%. In the rest-of-world, Astra's economics are more favorable, although performance has been disappointing. The CHARM study supported its cardiac failure label. DIRECT (Diabetic REtinopathy Candesartan Trials), presented in September 2008, demonstrated a strong trend in favor of treatment with Atacand in reducing the incidence of diabetic retinopathy in type 1 diabetes patients, although not statistically significant, and a significant increase in regression of diabetic retinopathy in Type 2 diabetes patients. Atacand's E.U. patent expired in June 2012. We forecast Atacand sales of \$495MM (-19%) in 2014, \$390MM in 2015, \$330MM in 2016, \$220MM in 2018, and \$160MM in 2020.

A RB New Prescription Comparison

ARB NEW PRESCRIPTION COMPARISON



Source: IMS America

Myalept Approved For Generalized Lipodystrophy

Metreleptin is a recombinant analog of the human hormone leptin and is designated as an orphan drug by both the FDA and EMA. It was acquired by Astra as part of the diabetes product acquisition from Bristol. At its December 2013 Adcom meeting, Metreleptin was recommended 11-1 as treatment for pediatric and adult generalized lipodystrophy (LD). However, the panel voted against (vote of 10-2) a recommendation for its use in partial LD, which had been the proposed indication. FDA approved Myalept for generalized lipodystrophy on February 25, 2014 with a REMS. The FDA is requiring seven studies (post-marketing requirements) for Myalept, including a long-term prospective observational study (product exposure registry), a study to assess for the immunogenicity (antibody formation), and an assessment and analysis of spontaneous reports of potential serious risks related to the use of Myalept. Eight additional studies are being requested as post-marketing commitments. Astra intends to pursue efforts for a partial claim. We forecast Myalept sales of \$20MM in 2014, \$40MM in 2015, \$60MM in 2016, \$100MM in 2018, and \$140MM in 2020.

Diabetes

Astra Becomes A Leading Player In Diabetes With Bristol Acquisition

In January 2014, Astra acquired Bristol's portion of their diabetes collaboration and paid Bristol \$3.4B in cash (\$2.7B plus \$0.6B for Forxiga U.S. approval and \$0.1B for Japan approval. Astra states that they have paid \$4.5B in total to Bristol regarding diabetes.

The acquisition provides Astra with a strong foothold in a large and growing market and positions the company as a leading player. There are over 350MM patients WW with diabetes and this is expected to grow to 550MM by 2030. As many as 50% of all

cases of diabetes remain undiagnosed, with 2/3^{rds} of these patients living in emerging markets. We estimate the 2013 diabetes market at roughly \$36B, growing to roughly \$55B by 2018.

Astra/Bristol Diabetes Collaboration Background

In January 2007, AstraZeneca and Bristol-Myers Squibb announced a collaboration to develop and commercialize saxagliptin (DPP IV inhibitor) and dapagliflozin (SGLT-2 inhibitor) for the treatment of Type 2 diabetes. Both compounds were discovered by Bristol-Myers Squibb. The agreements included an upfront payment of \$100MM by AstraZeneca to Bristol-Myers Squibb. From 2007 through 2009, the majority of development costs were funded by AstraZeneca. Additional development costs were shared equally. Bristol-Myers Squibb was also eligible to receive additional payments of up to \$650MM based on development and regulatory milestones for the two compounds. In addition, potential sales milestones up to \$300MM per product were possible. The companies jointly developed the clinical and marketing strategy of the compounds, and shared commercialization expenses and profits/losses equally on a global basis, excluding Japan. Bristol-Myers Squibb had manufactured both products and booked sales. The Astra/Bristol alliance provided a wide variety of non-insulin diabetes products, including one product in each of the three fastest growing categories (DPP-IV, SGLT-2, GLP-1).

In October 2012, Bristol acquired Amylin (AMLN) Pharmaceuticals for \$31/share (\$5.3B). The total cost of the acquisition was ~\$7B. Following completion of the acquisition, Bristol expanded its existing diabetes collaboration with AstraZeneca to incorporate the Amylin portfolio of products, including Byetta and Bydureon. Astra made a payment of \$3.4B to Amylin as a wholly owned subsidiary of Bristol in August 2012. Profits and losses from the collaboration were shared equally between Bristol and Astra.

Given Byetta's Struggles, Success of Acquisition Depends on Astra's Ability to Make Bydureon a Commercial Success

Byetta has struggled for several reasons, including PCP's preference to prescribe oral medications, the success of MRK's Januvia and NVO's Victoza, concerns over pancreatitis, and complex issues surrounding reimbursement. Bydureon (exenatide-LAR) is a first-to-market once-weekly GLP-1 analog. Given the sheer size of the diabetes market together with the added convenience, tolerability, and compliance associated with once-weekly GLP-1 formulations, Bydureon has the potential to become a \$1B+ drug over time. Bydureon was approved by FDA in January 2012.

GLP-1 Comparison

Drug	Dosing	HbA1c Reduction	Weight Reduction (kg)	Nausea Rate
Byetta (BMY/AZN)	BID SQ	0.79 ¹ -0.96 ⁴	2.87 ¹ -3.8 ⁴	25% ¹
Bydureon (BMY/AZN)	q week SQ	1.3 ²	2.3-2.6 ³	9% ²
Victoza (NVO)	q day SQ	0.99 ⁵ , 1.1 ¹ , 1.5 ²	2.21 ⁵ , 3.24 ¹	20% ² , 25% ¹ , 29.9% ⁵
Lixisenatide (SNY)	q day SQ	0.79 ⁴	2.8 ⁴	20-24%
Albiglutide (GSK)	q week SQ	0.78 ⁵	0.62 ⁵	9.9% ⁵
Dulaglutide (LLY)	q week SQ	1.3-1.59 ⁶	2.55 ⁶	13.6-16.9% ⁶
PC-DAC: Exenatide-4 (ConjuChem)	q week or twice weekly	0.8-1.4 ⁶	1.2 ⁶	23% ⁶

1) LEAD-6

2) DURATION 6

3) DURATION 2-4

4) GetGoal X

5) HARMONY-7

6) Phase II

Source: Cowen and Company

While several competitive once-weekly GLP-1 formulations are in development, the opportunity exists for Astra to improve the marketing of Byetta/Bydureon to drive franchise growth. In July 2013, Astra/Bristol indicated they will increase investment in Bydureon and limit investment in Byetta to combination therapies.

The new Bydureon dual chamber pen was approved in the U.S. in March 2014 and received a positive CHMP opinion in July 2014. It was filed in Japan in April 2014. It has the same size needle (23 gauge) as the current formulation and is comparable in size to other pens, although perhaps not as sleek. The new dual chamber device also requires reconstitution (by shaking), although this is easier than the previous form.

Astra has a suspension formulation in development (Phase III started Q1:13) that does not require reconstitution. In September 2014, the company released data from the Phase III DURATION-NEO-1 trial (n=377) which demonstrated that once-weekly 2mg exenatide suspension for autoinjection to be non-inferior to twice-daily 10mcg exenatide (Byetta) in reducing HbA1c at 28 weeks (-1.4% vs -1.0% respectively; p=0.007). Weight reductions and other glycemic measures were also similar, as were adverse effects. The company plans to file for approval in 2015.

A once-monthly version is in Phase II but appears to be facing some technical issues. We estimate Byetta sales of \$345MM (+67%) in 2014, \$430MM in 2015, \$500MM in 2016, \$640MM in 2018, and \$780MM in 2020. We estimate Bydureon sales of \$485MM in 2014, \$940MM in 2015, \$1,330MM in 2016, \$1,970MM in 2018 and \$2,560MM in 2020.

Onglyza Meeting Expectations In The U.S.; FDA CV Analysis Unlikely To Tarnish

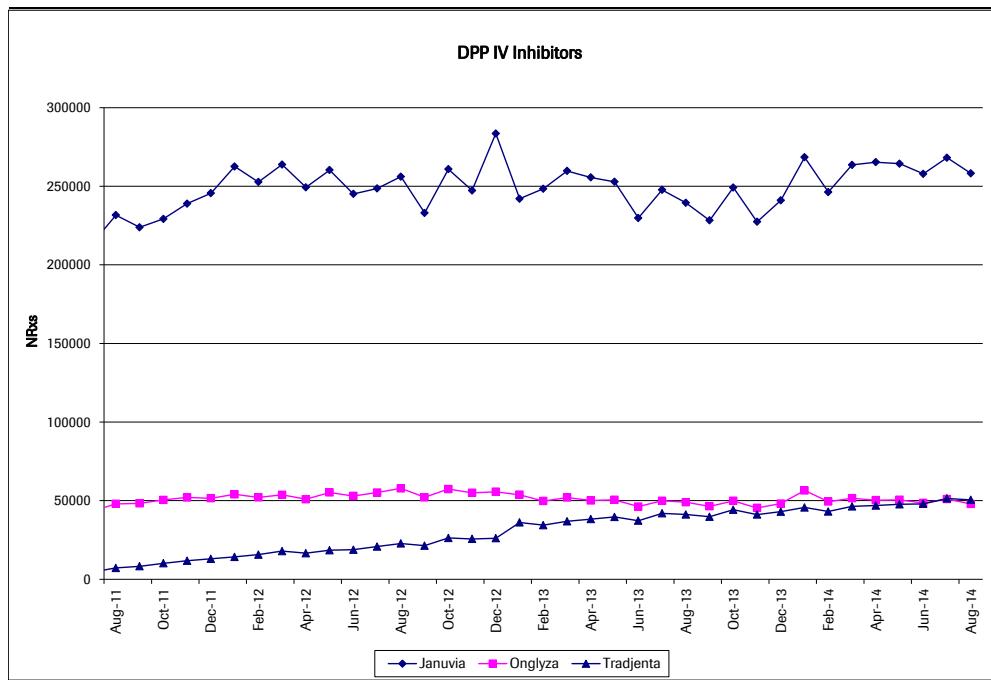
Onglyza (saxagliptin) has a label that is competitive with other agents in the DPP-IV class. Our physician consultants believe that there is little difference between the DPP-IV inhibitors and therefore much will depend on commercial prowess and formulary access. Onglyza's rollout has been tepid in the U.S. with 1% share of the oral anti-diabetes market in August 2014 (-3%Y/Y). We estimate Onglyza sales of \$950MM (+151%) in 2014, \$1,400MM in 2015, \$1,640MM in 2016, \$2,020MM in 2018, and \$2,400MM in 2020.

FDA Looking At SAVOR Trial Heart Failure Data

In June 2013, Astra and Bristol announced top line results of the “Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus” trial (SAVOR-TIMI 53), a multicenter, randomized, double-blind, placebo-controlled Phase IV study, to evaluate treatment with Onglyza in adult type 2 diabetes patients with cardiovascular risk factors. The study followed approximately 16,500 patients with type 2 diabetes, who had either a history of previous cardiovascular events or multiple risk factors for vascular disease, and includes patients with renal impairment. Onglyza met the primary safety objective of non-inferiority, and did not meet the primary efficacy objective of superiority, for a composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal ischemic stroke, when added to a patient's current standard of care (with or without other anti-diabetic therapies), as compared to placebo.

In February 2014, the FDA requested clinical trial data from SAVOR-TIMI 53 to investigate a possible association between Onglyza and heart failure. The request was based on a disclaimer to the study results published in the October 2013 *NEJM* which showed increased hospitalization rates for heart failure with Onglyza-treated patients. Astra has submitted the requested data to the FDA. The FDA did not request that patients stop taking the drug.

DPP IV Inhibitors



Source: IMS America

Onglyza: Full Results Of SAVOR Study As Expected

Complete data from the SAVOR trial were presented at ESC 2013. As noted above, Onglyza met its primary safety endpoint, but failed to meet to meet primary efficacy endpoint: Onglyza was non-inferior to placebo for CV endpoints (death, MI, stroke – primary endpoints). Onglyza did show an increase in hospitalization rates for CHF patients. However, our consultants believe the difference is minimal and not likely to be mechanism-based. The lack of pancreatitis or pancreatic cancer was also viewed

as a positive (though not surprising), and may enhance physician comfort with prescribing the DPP-IVs. In sum, our consultants believe SAVOR reaffirms the overall safety of this class of drugs, with no adverse effect on overall CV risk but also confirms that the benefits of DPP-IV inhibition are modest — implying a safe, but not highly effective treatment. A comparison of study results for Onglyza's SAVOR and Nesina's (alogliptin) EXAMINE are depicted below.

SAVOR and EXAMINE Study Endpoint

# patients	SAVOR Study Clinical Endpoints				EXAMINE Study Clinical Endpoints			
	Onglyza	Placebo	Hazard Ratio (Onglyza)	p-value	Alogliptin	Placebo	Hazard Ratio (alogliptin)	p-value
Efficacy Endpoints								
Primary: CV death, MI, stroke	613 (7.3%)	609 (7.2%)	1.00 (0.89-1.12)	0.99	305 (11.3%)	316 (11.8%)	0.96 (\leq 1.16)	0.32
Secondary: CV death, MI, stroke, hospitalization for UA/HF/revasc.	1,059 (12.8%)	1,034 (12.4%)	1.02 (0.94-1.11)	0.66	344 (12.7%)	359 (13.4%)	0.95 (\leq 1.14)	0.26
Death from any cause	420 (4.9%)	378 (4.2%)	1.11 (0.96-1.27)	0.15	153 (5.7%)	173 (6.5%)	0.88 (0.71-1.09)	0.23
Death from CV causes	269 (3.2%)	260 (2.9%)	1.03 (0.87-1.22)	0.72	89 (3.3%)	111 (4.1%)	0.79 (0.60-1.04)	0.10
MI	265 (3.2%)	278 (3.4%)	0.95 (0.80-1.12)	0.52	187 (6.9%)	173 (6.5%)	1.08 (0.88-1.33)	0.47
Ischemic stroke	157 (1.9%)	141 (1.7%)	1.11 (0.88-1.39)	0.38				
Hospitalization for unstable angina	97 (1.2%)	81 (1.0%)	1.19 (0.89-1.60)	0.24				
Hospitalization for heart failure	289 (3.5%)	228 (2.8%)	1.27 (1.07-1.51)	0.007				
Hospitalization for coronary revasc.	423 (5.2%)	459 (5.6%)	0.91 (0.80-1.04)	0.18				
Doubling of serum creat., dialysis, renal transplant, or SCr >6.0mg/dl	194 (2.2%)	178 (2.0%)	1.08 (0.88-1.32)	0.46				
Hospitalization for hypoglycemia	53 (0.6%)	43 (0.5%)	1.22 (0.82-1.83)	0.33				

Source: NEJM

SAVOR Study Safety Endpoints

	Onglyza	Placebo	p-value
# patients	8,280	8,212	
Thrombocytopenia	55 (0.7%)	65 (0.8%)	0.36
Lymphocytopenia	49 (0.6%)	40 (0.5%)	0.40
Severe infection	590 (7.1%)	576 (7.0%)	0.78
Opportunistic infection	21 (0.3%)	35 (0.4%)	0.06
Hypersensitivity reaction	93 (1.1%)	89 (1.1%)	0.82
Bone fracture	241 (2.9%)	240 (2.9%)	1.00
Skin reaction	228 (2.8%)	232 (2.8%)	0.81
Renal abnormality	483 (5.8%)	418 (5.1%)	0.04
Hypoglycemia - any	1,264 (15.3%)	1,104 (13.4%)	<0.001
Major	177 (2.1%)	140 (1.7%)	0.047
Minor	1,172 (14.2%)	1,028 (12.5%)	0.002
Cancer	327 (3.9%)	362 (4.4%)	0.15
Liver abnormality - any	55 (0.7%)	67 (0.8%)	0.28
AST >3x ULN	60 (0.7%)	61 (0.7%)	0.93
AST >10x ULN	12 (0.1%)	15 (0.2%)	0.57
ALT or AST >3x ULN & bili >2x ULN	13 (0.2%)	23 (0.3%)	0.097
Pancreatitis - any	24 (0.3%)	21 (0.3%)	0.77
Acute: definite or possible	22 (0.3%)	16 (0.2%)	0.42
Acute: definite	17 (0.2%)	9 (0.1%)	0.17
Acute: possible	6 (0.1%)	7 (0.1%)	0.79
Chronic	2 (<0.1%)	6 (0.1%)	0.18

Source: NEJM

Onglyza's efficacy appears in line with the class based on Phase III data presented at ADA and EASD 2008. The registrational program included Phase I/II data with subjects exposed to 20-80x the 5mg dose for up to 6 weeks. In addition, 670 subjects received 2-10x the 5mg dose for up to 12 weeks. The Phase III program was in line with the FDA guidance with respect to development of diabetes drugs and included over 1,000 patients treated with 10mg for more than two years and over 3,000 patients treated at any dose. Onglyza is approved for two doses (2.5 and 5mg) and has only one downward dose adjustment in renal impairment, unlike Januvia which has two adjustments depending on the severity of the renal disease. However, unlike Januvia, Onglyza is primarily metabolized through the CYP3A4/5 pathway and therefore patients on CYP3A4/5 inhibitors (e.g. ketoconazole, ritonavir, telithromycin) require the lower dose. Phase III trials raised some questions on Onglyza's safety profile, with reports of lymphocytopenia and thrombocytopenias. The thrombocytopenia was seen at doses not used in the Phase III trials, and the lymphocytopenia did not result in any clinical side effects. Onglyza's label, not surprisingly, includes in the laboratory section a discussion of dose-dependent increase in lymphocytes.

Comparison Of Marketed DPP-IV Inhibitors

Name	Januvia	Onglyza	Tradjenta	Nesina
Generic Name	sitagliptin	saxagliptin	linagliptin	alogliptin
Company	Merck	Bristol-Myers/AstraZeneca	Lilly/BI	Takeda
Stage of Development	Approved	Approved	Approved	Approved
Dose	100 mg QD 25-50mg QD for renal failure	5mg QD One downward dose-adjustment in renal failure patients; dose-adjustment when used with CYP inhibitors	5mg QD No dose adjustment for renal or hepatic impairment	25mg QD No dose adjustment for mild renal impairment; dose adjust to 6.25mg in moderate renal impairment or ESRD
HbA1C reduction (%)	-0.5 to -0.8	-0.4 to -0.9	-0.4 to -0.6	-0.4 to -1.0
ADME	Renal excretion	Liver metabolism; CYP3A4/5	90% excreted unchanged	60-71% excreted unchanged
Warnings/Precautions /Adverse Events	Post-marketing allergic reactions and Stevens-Johnson syndrome, pancreatitis	Hypersensitivity reactions; dose-dependent increase in lymphocytes	Nasopharyngitis, increased risk of pancreatitis	Pancreatitis, hypersensitivity reactions (anaphylaxis, angioedema, Stevens-Johnson syndrome), post marketing reports of non-fatal hepatic failure
Fixed dose combinations	Janumet (Januvia + met) approved U.S. & EU; Janumet XR (under review); Januvia+pioglitazone (development);	Kombiglyze (saxagliptin + met) approved U.S.; Kombiglyze XR (saxagliptin + metER) approved U.S.	Fixed dose combinations with met and metXR approved	Fixed dose combinations with metformin and pioglitazone approved

Source: Company data; ADA; EASD; www.januvia.com; www.onglyza.com; www.tradjenta.com; FDA label for Nesina

Kombiglyze XR Competes With Janumet XR

In November 2010, the FDA approved the once daily DPP-4/biguanide combination, Kombiglyze XR (Onglyza + Metformin XR), for the treatment of type 2 diabetes mellitus in adults. Kombiglyze XR enjoyed a first-to-market advantage; however, the approval of Merck's Janumet XR (Januvia + metformin XR) in February 2012 leveled the playing field. We view Januvia's dominant market share as a competitive advantage and believe that patients seeking a metformin XR combination product are more likely to use a Januvia-based drug. Kombiglyze will be used primarily in patients who have not been adequately controlled on metformin alone and in treatment-naïve patients who are unresponsive to changes in diet and exercise.

Forxiga Rolling Out In E.U. And U.S.

Forxiga/Farxiga (dapagliflozin) is once-daily SGLT-2 inhibitor. SGLT-2 inhibitors lower blood glucose levels by acting on the kidney where glucose is reabsorbed. Preventing the renal resorption of glucose promotes its urinary excretion, thereby lowering circulating glucose concentrations. This is an insulin independent mechanism. Dapagliflozin has demonstrated modest glucose and weight lowering and its side-effect profile requires elucidation. In July 2011, the FDA Endocrinologic and Metabolic Drugs Advisory Committee voted 6-9 against approval of dapagliflozin for the treatment of hyperglycemia in T2DM, stating that a sufficient risk-benefit ratio had not

been demonstrated. In October 2011, the FDA extended dapagliflozin's action date by three months to January 2012 with a request for additional data from recently completed and ongoing Phase III clinical trials (Studies 18 and 19). According to Astra, neither Study 18 nor 19 demonstrated an additional imbalance in the incidence of bladder cancer, breast cancer, overall malignancies, or liver toxicity. In January 2012, FDA issued a complete response letter for dapagliflozin.

Bristol refiled in July 2013, received a positive recommendation at its December 2013 Endocrine Adcom review, and was approved by the FDA in January, 2014 (U.S. name Farixa). Forxiga was approved in the E.U. in November 2012 and in Japan in March 2014. Xigduo (dapagliflozin + metformin) was approved in the E.U. in January 2014. Forxiga triple therapy (dapagliflozin, metformin, sulfonylurea) was submitted in E.U. in Q4:13. A triple combo of Onglyza (saxagliptin) + dapagliflozin + metformin is being evaluated in three Phase III studies in 1,000+ patients poorly controlled on metformin. The primary endpoint is HbA1c reduction at 24 weeks; first data (n=534) was presented at ADA 2014 which showed an HbA1c reduction of 1.47% for saxa+dapa vs a 0.88% reduction for saxa+placebo, and 1.2% reduction for dapa+placebo. We estimate Forxiga sales to be \$55MM in 2014, \$130MM in 2015, \$200MM in 2016, \$400MM in 2018, and \$600MM in 2020.

AdCom Review Largely Addressed All Prior Forxiga Concerns

Astra received solid support from the FDA AdCom Committee for Forxiga (dapagliflozin) in the treatment of type 2 diabetes. Concerns surrounding CV risk, bladder cancer, and liver toxicity that delayed dapa's prior submission were sufficiently addressed. Panel members believed that lingering concerns regarding CV effects in high risk patients and possible link to bladder and breast cancer could be adequately addressed in post-marketing studies.

The committee voted 10-4 that dapagliflozin had an acceptable CV risk profile relative to comparators. The panel largely believed that Astra met FDA guidelines for CV risk and that the overall population results were most informative. Sub group data, especially high-risk CV patients, were less convincing to some panel members, but the already started DECLARE-TIMI58 trial (completion date April 2019) to further evaluate CV outcomes was viewed as appropriate follow-up.

The committee was supportive of the oncology experts' view of the data on malignancy that dapa was unlikely to be the cause of the numerical imbalance in bladder cancer. The expert opinions suggested that the risk of bladder cancer caused by dapa was not convincing and were reassured by the high percentage of cancers that occurred in 6 months (too soon for drug induced), most cases had pre-existing hematuria (possible sign of bladder cancer), and the distribution of all cancers reflected a normal population. Committee felt post-market surveillance should be required (and which is part of DECLARE). Breast cancer (a more common malignancy) is also included in surveillance in the DECLARE trial.

Hepatotoxicity concerns were sufficiently addressed. The one case of liver toxicity, after additional follow-up, appeared unlikely to be caused by dapa. A liver expert on the panel felt that the data showing increased liver enzymes was reflective of underlying disease and not due to dapa. Overall, the panel felt there was a lack of evidence supporting liver abnormalities, but felt that monitoring of liver toxicities post-marketing was warranted.

Phase III Data Show Benefits of Forxiga As Add-on Therapy

At EASD 2013, Phase III data confirmed dapagliflozin effectiveness as add-on therapy by demonstrating significantly reduced HbA1c vs. placebo at 24 weeks (mean change from baseline of -0.86%) in type II diabetic patients inadequately controlled on metformin/sulfonylurea. Dapagliflozin also showed HbA1c levels below 7%, improvements in FBG, reduction in body weight, and reductions in SBP compared to placebo. Adverse effects were similar to earlier studies, most mild/moderate, including hypoglycemia, UTI, genital infection, and renal complications (1.8% vs. 0% for placebo including one case of pyelonephritis).

Dapagliflozin Phase III Program

	Enrollment	Start Date	Completion Date
A Phase III Study of BMS-512148 (Dapagliflozin) in Asian Patients With Type 2 Diabetes Who Are Not Well Controlled With Diet and Exercise	378	June 2010	April 2012
Efficacy and Safety of Dapagliflozin in Combination With Metformin in Type 2 Diabetes Patients	816	March 2008	January 2013
Glycemic Efficacy and Renal Safety Study of Dapagliflozin in Subjects With Type 2 Diabetes Mellitus and Moderate Renal Impairment	252	June 2008	July 2011 (still listed as ongoing)
Evaluation of the Effect of Dapagliflozin in Combination With Metformin on Body Weight in Subjects With Type 2 Diabetes	182	February 2009	December 2011
Evaluate Efficacy and Safety in Japanese Subjects With Type 2 Diabetes Mellitus	255	February 2011	March 2012
Efficacy and Safety in Patients With Type 2 Diabetes Mellitus and Cardiovascular Disease	964	March 2010	December 2012
Efficacy and Safety in Patients With Type 2 Diabetes Mellitus, Cardiovascular Disease and Hypertension	922	February 2010	December 2012
Evaluate Safety as Mono or Combination Therapies With Anti-diabetes Mellitus Drugs in Japanese Subjects With Type 2 Diabetes Mellitus	700	February 2011	September 2012

Source: clinicaltrials.gov

Dapagliflozin 52-Week Phase III Data Were Robust

In September 2010, Bristol released data from its randomized double-blind Phase III study of dapagliflozin in adult patients with type 2 diabetes who were not well controlled on metformin monotherapy ($\geq 1500\text{mg/day}$). The 52-week, 814-patient study met its primary endpoint and showed that treatment with dapagliflozin (n=406, starting dose of 2.5mg QD titrated up to 10mg QD) was non-inferior to treatment with sulfonylurea glipizide (n=408, starting dose of 5mg QD titrated up to 20mg QD) in lowering HbA1c levels on top of metformin therapy. The measure of non-inferiority was defined as the treatment group difference in HbA1c reduction of <0.35% when dapagliflozin or glipizide were added to metformin monotherapy. Patients treated with dapagliflozin plus metformin achieved an adjusted mean reduction in HbA1c from baseline of -0.52%, which was directly comparable to the adjusted mean reduction in

HbA1c from baseline for patients treated with glipizide plus metformin (net improvement of 0.0%: 95% CI: -0.11, 0.11). The study also met key secondary endpoints for the dapagliflozin plus metformin combination at Week 52, including a reduction in total body weight from baseline of 3.22kg ($p < 0.0001$) and a statistically significant lower number of patients on dapagliflozin plus metformin reported ≥ 1 hypoglycemic events compared to patients receiving glipizide plus metformin (3.5% vs. 40.8%; $p < 0.0001$). In the study, patients receiving glipizide plus metformin therapy achieved a weight gain of 1.44kg ($p < 0.0001$). At Week 52, a significantly greater percentage of patients receiving dapagliflozin plus metformin achieved a weight loss of $\geq 5\%$ at baseline compared to patients receiving glipizide plus metformin (33.3% vs. 2.5%; $p < 0.0001$).

Patients receiving dapagliflozin plus metformin treatment experienced a comparable rate of AEs and serious AEs at Week 52 compared to patients receiving glipizide plus metformin therapy (AEs: 78.3% vs. 77.9%, respectively; SAEs: 8.6% vs. 11.3%, respectively) with the most common treatment-related AEs for patients on dapagliflozin plus metformin versus glipizide plus metformin being nasopharyngitis (10.6% vs. 15.0%), hypertension (7.4% vs. 8.6%), and influenza (7.4% for both treatment groups). Patients who discontinued from the study were higher for the dapagliflozin plus metformin treatment group compared to the glipizide plus metformin treatment group (9.1% vs. 5.9%). Signs and symptoms of urinary tract infections and genital infections for patients receiving dapagliflozin plus metformin were 10.8% and 12.3%, respectively, which were higher than the signs and symptoms rates for patients treated with glipizide plus metformin, 6.4% and 2.7%, respectively. One patient in the dapagliflozin plus metformin treatment group and one patient in the glipizide plus metformin group discontinued the trial due to a urinary tract infection. Three patients in the dapagliflozin plus metformin treatment group discontinued the trial due to a genital infection and two patients in the glipizide plus metformin group experienced pyelonephritis. Our experts believe that the adoption of dapagliflozin will depend on the incidence and severity of these types of infections. Patients treated with dapagliflozin plus metformin showed a reduction in systolic and diastolic blood pressure of 4.3mmHg and 1.6mmHg, respectively, compared to an systolic increase of 0.8mmHg and a diastolic reduction of 0.4mmHg for patients treated with glipizide plus metformin.

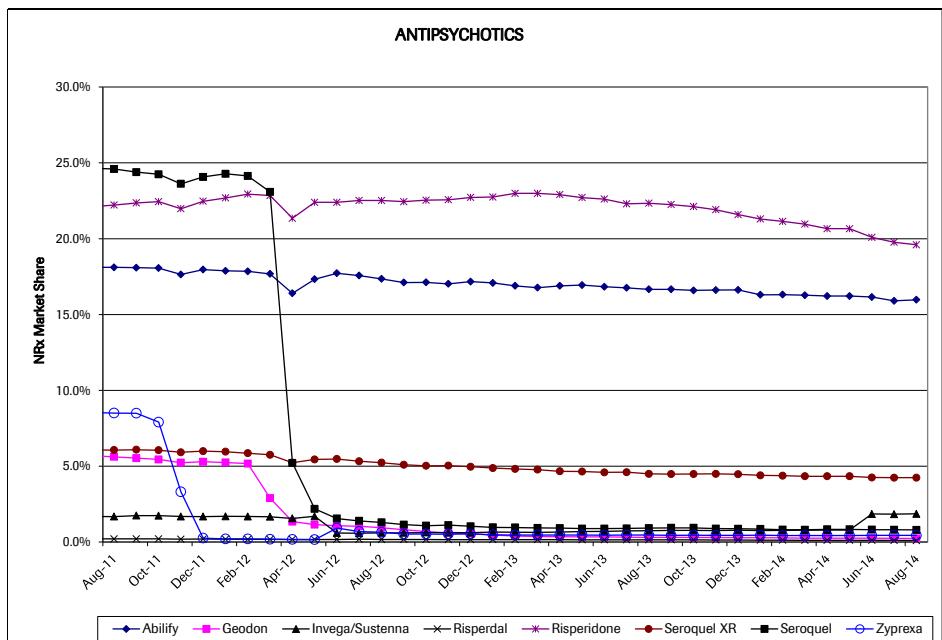
CNS

Seroquel Franchise In Decline Post Loss Of IR Exclusivity

Quetiapine is considered the most widely applicable anti-psychotic. In March 2012, Seroquel IR held a 23.1% U.S. prescription share of the antipsychotic market, but only 0.9% in August 2013 post its March 2012 LOE. As of August 2014, Seroquel XR held a 4.2% share of the antipsychotic market, a 1% y/yr decline due to the introduction of IR generics. Seroquel benefited from a favorable side-effect profile and extensive use in bipolar disorder. Seroquel is indicated for the treatment of: 1) schizophrenia, 2) acute manic episodes associated with bipolar disorder, 3) maintenance of bipolar disorder, 4) depressive episodes associated with bipolar disorder, and 5) adjunctive treatment to antidepressants in patients with MDD. Astra had sought indications for acute monotherapy and maintenance monotherapy for the treatment of MDD but received a complete response letter; Astra will not pursue this claim further. As a monotherapy, Seroquel would have been differentiated from Bristol's antipsychotic Abilify that is also approved as an adjunctive treatment for MDD. Seroquel was approved for MDD in the E.U. in September 2010. Seroquel has been approved for the treatment of pediatric patients with schizophrenia (13-17 years old) and bipolar mania (10-17 years old). We estimate Seroquel IR sales of \$260MM (-25%) in 2014, \$145MM in 2015, \$105MM in

2016, \$50MM in 2018, and \$20MM in 2020 and Seroquel XR sales of \$1.22B (-9%) in 2014, \$1.125B in 2015, \$1.07B in 2016, \$340MM in 2018, and \$205MM in 2020, post the 2017 patent expiration.

Antipsychotic Market Monthly Total Prescription Share



Source: IMS America

Side-Effect Profile A Major Driver

Our psychiatric physician consultants in the U.S. and Europe believe that the main uses of Seroquel are for the treatment of psychosis and mood disorders in patients susceptible to EPS side effects and as adjunctive therapy to other atypicals. This population includes the elderly with Alzheimer's or Parkinson's disease and adolescents with psychoses. We estimate that these populations account for up to 70% of Seroquel use in the U.S. Our physician consultants also note that Seroquel's sedating effect is particularly useful in hospitalized non-schizophrenic psychosis patients. The U.S. National Economic Development Board suggests that over 60% of atypical antipsychotic sales are through Medicaid and over 50% are for off-label indications. Off-label use represents a significant cost of treating the psychotic elderly. This use of Seroquel is supported by a plethora of small studies (10 to 20 patients from single centers) and a single 250-patient study looking at the safety and efficacy of Seroquel in elderly patients with Parkinson's disease, dementia and psychosis.

Adverse Events Comparison Of Seroquel And Other Atypical Antipsychotics

Drug	Brand Name	Incidence Of Adverse Event				
		Weight Gain >7%	Warning ECG Prolongation	Increased Prolactin	Somnolence	Discontinuing Therapy
Risperidone	Risperdal	18%	No	Yes	8%	10%
placebo		9%			1%	7%
Olanzapine	Zyprexa	29%	No	Yes	29%	5%
placebo		3%			13%	6%
Ziprasidone	Geodon	10%	Yes	Yes	14%	4%
placebo		4%			7%	2%
Aripiprazole	Abilify	8%	No	No	11%	7%
placebo		3%			8%	9%
Quetiapine	Seroquel	23%	No	No	18%	4%
placebo		6%			11%	3%
Paliperidone	Invega	9%	No	Yes	11%	5%
placebo		5%			7%	5%

Source: Product labels

Resolution Of Seroquel XR U.S. Patent Litigation Removes Lingering Risk

AstraZeneca lists two patents in the FDA's Orange Book referencing Seroquel XR: the '288 patent covering the active ingredient and the '437 patent covering extended-release formulations, processes and methods.

In October and November 2008, AstraZeneca received Paragraph IV Certification notice-letter from Handa advising that it had submitted an ANDA seeking approval to market 50mg and 150mg versions of Seroquel XR tablets. In October and then in December 2008, AstraZeneca filed a lawsuit in District of New Jersey against Handa alleging infringement of AstraZeneca's patents covering the active ingredient and formulation of Seroquel XR 50mg and 150mg tablets. In September 2011, Astra entered into a settlement with Handa and granting a license to enter the U.S. market with generic Seroquel XR on November 1, 2016.

In January 2009, AstraZeneca received a Paragraph IV Certification notice-letter from Accord advising that it had submitted an ANDA seeking approval of 150mg Seroquel XR tablets before expiration of the '437 patent. In February 2009, AstraZeneca filed suit against Accord triggering a 30-month stay. In March 2010, AstraZeneca received a Paragraph IV Certification notice-letter from Anchen seeking approval to market generic versions of 150, 200, 300 and 400mg Seroquel XR tablets. In April 2010, AstraZeneca filed a lawsuit in US District Court, District of New Jersey against Anchen. In October 2011, Astra settled with Accord, granting a license effective November 1, 2016.

In August 2012, AZN commenced patent infringement action against Amneal in the New Jersey District Court. In September 2012, AZN received a Paragraph IV notice letter from Lupin relating to Seroquel XR..

The U.S. District Court of New Jersey found the formulation patent to be valid and enforceable in March 2012. The U.S. District Court ruled that Anchen Pharmaceuticals, Osmotica Pharmaceutical Corporation, Torrent Pharmaceuticals, and Mylan Pharmaceuticals have infringed upon the Seroquel XR formulation patent. The decision was appealed. In January 2013, AstraZeneca settled its patent infringement action against Amneal by granting a license to the Seroquel XR product patent, effective November 1, 2016. In February 2013 and April 2013, Astra settled with Torrent and Lupin, respectively, granting both a license effective November 1, 2016.

The formulation patent for Seroquel XR was ruled invalid by the High Court in the UK. The District Court in The Hague upheld the validity of the patent. A hearing regarding the validity of the Seroquel XR formulation patent has been held in Spain; the validity of the patent was upheld. Generic versions of Seroquel XR have been launched in Germany, Austria, and Denmark. However, in September 2012, the Regional Court in Düsseldorf, Germany affirmed preliminary injunctions against five generic manufacturers. However, in November 2012, the Federal Patent Court found the patent invalid.

Lilly To Collaborate With AstraZeneca On BACE Inhibitor

In September 2014, AstraZeneca and Lilly announced an agreement to co-develop and commercialize AZD3293, an oral BACE inhibitor for Alzheimer's that has completed Phase I trials. The phase I studies demonstrated that AZD3293 reduces beta-amyloid in the CSF of Alzheimer's patients and healthy volunteers. Lilly will pay AZN \$50MM upfront and up to \$500MM in development and regulatory milestones. Lilly will lead clinical development and Astra will be responsible for manufacturing. The two companies will share costs equally for development and commercialization and net-revenues post-launch. The companies intend to quickly initiate Phase II/III trials in early Alzheimer's.

Respiratory/Inflammatory

Pipeline Well Balanced Between Small Molecules And Biologics

A summary of Astra's respiratory and inflammation portfolio is below:

Summary Of Respiratory/Inflammation Portfolio

Phase I		Phase II		Phase III/Registration	
Small Molecule	Large Molecule	Small Molecule	Large Molecule	Small Molecule	Large Molecule
AZD7624	MEDI4920	AZD2115	mavilimumab	PT003	brodalumab
AZD8848	MEDI5872	PT010	sifalimumab	lesinurad	benralizumab
AZD1419		RDEA3170	anifrolumab	PT001	
AZD7594			AZD9412		
			MEDI7183		
			MEDI2070		
			MEDI9929		
			tralokinumab		

Source: Company data

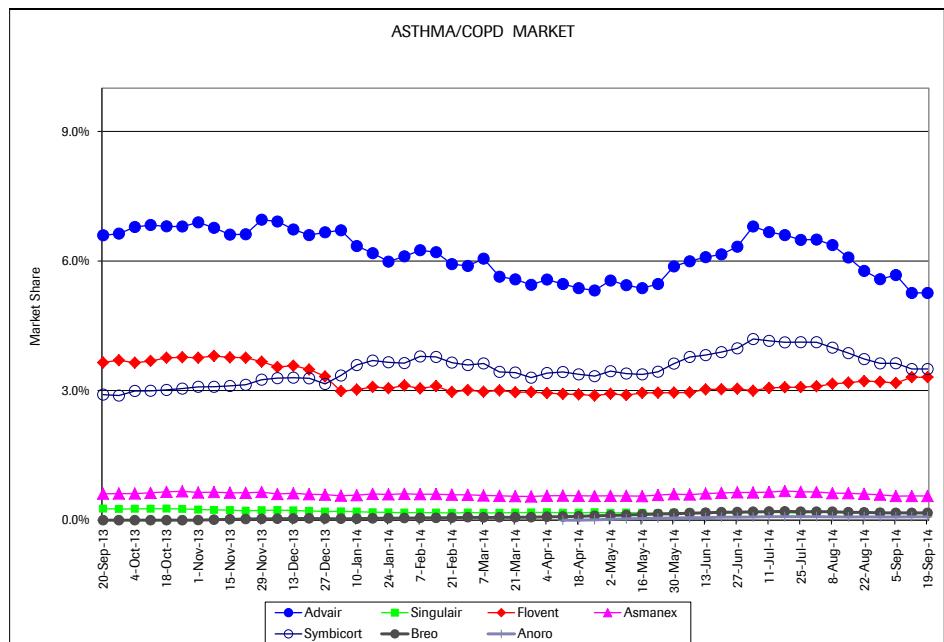
Symbicort Should Grow But Generics A Risk; Generic Filed In E.U.

Symbicort is an inhaled combination of budesonide (ICS) and formoterol (LABA) indicated for the treatment of asthma and COPD (88 countries ex-U.S.). AstraZeneca launched Symbicort pMDI (budesonide/formoterol) in the U.S. in July 2007 for the maintenance treatment of asthma in patients age 12 and older based on an NDA package that included 27 trials using the "Turbuhaler" dry powder device. The filing included the OPTIMA and FACET trials which showed that the combination of budesonide and formoterol reduces exacerbations and improves lung function. In Europe, the adjustable dose version of Symbicort dominates. However, U.S. physicians traditionally have been reluctant to place dosing in the hands of individual patients. Therefore, AstraZeneca pursued Symbicort at two fixed doses in the U.S. Superiority

of Symbicort has only been demonstrated with the adjustable dosing regimen and we expect this factor to be a hurdle in promoting the fixed dose.

Budesonide is an important alternative inhaled steroid, given that it shares Flovent's (fluticasone) efficacy but with less systemic absorption. Additionally, patients might benefit from the faster onset of action of formoterol, the long-acting beta agonist in Symbicort (as opposed to salmeterol, the long-acting beta agonist in GlaxoSmithKline's Advair). This has potential utility in an acute asthmatic attack. However, other than these two attributes, there appears to be little to distinguish Advair from Symbicort. In February 2009, FDA approved Symbicort 16-4.5 mcg for maintenance therapy in COPD including emphysema and chronic bronchitis. This puts Symbicort on equal footing to Advair in the U.S. The pediatric (children ages 6-11) sNDA for asthma received a CRL in April 2009 requiring additional trials which have not been done. In August 2009, Astra and Astellas announced that they had entered into a collaboration in Japan. Symbicort was launched in Japan and approved in Canada in January 2010. We forecast Symbicort sales of \$3.77B (+8%) in 2014, \$3.8B in 2015, \$3.515B in 2016, \$2.805B in 2018, and \$2.095B in 2020. Admittedly, our estimates are at risk pending additional visibility on generic competition.

Asthma/COPD Market



Source: IMS America

E.U. Generics a Looming Threat

Teva received approval of its generic Symbicort, called DuoResp Spiromax and BiResp Spiromax, from EMA in February 2014. Approval is anticipated for both asthma and COPD.

Pulmicort Declining In U.S./E.U. Due To Generic Competition

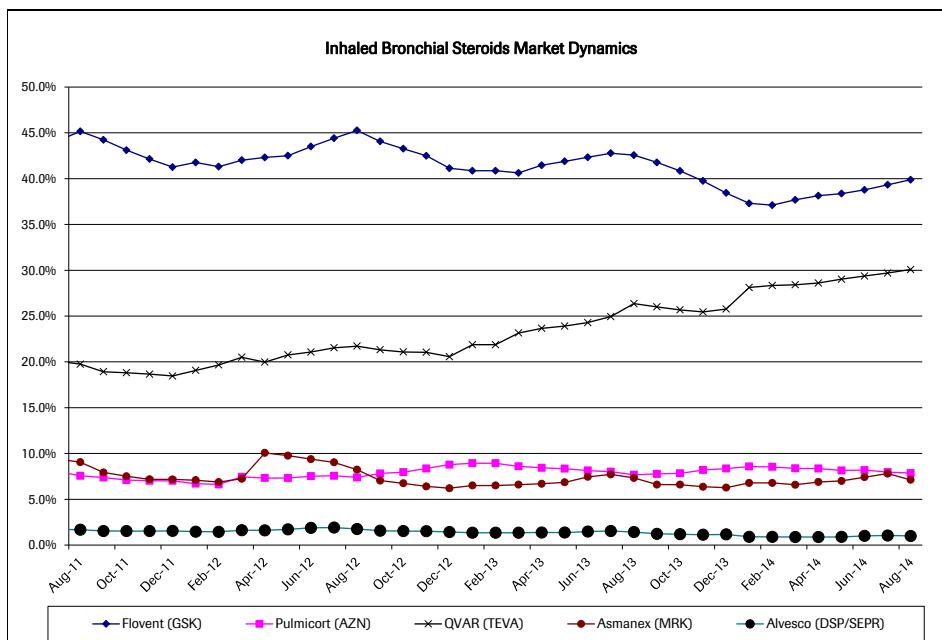
Pulmicort (budesonide) is an inhaled corticosteroid indicated for maintenance treatment of asthma in children and adults. In some countries, Pulmicort is also indicated for maintenance treatment of COPD. Pulmicort is available in three

administration forms: Pulmicort Turbuhaler, a dry powder inhaler; Pulmicort Respules, a nebulizing suspension; and Pulmicort pMDI, a pressurized metered-dose inhaler. In the U.S., Pulmicort Respules is indicated for maintenance therapy in pediatric patients 12 months to 8 years and constitute 90% of the franchise sales.

In November 2008, Teva launched at-risk its generic Pulmicort Respules after FDA denied AstraZeneca's Citizen's Petition. AstraZeneca won a temporary restraining order (TRO) against Teva requiring it not ship additional supply. The TRO prohibited further distribution of AstraZeneca's authorized generic that was being distributed by PAR. On November 25th, 2009 the day of the preliminary injunction hearing, AstraZeneca announced that it had settled with Teva. The agreement allowed Teva to commercialize its version of the Respules under an exclusive license beginning December 15, 2009 for undisclosed royalties. Teva agreed to pay damages for the unauthorized launch of its generic but allowed for any shipped generic to remain in the market. AstraZeneca discontinued its agreement with PAR to sell the authorized generic. In March 2009, the FDA granted Apotex approval for its generic Pulmicort Respules. Astra then filed suit following Apotex's indication of intent to launch at risk its generic. In May 2009, the U.S. District Court for the District of New Jersey granted an injunction barring Apotex from launching a generic version of Pulmicort Respules. Apotex was denied an appeal of the PI by the Court of Appeals of the Federal Circuit.

In April 2013, the U.S. District Court for the District of New Jersey ruled that AZN's '603 patent is invalid; Astra appealed and an injunction was issued in May 2013 until the Court rules on Astra's appeal. In October 2013, the Appeals court reversed and remanded for further proceedings the decision that the generics do not infringe patent '834 but upheld the decision that the '603 is invalid. In December 2013, the Court granted Astra's motion and temporarily enjoined the generics from entering the market until a resolution of Astra's motion for a preliminary injunction. A trial is scheduled to start on October 6th, 2014; the current injunction preventing an at-risk launch by generics will remain in place until a decision is issued after the trial. Pulmicort sales are forecast to be \$890MM (+3%) in 2014, \$850MM in 2015, \$800MM in 2016, \$750MM in 2018, and \$705MM in 2020.

Inhaled Bronchial Steroids Market Dynamics



Source: IMS America

Almirall Acquisition Beefs Up Respiratory Portfolio

In July 2013, Astra announced the acquisition of the rights to Almirall's respiratory business for \$875MM upfront and up to an additional \$1.22B in potential milestone payments. The company expects the transaction to close by the end of 2014 and be neutral to Core EPS in 2015 and accretive starting in 2016.

The products/rights acquired include: Eklira Genuair (LAMA aclidinium in dpi) - approved for COPD in EU; LAS40464 (LAMA/LABA, aclidinium/formoterol) – filed in EU, in trials in US; LAS10097 (abediterol) – once-daily LABA in Phase II; LAS191351 and LAS194871 – both MABAs in pre-clinicals; LAS190792 – MABA in Phase I; and multiple pre-clinical programs.

With roughly \$5B+ in total respiratory sales, Almirall adds only modest near-term revenues (estimated at \$150MM for 2014), but strengthens the pipeline (with several new compounds to complement the ones acquired in 2013 with the Pearl acquisition), provides an approved dry powder inhaler to go along with their metered dose device, and positions the company to create a broad portfolio of new compounds for the respiratory market in the coming years.

AZN's Benralizumab In Phase III Asthma And COPD Studies

Benralizumab is an anti-IL-5R α antibody targeting asthmatics with eosinophils (represents ~40-60% of severe asthmatics). Given that high eosinophil count is associated with asthma exacerbations, depleting eosinophils by blocking IL-5R α is a logical strategy for the treatment of severe asthma. Astra believes targeting the receptor and killing associated eosinophils is superior to targeting IL-5 itself. Astra is pursuing use in asthma and COPD. We estimate benralizumab sales of \$25MM in 2017, \$50MM in 2018, and \$100MM in 2020.

Asthma: A Phase III trial (Windward program) began in October 2013. The first study, CALIMA, will determine whether benralizumab reduces the number of exacerbations in patients with severe asthma uncontrolled on steroids and LABAs. The two pivotal studies will be SIROCCO (benralizumab + high-dose inhaled steroids+ LABA) and PAMPERO (benralizumab + medium-dose inhaled steroid + LABA). There will also be an oral corticosteroid reducing trial (ZONDA), and a long-term safety trial (BORA). Astra expects to file in 2016.

At ATS 2014, AstraZeneca reported data from a Phase II study which demonstrated a statistically significant reduction in asthma exacerbations (of 41%) at 52 weeks with 100mg benralizumab compared to placebo for patients who were EOS+. In the EOS-cohort, the reduction with benralizumab was only 22%. A further breakdown of EOS+ patients showed greater reductions in exacerbations in patients with higher levels of eosinophilia; exacerbation reduction reached 70% in the group with the highest levels of eosinophils. Statistical improvements in FEV1 occurred in all groups; and again, patients with highest eosinophil levels showed greatest improvement. Benralizumab is given by SC injection every 4-8 weeks. Benralizumab is currently in two Phase III studies which are expected to complete in Q1:16.

COPD: Results for a Phase IIa study of benralizumab in COPD patients did not show a reduction in exacerbations in the overall group, but did show decreases in patients with elevated eosinophils (~one-third of severe COPD). A sustained improvement in FEV1 was seen after the first dose in all patients.

Astra initiated the Phase III Voyager program in Q2:14 evaluating benralizumab in patients with moderate to very severe COPD and high risk of exacerbations. The two pivotal studies are GALATHEA and TERRANOVA. Patients included have a wide range of eosinophil levels. The primary endpoint is reduction in rate of exacerbations; the secondary endpoints include FEV1 and quality of life measures.

AZN's Tralokinumab In Phase III For Asthma

Tralokinumab is a targeted antibody against IL-13 for the treatment of severe, inadequately controlled asthma. IL-13 is a central mediator of asthma. Early clinical data shows tralokinumab improved FEV1 after 90 days of treatment and that the treatment effect was maintained for 170 days. Results from a Phase IIB study in severe uncontrolled asthma were presented in May 2014 at ATS, which showed that tralokinumab did not meet the primary endpoint of reduction in exacerbation rate in the all-comers population, but significant reductions were reported in the high- periostin sub-population. A Phase III trial was initiated in August 2014 in patients with severe uncontrolled asthma. This trial will enroll 3,250 patients and is expected to complete in November 2017.

Tralokinumab is also being evaluated in a Phase II trial for IPF (idiopathic pulmonary fibrosis) and may provide another opportunity for IL-13. We estimate tralokinumab sales of \$25MM in 2017, \$50MM in 2018, and \$100MM in 2020.

Several Compounds In Phase II/III Development For Respiratory Diseases

AZD2115 - is a bifunctional dual LABA and LAMA (MABA) with the potential to provide dual bronchodilation. AZD2115 has been tested at three doses, all three of which increased FEV1 by ~320-420mL. The linker between the LABA and LAMA portions of the molecule is critical to the activity of AZD2115. The MABA will be used in combination with AZD5423 to create a triple therapy combination.

PT003 – is a fixed dose combination of formoterol fumarate (LABA) and glycopyrrolate (LAMA) delivered in a pMDI using a novel co-suspension formulation technology. A global Phase III study (PINNACLE) was initiated in July 2013 to evaluate effectiveness in moderate-to-severe COPD patients. PT003 is the lead compound from the June 2013 acquisition of Pearl Therapeutics.

PT010 – a triple therapy LAMA/LABA/ICS currently in Phase II and expected to be in Phase III mid-2015, and in the market for asthma and COPD in 2020. AZN believes its device, product formulation, and twice-daily dosing will be key differentiating factors, and that budesonide (steroid) has unique characteristics.

MEDI9929/AMG157 – is anti-TSLP; a May 2014 NEJM article discussed the agent's effects on allergen-induced asthma. This is the first study in humans. MEDI9929 reduced allergen-induced bronchoconstriction and airway inflammation with an acceptable safety profile. No dose-limiting toxicity has been observed. A Phase II study in severe asthma is enrolling patients.

SNG001 – an inhaled interferon-beta targeting viral infections in patients with severe asthma which Astra licensed from Synairgen in June 2014; Astra will pay \$7.25MM upfront and up to \$225MM in milestone payments as well as tiered royalties on future sales. Astra is also responsible for the development costs. A Phase IIa study is expected to start in early 2015 in patients with severe asthma.

Several other Phase I/II assets in development for various indications are detailed below:

Respiratory Phase I/II Programs

Disease Area	Asset	Mechanism	Phase
COPD	AZD7624	p38i	I
	AZD7594	SGRM	I
	AZD2115	MABA	II
	AZD9412	inhaled betalFN	II
	PT010	LABA/LAMA/ICS	II
Asthma	AZD8848	TLR7 agonist	I
	AZD1419	TLR9	I
	AZD7594	SGRM	I
	AZD9412	inhaled betalFN	II
	MEDI19929	TSLP	II
	tralokinumab	IL-13	II

Source: Company data

Lesinurad Phase III Data Positive

In April 2012, Astra announced the acquisition Ardea Biosciences for \$1.2B. The acquisition gave Astra rights to lesinurad, Ardea's Phase III URAT1 inhibitor for the treatment of hyperuricaemia associated with gout.

In August 2014, top-line data from the pivotal Phase III trials CLEAR1, CLEAR2, and CRYSTAL was released. In these trials, lesinurad was used in combination with allopurinol or febuxostat (xanthine oxidase inhibitors). In CLEAR1 and CLEAR2, lesinurad 200mg or 400mg once daily plus allopurinol met the primary endpoint of a

statistically significant higher percentage of patients achieving the target sUA goal of <6.0mg/dL at 6 months compared to allopurinol alone.

In CRYSTAL, lesinurad 400mg plus febuxostat met the primary endpoint of a statistically higher percentage of patients achieving the target sUA goal of <5.0mg/dL compared to febuxostat alone at 6 months. The 200mg lesinurad dose plus febuxostat did not meet this endpoint (although was superior at other time points). The most common adverse events in all trials were respiratory tract infections, nasopharyngitis, arthralgia, and back pain. Renal-related events with lesinurad 200mg plus XO inhibitor was similar to XO alone. However, the incidence was higher with the 400mg lesinurad dose.

Full data from these studies will be provided in Q4:14 with regulatory filings for the 200mg dose (as combo therapy) expected in the U.S. and EU by year end. We estimate lesinurad sales of \$25MM in 2016, \$75MM in 2018 and \$125MM in 2020.

Top-Line Phase III LIGHT Data Raised Safety Concerns

In December 2013, Astra released top-line data from the six-month, LIGHT trial which evaluated 400mg of lesinurad once daily vs. placebo in 214 patients who were intolerant to xanthine oxidase inhibitors (allopurinol, febuxostat). The study met its primary endpoint with a statistically significant higher percentage of patients meeting the sUA target of <6.0mg/dL vs. placebo. The company indicated that lesinurad patients were more likely to have elevated serum creatinine and adverse renal events, including serious adverse events. Other common SEs noted were diarrhea, nausea, and constipation. Full data is expected in Q4:14.

Combo Therapy May Be Best Opportunity

Our consultants think that lesinurad's efficacy as a monotherapy is on par with 300mg of allopurinol. Thus, only those patients with a baseline sUA of 7-9mg/dL may benefit from lesinurad monotherapy while those patients with higher levels of sUA would not reach a goal of serum uric acid <6mg/dL. Therefore, they think real commercial potential for this drug is as a combination therapy.

Safety Looks To Be Key Factor

Consultants note that lesinurad's safety data to date is limited. The serious adverse effects cited (but not yet specified) in the LIGHT trial warrant further review and safety findings in the remaining Phase III programs will likely be key to future development. In addition, while a primary endpoint of reduction in serum uric acid is acceptable to the FDA for approval, regulatory agencies are also interested in specific, more clinically relevant, secondary endpoints such as flare reduction, improvement in quality of life, and tophi reduction. However, doctors believe that while testing these endpoints is important, no drug has been able to meet these clinical endpoints in less than a year except for Savient's Krystexxa. Thus, while important, these clinical measures have been hard to achieve.

Brodalumab Successful In Phase III Plaque Arthritis and Phase II Psoriatic Arthritis Trials

In May 2014, Astra (with partner Amgen) reported results from a Phase III study (AMAGINE-1) of brodalumab (IL-17 inhibitor) in patients with moderate-to-severe plaque psoriasis. Primary (PASI75, sPGA 0 or 1) and secondary endpoints (PASI 90 and PASI 100) at 12 weeks were met at both doses evaluated. At the 210mg dose, 83.3% of patients achieved PASI75 and 60.3% at 140mg. PASI90 was reached by

70.3% of patients at the 210mg and 42.5% at the 140mg. Serious side effects occurred in 1.8% of the 210mg group and 2.7% of the 140mg arm compared to 1.4% for placebo. Two other Phase III studies are in progress (AMIGINE-2 and -3) which are evaluating brodalumab at different dose schedules and compared to ustekinumab and placebo in patients with moderate-to-severe plaque psoriasis. Top-line data from these trials is expected in Q4:14. We estimate brodalumab sales of \$50MM in 2016, \$100MM in 2018, and \$150MM in 2020.

In June 2014, Astra/Amgen reported results from a Phase II trial of brodalumab given SC at 140mg or 280mg (on day 1, weeks 1 and 2, then q2 wks.) in patients with active psoriatic arthritis. The study met its primary endpoint by showing superiority to placebo in ACR20 responses (a 20% improvement in baseline) at week 12. The 140mg brodalumab arm reported 37% of patients at ACR20, 39% of the 280mg brodalumab arm, and 18% for placebo. The responses improved through week 24 and were sustained through 52 weeks. Serious AEs occurred in 3% of the brodalumab patients vs. 2% in placebo and included skin infections (including 2 cases cellulitis), abdominal pain and cholecystitis. No significant neutropenia was reported. Two Phase III studies (AMVISION-1 and AMVISION-2) are in progress for psoriatic arthritis. Brodalumab is also being studied in asthma (Phase II).

An update of compounds in the Inflammatory pipeline are shown below. Both mavrilimumab (RA) and sifalimumab (SLE) met endpoints in Phase IIb studies announced in May 2014.

Inflammation Phase I/II Programs

Disease Area	Asset	Mechanism	Phase
Crohn's Disease	MEDI2070	IL-23	II
	MEDI7183	$\alpha 4\beta 7$	II
SLE	MEDI5872	B7RP1	I
	anifrolumab	INF α R	II
	sifalimumab	INF α	II
MS	MEDI-551	CD19	I
Ulcerative Colitis	MEDI7183	$\alpha 4\beta 7$	II
Primary Sjogren's Syndrome	MEDI4920	CD40L	I
Gout	RDEA3170	URAT1	II
Rheumatoid Arthritis	mavrilimumab	GM-CSFR	II

Source: Company data

A summary of anticipated H2: 14 respiratory and inflammation news flow is below:

2014 Respiratory And Inflammation News Flow

Timeline	Asset	Indication	Clinical Data and Potential Milestones
H2:14	brodalumab	plaque psoriasis	Phase III data (AMIGINE-1)
	mavrilimumab	RA	Phase IIb data at ACR (November)
	sifalimumab, MEDI-546	SLE	Phase IIb data at ACR (November)
	anifrolumab, MEDI-545	SLE	Phase IIb data at ACR (November)
	lesinurad	gout	Full Phase III data; U.S. and EU filing

Source: Company data

Gastrointestinal

Big Nexium Decline Post May 2014 U.S. Patent Expiration

AstraZeneca led the peptic ulcer market with its Nexium/Prilosec proton pump inhibitor (PPI) franchise. Nexium's share in May 2014 was 9.9% with new prescriptions down 13% year over year. However, by patent litigation settlement, the first-to-file generic (Ranbaxy) could have entered the market on May 27, 2014. But Ranbaxy has internal issues, which have prevented it from garnering final FDA approval. To date, no generics have launched. Post Ranbaxy's launch and once its six-month exclusivity expires, we anticipate that many generics will launch.

In Europe, AstraZeneca defended both the MUPS (multiple unit pellets) formulation and process patents, securing the MUPS patent expiration date of August 2015. The MUPS process and formulation patents are used for both Nexium and Losec tablets.

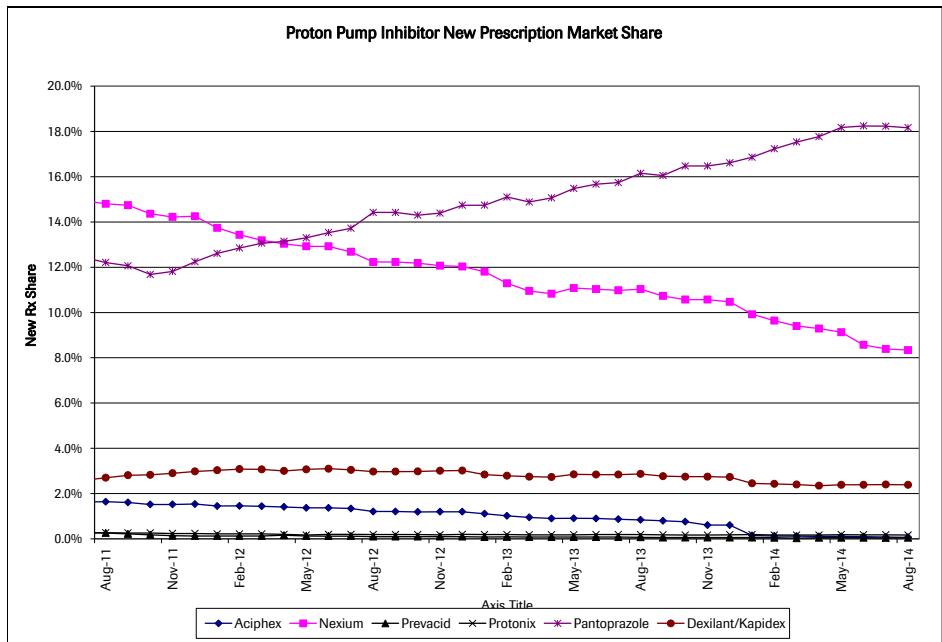
In January 2010, the District Court of Copenhagen granted AstraZeneca a preliminary injunction against Sandoz. Several injunctions have been filed against Sandoz and other generic companies in Portugal, Austria, and Slovakia. In Canada in March 2013, the Court prohibited Ranbaxy from launching until June 2015. A patent trial in Australia occurred in May 2013 versus Ranbaxy; a decision is pending. A final approval hearing on the topic of fraudulent sales and marketing practices associated with Nexium is pending in a Massachusetts Court with a trial scheduled for October 2014.

We estimate Nexium sales of \$3.275B (-15%) in 2014, \$1.885B in 2015, \$1.875B in 2016, \$1.935B in 2018, and \$2.06B in 2020, with the recovery in out year sales driven by emerging markets.

OTC Nexium Launched By Pfizer

In August 2012, Astra announced the sale of WW Nexium OTC rights to Pfizer for an upfront payment of \$250MM. Astra recognized the upfront payment as other income in 2012 (added ~\$0.16/share). Sales of Nexium OTC will trigger a contingent payment from Astra to Merck in 2014 (amount not disclosed). Nexium OTC has been approved and rollout is underway. Astra is eligible to receive milestone and royalty payments based on Nexium OTC launches and sales (details not disclosed), although royalty payments are not expected to contribute significantly to Astra revenue over time.

Proton Pump Inhibitor New Prescription Market Share



Source: IMS America

Movantik Approved For Once-Daily Use In OIC

Movantik (naloxegol) is an orally administered PEGylated formulation of the opioid antagonist naloxol, which targets mu-opioid receptors within the enteric nervous system, for the potential treatment of opioid-induced constipation. Naloxegol was licensed from Nektar. In November 2012, Astra announced positive top-line results from two Phase III trials and one safety extension trial in patients with non-cancer related pain and opioid-induced constipation. Both KODIAC-04 and -05 met their primary endpoint of percentage of OIC responders versus placebo over 12-weeks where the responder was defined as having at least three spontaneous bowel movements per week for at least nine out of 12 weeks, and at least three out of the last weeks. Updated safety data from naloxegol's KODIAK-08 Phase III 52-week safety and tolerability study in OIC (opioid induced constipation) was presented at the ACG in October 2013 and reiterated that there were just 2 MACE events in each arm of the study, which was randomized 2:1, naloxegol: usual care (UC). It was also disclosed that the MACE were not related to study drug. In addition, naloxegol's remaining safety and tolerability was disclosed and appears acceptable.

In June 2014, an FDA Adcom voted that this class of drugs (PAMORA) does not require CV outcome studies for approval, although post-approval data collection was recommended. Movantik was approved in September 2014 becoming the first once daily oral PAMORA available for chronic non-cancer pain. Movantik has also been filed in the EU (trade name Moventig) and Canada and received a positive CHMP opinion in September 2014. Movantik will be available in the U.S. in H1:15. We estimate Movantik sales of \$50MM in 2015, \$100MM in 2016, \$200MM in 2018, and \$300MM in 2020.

Infectious Diseases

FluMist Growing Modestly

FluMist, an intranasal influenza vaccine approved for use in healthy individuals aged 5 to 49, has not been able to compete effectively with the injectable vaccine. However, the second generation benefits from a broader label for individuals aged 2 through 49 years (approved September 2007), and data showing it is more effective than traditional injectable vaccine. Given that manufacturing issues are resolved and ACIP recommendation has been received, FluMist appears on track to realize its potential as a needle-free influenza vaccine. FluMist is however prohibited for use in children aged 2 to 17 with asthma and children aged 24-59 months with recurrent wheezing in the U.S., but AstraZeneca stated that this accounts for only 20% of the target population. In February 2011, Fluenz (E.U. name) was granted approval by the European Commission for children 24 months to less than 18 years of age. FluMist Quadrivalent was approved in the U.S in February 2012. In December 2013, the EC granted Marketing Authorization for Fluenz Tetra, a nasal 4-strain influenza vaccine for use in children/adolescents age 2-18 years old. Tetra will replace the existing Fluenz 3-strain vaccine starting in the 2014-15 flu season. We peg FluMist sales of \$245MM (flat) in 2014, \$245MM in 2015, \$255MM in 2016, \$275MM in 2018, and \$295MM in 2020.

Synagis Treading Water

Synagis is a humanized monoclonal antibody for the prevention of lower respiratory tract disease resulting from respiratory syncytial virus (RSV) in pediatric patients. RSV is the leading cause of respiratory tract infections in infants and young children. It is estimated that more than 125,000 infants/children are hospitalized each year due to RSV infection. Synagis was launched in 1998 and has almost fully penetrated the less-than-32 weeks and greater-than-32 weeks high-risk segments. Penetration into the 250K 32-35 week cohort has remained elusive, as there is tenuous medical need and lack of pharmacoeconomic data in this group. ACIP guidance has limited broader use of Synagis outside of its label which resulted in a softening in sales. We forecast Synagis sales of \$1,015MM (-4%) in 2014, \$1,025MM in 2015, \$1,035MM in 2016, \$1,055MM in 2018, and \$1,075MM in 2020.

Antibiotic CAZ-AVI Meets Primary Endpoint In Phase III Trial

CAZ-AVI is an antibiotic consisting of the cephalosporin ceftazidime plus the next-generation non-beta lactam beta-lactamase inhibitor avibactem. It is being developed for a broad range of serious Gram-negative infections, primarily those resistant to standard antibiotics. The RECLAIM-1 and RECLAIM-2 Phase III trials (n=1,066 for both) evaluated patients with complicated intra-abdominal infections (cIAI). In both studies CAZ-AVI was administered intravenously as a 2 hour infusion along with metronidazole. The studies were analyzed as a single pooled dataset (per FDA and EMA) and demonstrated that CAZ-AVI was non-inferior to metropenam based on primary endpoint of clinical cure rate at 28-35 days. The adverse event rate was similar for both arms, with diarrhea, nausea, vomiting and fever being the most common. Other trials are ongoing in complicated urinary tract infections and nosocomial pneumonia in patients with ceftazidime-resistant infections.

Full data will be provided at a future medical meeting in 2015. An EU filing is expected in Q1:15. CAZ-AZI is jointly developed with Forest/Actavis. Astra hold the global

rights, ex U.S. We estimate CAZ-AVI sales of \$50MM in 2016, \$100MM in 2018, and \$150MM in 2020.

Pain/Other

Vimovo (Nexium/Naproxen) A Modest Success

On April 30, 2010 FDA approved Vimovo for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. Vimovo (PN 400) is the combination of enteric coated (EC) naproxen and immediate release esomeprazole. The NDA submission was based on data from two pivotal studies (301/302) under a special protocol assessment agreed with the FDA, which met their primary endpoints. In the 301/302 studies, significantly fewer subjects taking Vimovo experienced endoscopically confirmed gastric ulcers compared to subjects receiving EC naproxen. The primary endpoint was the cumulative incidence of gastric ulcers through six months. In each of the trials, approximately 400 subjects received either Vimovo or EC naproxen (500 mg), twice daily, over a six-month treatment period. Subjects underwent upper endoscopies at baseline and at one, three, and six months.

Lack of compliance with gastroprotection in patients taking NSAIDs has been demonstrated as a risk factor for developing NSAID-related GI complications. Up to 60MM people in the U.S. regularly take NSAIDs, with serious GI effects developing in 1-2%. Roughly 65% of NSAID use is in the chronic setting, and approximately 25-30% of NSAID prescriptions are accompanied by a gastroprotective agent. In November 2010, marketing and pricing approval was granted for Vimovo in the UK. Astra divested U.S. rights to Vimovo, but retained ROW rights. We forecast sales of \$110MM (+21%) in 2014, \$130MM in 2015, \$150MM in 2016, \$190MM in 2018, and \$230MM in 2020.

MedImmune Receives Royalty On Merck And GSK HPV Vaccines

MedImmune held worldwide HPV intellectual property and monetized that asset through royalty-bearing licenses with GlaxoSmithKline and Merck for their HPV vaccines. We estimate that MedImmune receives an approximate 6% royalty on sales of either Merck's Gardasil or GlaxoSmithKline's Cervarix.

AstraZeneca Key Upcoming Events

Time Frame	Event Type	Product	Event
2014	Clinical	AZD9291 (EGFR-TKI)	Phase III start in 1st line NSCLC (2nd line already started)
		AZD9293 (BACE)	Phase I first patient data at CTAD in Q4:14
		Brodalumab	Phase III topline data for 2 studies vs. Stelara in plaque psoriasis in Q4:14
		Lesinurad	Phase III full data on 3 combo studies Q4:14 in gout
		Mavrilimumab	Potential start Phase III in RA; Phase IIb data at ACR
		MEDI4736 (anti PD-L1)	Phase III start in SCCHN (head and neck) (already started Phase III in NSCLC)
		Sifalimumab/anifrolumab	SLE; Ph IIb topline results at ACR
	Regulatory	Brilinta	ACS approval in Japan Q3:14
		Bydureon Dual Chamber Pen	E.U. approval
		CAZ AVI	E.U. filing for serious bacterial infections in Q4:14
		Forxiga + Onglyza FDC	U.S. filing for T2DM Q4:14
		Iressa	U.S. re-filing for EGFRm+NSCLC in Q3:14
		Lesinurad	Regulatory filing in U.S and EU combo therapy (gout)
		Myalept	E.U. filing in Q4:14; lipodystrophy
Corporate		Olaparib	CHMP opinion Q4:14 (ovarian)
		Xigduo XR (Forxiga + metformin)	U.S. approval; PDUFA October 29th
		Almirall Respiratory acquisition	Closing by year end 2014
		Investor Day	November 18th, London

Source: Company data

AstraZeneca 2013-20 Balance Sheet Analysis (\$MM)

	2013A	2014E	2015P	2016E	2017P	2018P	2019P	2020P
Assets:								
Cash and Cash Equivalents	\$9,217	\$8,995	\$5,048	\$5,416	\$5,593	\$5,561	\$5,662	\$6,147
Inventories	1,909	2,200	2,200	2,100	2,050	2,050	2,150	2,300
Trade and Other Receivables	7,879	7,800	7,650	7,700	7,150	7,350	7,900	8,550
Other Current Assets	1,330	1,250	1,250	1,250	1,150	1,200	1,300	1,400
Total Current Assets	20,335	20,245	16,148	16,466	15,943	16,161	17,012	18,397
Property, Plant & Equipment	\$5,818	\$6,200	\$6,100	\$6,200	\$5,700	\$5,900	\$6,350	\$6,900
Goodwill	9,981	11,500	11,450	11,400	11,350	11,300	11,250	11,200
Intangibles	16,047	21,000	21,000	21,000	21,000	21,000	21,000	21,000
Other Long-Term Assets	2,513	2,000	2,000	2,000	2,000	2,000	2,000	2,000
Deferred Tax Assets	1,205	1,400	1,400	1,400	1,400	1,400	1,400	1,400
Total Long-Term Assets	35,564	42,100	41,950	42,000	41,450	41,600	42,000	42,500
Total Assets	\$55,899	\$62,345	\$58,098	\$58,466	\$57,393	\$57,761	\$59,012	\$60,897
Liabilities:								
Short-Term Loans And Borrowings	\$1,788	\$2,500	\$2,000	\$2,000	\$2,000	\$2,000	\$2,000	\$2,000
Trade And Other Payables	10,362	10,550	10,550	10,200	9,900	10,000	10,450	11,000
Other Current Liabilities	3,901	3,550	3,550	3,500	3,350	3,400	3,550	3,700
Total Current Liabilities	16,051	16,600	16,100	15,700	15,250	15,400	16,000	16,700
Interest Bearing Loans And Borrowings	8,588	7,500	7,500	7,000	6,500	6,000	5,500	5,000
Other Long-Term Liabilities	8,007	12,500	12,500	12,500	12,500	12,500	12,500	12,500
Total Long-Term Liabilities	16,595	20,000	20,000	19,500	19,000	18,500	18,000	17,500
Total Liabilities	\$32,646	\$36,600	\$36,100	\$35,200	\$34,250	\$33,900	\$34,000	\$34,200
Net Equity	\$23,253	\$25,745	\$21,998	\$23,266	\$23,143	\$23,861	\$25,012	\$26,697

Company reports; Cowen and Company estimates

AstraZeneca 2013-20 Working Capital Analysis (\$MM)

	2013A	2014E	2015P	2016E	2017P	2018P	2019P	2020P
Inventories	\$1,909	\$2,200	\$2,200	\$2,100	\$2,050	\$2,050	\$2,150	\$2,300
COGS	\$4,633	\$4,815	\$4,807	\$4,649	\$4,514	\$4,565	\$4,773	\$5,017
Inventory Turns	2.4	2.2	2.2	2.2	2.2	2.2	2.2	2.2
Months	4.9	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Accounts Receivable	\$7,879	\$7,800	\$7,650	\$7,700	\$7,150	\$7,350	\$7,900	\$8,550
Sales	\$25,711	\$25,865	\$25,350	\$25,825	\$23,760	\$24,675	\$26,515	\$28,670
Receivables Days	111.9	110.0	110.0	109.0	110.0	109.0	109.0	109.0
Other Current Assets	\$1,330	\$1,250	\$1,250	\$1,250	\$1,150	\$1,200	\$1,300	\$1,400
% of Sales	5.2%	4.9%	4.9%	4.9%	4.9%	4.9%	4.9%	4.9%
Accounts Payable	\$10,362	\$10,550	\$10,550	\$10,200	\$9,900	\$10,000	\$10,450	\$11,000
COGS	\$4,633	\$4,815	\$4,807	\$4,649	\$4,514	\$4,565	\$4,773	\$5,017
Payables Days	816.3	800.0	800.0	800.0	800.0	800.0	800.0	800.0
Other Current Liabilities	\$3,901	\$3,550	\$3,550	\$3,500	\$3,350	\$3,400	\$3,550	\$3,700
% of COGS	84%	74%	74%	75%	74%	74%	74%	74%
Net Working Capital (Ex. Cash, Debt)	(\$3,145)	(\$2,850)	(\$3,000)	(\$2,650)	(\$2,900)	(\$2,800)	(\$2,650)	(\$2,450)

Source: Company reports; Cowen and Company estimates

AstraZeneca 2013-20 Cash Flow Analysis (\$MM)

	2013A	2014E	2015P	2016E	2017P	2018P	2019P	2020P
<u>Operating Activities</u>								
Net Income (Operations)	\$6,320	\$5,538	\$5,143	\$5,442	\$4,669	\$5,086	\$5,555	\$6,149
Depreciation & Amort.	4,583	3,000	3,000	3,050	3,050	3,100	3,100	3,150
Change in Working Capital	1,490	(295)	150	(350)	250	(100)	(150)	(200)
Other, net	(4993)	(2500)	(2500)	(2500)	(2500)	(2500)	(2500)	(2500)
Net Cash Provided By Operations	\$7,400	\$5,743	\$5,793	\$5,642	\$5,469	\$5,586	\$6,005	\$6,599
<u>Investing Activities</u>								
Capital Expenditures Net	(\$673)	(\$800)	(\$850)	(\$900)	(\$950)	(\$950)	(\$1,000)	(\$1,000)
Asset Sales (net)	0	0	0	0	0	0	0	0
Acquisitions	(2,439)	(4,300)	0	0	0	0	0	0
Other, net	223	0	0	0	0	0	0	0
Net Cash Provided By Investing	(\$2,889)	(\$5,100)	(\$850)	(\$900)	(\$950)	(\$950)	(\$1,000)	(\$1,000)
<u>Financing Activities</u>								
Long-Term Debt Financings	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Equity Financings	0	0	0	0	0	0	0	0
Net Debt Payments	(32)	(1,000)	(500)	(500)	(500)	(500)	(500)	(500)
Dividend Payments	(3,461)	(3,590)	(3,575)	(3,565)	(3,550)	(3,535)	(3,520)	(3,505)
Share Repurchase	0	0	(500)	(500)	(500)	(500)	(500)	(500)
Other, net	446	0	0	0	0	0	0	0
Net Cash Provided By Financing	(\$3,047)	(\$4,590)	(\$4,575)	(\$4,565)	(\$4,550)	(\$4,535)	(\$4,520)	(\$4,505)
Net Change in Cash & Equivalents	\$1,464	(\$3,947)	\$368	\$177	(\$31)	\$101	\$485	\$1,094
Ending Cash & Equivalents	\$8,995	\$5,048	\$5,416	\$5,593	\$5,561	\$5,662	\$6,147	\$7,241

Source: Source: Company reports; Cowen and Company estimates

AZN DCF Analysis

9/26/14												
<i>Assumptions</i>												
Share Price	\$72		<i>Output</i>									
			Equity Value		\$93,884							
			Estimated Share Price		\$75							
Discount Rate	8.8%		Net Cash		(\$1,159)							
Shares Outstanding	1,260		Enterprise Value		\$95,043							

AZN DCF

	2019A	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2021P	2022P	2023P	2024P	2025P	Terminal
Total Revenues	\$25,711	\$25,865	\$25,350	\$25,825	\$23,760	\$24,675	\$26,515	\$28,670	\$30,677	\$32,518	\$34,143	\$35,851	\$37,285	
% Change	-8%	+1%	-2%	+2%	-8%	+4%	+7%	+8%	+7%	+6%	+5%	+5%	+4%	
Cost of Goods	\$4,939	\$5,110	\$5,082	\$4,954	\$4,824	\$4,880	\$5,093	\$5,342	\$5,675	\$6,016	\$6,317	\$6,632	\$6,898	
Gross Profit	\$20,772	\$20,755	\$20,263	\$20,872	\$18,936	\$19,795	\$21,422	\$23,328	\$25,002	\$26,502	\$27,827	\$29,218	\$30,387	
Gross Margin - Total	80.8%	80.2%	79.9%	80.8%	79.7%	80.2%	80.8%	81.4%	81.5%	81.5%	81.5%	81.5%	81.5%	
SG&A	\$8,865	\$9,655	\$9,140	\$9,250	\$8,250	\$8,520	\$9,490	\$10,580	\$11,350	\$12,031	\$12,804	\$13,444	\$13,982	
% of Revs	34.5%	37.3%	36.1%	35.8%	34.7%	34.5%	35.8%	36.9%	37.0%	37.0%	37.5%	37.5%	37.5%	
R&D	\$4,269	\$4,775	\$4,850	\$5,000	\$5,100	\$5,200	\$5,300	\$5,400	\$5,829	\$6,178	\$6,487	\$6,812	\$7,084	
% of Revs	16.6%	18.5%	19.1%	19.4%	21.5%	21.1%	20.0%	18.8%	19.0%	19.0%	19.0%	19.0%	19.0%	
Operating Expenses	\$13,134	\$14,430	\$13,990	\$14,250	\$13,350	\$13,720	\$14,790	\$15,980	\$17,179	\$18,210	\$19,291	\$20,256	\$21,066	
% of Revenues	51.1%	55.8%	55.2%	55.2%	56.2%	55.6%	55.8%	55.7%	56.0%	56.0%	56.5%	56.5%	56.5%	
Other operating income	\$752	\$1,085	\$850	\$860	\$870	\$880	\$890	\$900	\$925	\$950	\$975	\$1,000	\$1,000	
Operating Income	\$8,390	\$7,410	\$7,123	\$7,482	\$6,456	\$6,955	\$7,522	\$8,248	\$8,748	\$9,242	\$9,511	\$9,963	\$10,321	
% Operating Margin	32.6%	28.6%	28.1%	29.0%	27.2%	28.2%	28.4%	28.8%	28.5%	28.4%	27.9%	27.8%	27.7%	
Non-operating income	0	0	0	0	0	0	0	0	0	0	0	0	0	
EBIT	\$8,390	\$7,410	\$7,123	\$7,482	\$6,456	\$6,955	\$7,522	\$8,248	\$8,748	\$9,242	\$9,511	\$9,963	\$10,321	
% of Revs	32.6%	28.6%	28.1%	29.0%	27.2%	28.2%	28.4%	28.8%	28.5%	28.4%	27.9%	27.8%	27.7%	
D&A	\$4,583	\$3,000	\$3,000	\$3,050	\$3,050	\$3,100	\$3,100	\$3,150	\$3,200	\$3,200	\$3,250	\$3,250	\$3,300	
EBITDA	\$12,973	\$10,410	\$10,123	\$10,532	\$9,506	\$10,055	\$10,622	\$11,398	\$11,948	\$12,442	\$12,761	\$13,213	\$13,621	
% of Revs	50.5%	40.2%	39.9%	40.8%	40.0%	40.8%	40.1%	39.8%	38.9%	38.3%	37.4%	36.9%	36.5%	
Net Interest Income (Expense)	(\$445)	(\$555)	(\$530)	(\$505)	(\$470)	(\$435)	(\$400)	(\$365)	(\$100)	(\$100)	(\$100)	(\$100)	(\$110)	
Pre-Tax Income	\$7,945	\$6,855	\$6,593	\$6,977	\$5,986	\$6,520	\$7,122	\$7,883	\$8,648	\$9,142	\$9,411	\$9,863	\$10,211	
Taxes	\$1,610	\$1,324	\$1,450	\$1,535	\$1,317	\$1,434	\$1,567	\$1,734	\$1,902	\$2,011	\$2,070	\$2,170	\$2,246	
Income Tax Rate	20.3%	19.3%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	
Net Income	\$6,326	\$5,531	\$5,143	\$5,442	\$4,669	\$5,086	\$5,555	\$6,149	\$6,745	\$7,131	\$7,340	\$7,693	\$7,965	
% of Revs	24.6%	21.4%	20.3%	21.1%	19.6%	20.6%	21.0%	21.4%	22.0%	21.9%	21.5%	21.5%	21.4%	
NOPAT	\$6,780	\$6,086	\$5,673	\$5,947	\$5,139	\$5,521	\$5,955	\$6,514	\$6,845	\$7,231	\$7,440	\$7,793	\$8,075	
<i>Adjustments:</i>														
Capex	(\$673)	(\$800)	(\$850)	(\$900)	(\$950)	(\$950)	(\$1,000)	(\$1,000)	(\$1,050)	(\$1,100)	(\$1,150)	(\$1,200)	(\$1,275)	
Depreciation & Amortization	\$4,583	\$3,000	\$3,000	\$3,050	\$3,050	\$3,100	\$3,100	\$3,150	\$3,200	\$3,200	\$3,250	\$3,250	\$3,300	
Change In Working Capital	\$1,490	(\$295)	\$150	(\$350)	\$250	(\$100)	(\$150)	(\$200)	(\$150)	(\$180)	(\$200)	(\$150)	(\$100)	
Operating Free Cash Flow	\$11,726	\$7,436	\$7,443	\$7,242	\$7,019	\$7,136	\$7,505	\$8,099	\$8,745	\$9,051	\$9,240	\$9,593	\$9,890	\$112,383

Source: Company data, Cowen and Company.

ASTRAZENECA R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Analgesia/Anesthesia							
Diprivan				.	Q4:14		Conscious sedation; Japan, est, filing Q4:2014
AZD 5213			.				H3AN; neuropathic pain; Tourette's syndrome
Arthritis/Inflammation							
Brodalumab			.				IL-17R MAb; psoriatic arthritis, three Phase III studies vs. ustekinumab and/or placebo
Lesinurad			.		Q4:14		Selective uric acid reabsorption inhibitor (URAT1); chronic management of hyperuricemia in patients with gout; safety a concern
Mavrilimumab			.				CAM-3001; anti-GM-CSFR Mab; rheumatoid arthritis
MEDI-2070			.				Anti-IL-23 MAb; Crohn's disease; with Amgen
RDEA3170			.				Next generation selective URAT1 inhibitor; chronic management of hyperuricemia in gout patients
Sifalimumab			.				MEDI-545; anti-IL-23 Mab; myositis, systemic lupus erythematosis
Cancer/Oncology/Hematology							
Olaparib			.	.			AZD 2281; oral PARP inhibitor; filed in EU and U.S. for BRCAm PSR ovarian cancer; FDA requested additional efficacy data in June, 2014; PIII 1st line BRCAm ovarian cancer; 2nd line gastric cancer, adjuvant and metastatic breast cancer;
Caprelsa			.		2016		VEGFR / EGFR tyrosine kinase inhibitor with RET kinase activity; differentiated thyroid cancer
Faslodex			.		2016		Anti-estrogen; 1st line advanced breast cancer
Iressa			.		2015		EGFR-TK inhibitor; NSCLC; treatment beyond progression
MEDI-4736		⇒	.				Anti-PD-L1 Mab; NSCLC
AZD 9291			.				Advanced T790M+NSCLC; epidermal growth factor inhibitor; PI solid tumors
Selumetinib (AZD 6244)			.	.	2015-17		MEK inhibitor; 2nd line advanced KRAS+, NSCLC, differentiated thyroid cancer, uveal melanoma; PII 2nd line KRAS- NSCLC
Moxatumomab pasudotox		.	.	.	2018		Anti-CD22 recombinant immunotoxin; hairy cell leukemia; PI for pALL
Tremelimumab		.	⇒	.			Anti-CTLA4 ; mesothelioma; in combo with Iressa for NSCLC
AZD 1775			.				Wee-1 inhibitor; ovarian cancer
AZD 2014			.				mTOR serine/threonine kinase inhibitor; solid tumors
AZD 4547			.				FGFR tyrosine kinase inhibitor; solid tumors
AZD 5363			.				AKT inhibitor; solid tumors
MEDI-573			.				Anti-IGF MAb; MBC
Volitinib		⇒	.				AZD 6094; MET inhibitor; papillary renal cell carcinoma
MEDI-551		.	.				Anti-CD19 MAb; CLL, DLBCL; PI in combo with Rituximab for hematological malignancies
AZD 1208		.					PIM kinase inhibitor; hematological malignancies
AZD 6738		.					ATR; CLL/head & neck
AZD 8186		.					P13 kinase beta inhibitor; solid tumors
AZD 9150		.					STAT3 inhibitor; hematological malignancies
AZD5312		.					Androgen receptor inhibitor; prostate cancer
MEDI-0639							Anti-DLL-4 Mab; solid tumors
MEDI-0680		.					Anti-PD-1 Mab; solid tumors
MEDI-3617		.					Anti-ANG-2 Mab; solid tumors
MEDI-4736		.					Anti-PD-L1 Mab; solid tumors; combo with tremelimumab, solid tumors; combo with dabrafenib + trametinib; melanoma

ASTRAZENECA R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
MEDI-565		.					Anti-CEA BiTE; solid tumors
MEDI-6469		.					Murine anti-OX40 Mab; solid tumors
Cardiovascular							
Brilinta				.	2015-18		AZD 6140; reversible ADP receptor antagonist; oral; PEGASUS-TIMI 54 outcomes study in 2014; EUCLID outcomes study in patients with PAD; SOCRATES outcomes study in stroke/TIA; THEMIS outcomes study in Type 2 diabetes and CAD
FG-4592			⇒	.	2016-18		Roxadustat; hypoxia-inducible factor inhibitor; anemia in CKD/ESRD
Myalept				.	2015		Leptin analog; lipodystrophy; EU
AZD 1722		.					Tenapanor; NHE3 inhibitor; complications of end-stage renal disease and chronic kidney disease with T2DM; with Ardelyx
AZD-4901		.					NK3; polycystic ovarian syndrome
MEDI-6012		.					LCAT; acute coronary syndrome
MEDI-8111		.					Rh-factor II; trauma/bleeding
Central Nervous System							
AZD 3241		.					Inhibitor of myeloperoxidase (MPO); Parkinson's disease
AZD 3293		.					Beta secretase inhibitor; Alzheimer's disease; with LLY
AZD 6423		.					NMDA; suicidal ideation
Diabetes							
Xigduo				.			Forxiga/Metformin FDC; filed in U.S.; approved in EU
Bydureon				.			EXSCEL outcomes study; PIII weekly suspension formulation; Dual Chamber Pen filed in EU
Forxiga			.				Dapagliflozin; sodium-glucose cotransporter-2 (SGLT2) inhibitor; PIII triple therapy with metformin and SU (approved in EU); DECLARE outcomes study 2020
SaxaDapa FDC			.	2015			DPP-4 inhibitor/SGLT2 inhibitor
Endocrine/Metabolic/Hormone							
AZD 1979		.					Melanin concentrating hormone (MCH) receptor; obesity
Gastrointestinal							
Movantik				Nov-13			NKTR-118; oral peripherally-acting opioid antagonist; opioid-induced constipation; FDA AdCom June 2014
Entocort			.	2015			Glucocorticoid steroid; Crohn's disease/ulcerative colitis; Japan
MEDI-7183		.					Anti-A4b7 ; Crohn's disease, ulcerative colitis
Immunological							
Brodalumab			.				Anti-IL-17R Mab; psoriasis; AMAGINE-1 Phase III trial met all primary and secondary endpoints
Anifrolumab		.					MEDI-546; anti-IFNaR Mab; SLE
MEDI-4920		.					Anti-CD40L Mab; primary Sjögren's syndrome
MEDI-551		.					Anti-CD19 MAb; multiple sclerosis
MEDI-5872		.					Human monoclonal antibody binds to B7 related protein (B7RP-1) and prevents interaction with inducible co-stimulator (ICOS) on activated T cells; SLE; with Amgen
Infectious Disease							
CAZ AVI (CAZ104)			.	H2:14			Beta lactamase inhibitor/cephalosporin; serious infections; hospital acquired pneumonia; ventilator-associated pneumonia; EU
AZD 5847		.					Oxazolinone antibacterial inhibitor; tuberculosis

ASTRAZENECA R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
CXL			.				Beta lactamase inhibitor/cephalosporin; MRSA; EU
ATM AVI		.					BL/BLI; targeted serious bacterial infections
AZD 0914	.						GyrAR; serious bacterial infections
MEDI-4893	.						Staph alpha toxin YTE MAB; hospital-acquired pneumonia/serious S. aureus infection
Respiratory							
Benralizumab			.	2016-18			Anti-IL-5R MAb; severe asthma, COPD
LAS40464			.	.			Aclidinium/formoterol combo; COPD; filed in EU; PIII U.S.; from Almirall
PT001 GP			.	2015-16			LAMA; COPD
PT003 GFF			.	2015-16			LABA/LAMA; COPD
Symbicort			.				Breath Actuated Inhaler; asthma; COPD
Tralokinumab		⇒	.				Anti-IL-13 MAb; asthma
AZD 2115	.						MABA; COPD
AZD 9412 (SNG001)	.						Inhaled interferon β; asthma/COPD
Brodalumab	.						Anti-IL-17R Mab; asthma/IPF
LAS100977	.						Abediterol; once-daily LABA; asthma/COPD; from Almirall
MEDI-9929		⇒	.				Human monoclonal antibody that blocks the interaction of thymic stromal lymphopoietin (TSLP) with TSLP receptor; asthma; with Amgen
PT010		⇒	.				LAMA/LABA/ICS; COPD
AZD 1419	.						TLR9 antagonist; asthma
AZD 7594	.						Inhaled SGRM; asthma/COPD
AZD 7624	.						Inhaled p38 inhibitor; COPD
AZD 8848	.						Inhaled TLR7 antagonist; asthma
LAS190792	.						Dual long-acting MABA, which combines two bronchodilator mechanisms in a single molecule; COPD; from Almirall
LAS184871	.						MABA; COPD; from Almirall
LAS191351	.						MABA; COPD; from Almirall
Vaccines							
MEDI-550	.						MEDI-566; pandemic influenza virus vaccine
MEDI-559	.						RSV vaccine
MEDI-7510	.						RSV sF+GLASE; prevention of RSV disease in older adults
MEDI-8897	.						Anti-RSV MAb-YTE; passive RSV prophylaxis
Total Drugs In Development	2	31	25	26	3		87

Progress since last update in bold; movement marked by arrow

Investor Relations Contacts: Stephan Trenby 011-46-8553-26107
James Ward-Lilley 44 20 7604 8122
Karl Hard 44 20 7604 8122

Price: \$51.18 (09/30/2014)
Price Target: \$59.00

OUTPERFORM (1)

Steve Scala, R.Ph., CFA
617.946.3923
steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA
617.946.3857
kathy.miner@cowen.com

Jean Perreault
617.946.3967
jean.perreault@cowen.com

Key Data	
Symbol	NYSE: BMY
52-Week Range:	\$57.49 - 45.70
Market Cap (MM):	\$84,851.6
Net Debt (MM):	\$68.0
Cash/Share:	\$2.76
Dil. Shares Out (MM):	1,657.9
Enterprise Value (MM):	\$81,589.6
ROIC:	9.5%
ROE (LTM):	19.3%
BV/Share:	\$9.29
Dividend:	\$1.44
Yield:	2.81%

FY (Dec)	2013A	2014E	2015E
Earnings Per Share			
Q1	\$0.42	\$0.45A	\$0.53
Q2	\$0.44	\$0.48A	\$0.44
Q3	\$0.46	\$0.40	\$0.43
Q4	\$0.51	\$0.47	\$0.40
Year	\$1.82	\$1.80	\$1.80
P/E	28.1x	28.4x	28.4x
Consensus EPS	\$1.82	\$1.79	\$1.74

Consensus source: Thomson Reuters

Revenue (MM)			
Year	\$16,385.0	\$15,480.0	\$14,540.0
Prior Year	-	\$15,565.0	\$14,825.0
EV/S	5.0x	5.3x	5.6x

Bristol-Myers Squibb

Leading Position In Key New Product Areas, Albeit With Some Risk

The Cowen Insight

An impressive array of new products with sizable potential provide an additional boost to an already solid underlying outlook.

We believe the leverage potential offered by new drugs justifies and supports BMY's above-average P/E multiple. Several new products/formulations could have \$1B+ potential, and important clinical data is on the way. This portfolio could give upside to an otherwise solid growth outlook for BMY and generate much news flow. A management team that has a solid track record of reshaping the business provides additional appeal to this powerful product story.

Higher Spending Keeps 2014-16 In Check, But Sizable Gains On Tap 2017-20

Revenue growth is dampened in 2014 by the diabetes sale; EPS looks to be -1% to +3% in 2014-16 as higher spending on new products limits gains. For 2017-20 we forecast sales to grow 7-12% and EPS 8-16% as new products gain traction.

Opdivo May Be First Approved For Lung Cancer

Bristol has filed Opdivo (nivolumab) in NSCLC in the EU and the rolling submission continues in the U.S. In advanced melanoma, the FDA has granted Opdivo Breakthrough Therapy status and has accepted for priority review the BLA for Opdivo with a PDUFA date of March 30, 2015. In the EU, the filing has been validated for review by the MAA in advanced melanoma; the application has also been granted accelerated assessment.

Nivolumab is in Phase III trials in NSCLC, renal cell carcinoma, and melanoma, with key data, particularly in lung, due late 2014. Most notable data readouts in 2014 are: 1) Phase II, 3rd line, squamous NSCLC (basis for rolling submission); 2) interim Phase III squamous NSCLC with OS endpoints; and 3) interim Phase III non-squamous NSCLC with OS endpoint. If successful, then these trials would be registration. Bristol also is distinguished by having other immune-targeted agents in development, including urelumab (anti-CD137), lirilumab (anti-KIR), denenicokin (IL-21), LAG3 antibody and many combination studies under way. We estimate Nivolumab sales of \$100MM in 2015, \$500MM in 2016, and \$5B in 2020.

Eliquis Rollout Gaining Momentum

Eliquis share has ramped from 9.3% share in July 2013 to 20.4% in August 2014. Very positive data from AVERROES and ARISTOTLE distinguish Eliquis as the best-in-class anticoagulant and contribute to the strong label. New indications were approved in Q3:14 in the U.S. and EU for DVT and PE treatment and prevention of recurrent DVT's and PE's. We believe these factors ultimately will make Eliquis very successful. Eliquis sales are forecast at \$680MM in 2014, and \$2.4B in 2020.

Cancer And Immunology

Opdivo (Nivolumab) Harbors Great Promise; Combinations Likely, But Monotherapy Lead Narrowing

Programmed Death 1, or PD-1, is a 268 amino acid Type I membrane protein and is a member of the extended CD28/CTLA-4 family of T cell regulators. PD-1 is expressed on the surface of activated T cells, B cells, and macrophages, suggesting that compared to CTLA-4, PD-1 more broadly negatively regulates immune responses. Bristol acquired North American rights to MDX-1106/BMS-936558, a PD-1 monoclonal blocking antibody, through the acquisition of Medarex in 2009. In September 2011, Bristol and Ono Pharmaceuticals announced an agreement to expand Bristol's territorial rights to develop and commercialize the anti-PD-1 antibody in the rest of the world (excluding Japan, Korea, and Taiwan where Ono maintains rights). We assume Ono will receive a mid-single digit royalty on U.S. sales and a mid-to-high single digit royalty outside of the United States. In July 2014, Ono received Japanese approval for nivolumab in advanced melanoma, marking the first approval of a PD-1 by a major regulatory agency. Nivolumab is priced at roughly \$8,400/dose, and is dosed every 3 weeks until progression, which annualizes to about \$145,000.

Opdivo (nivolumab) has shown early promise in preclinical models and ongoing clinical trials. Post positive Phase I data, Bristol was the first to move its PD-1 antibody into Phase III development in NSCLC, mRCC, and melanoma. Phase III trials are scheduled to complete in late 2014 in NSCLC, 2015 in melanoma, and 2016 in mRCC. Combination studies with Yervoy, IL-21, and a KIR-1 antibody are under way. There are currently over 35 ongoing trials evaluating nivolumab, covering more than 8 types of tumors including clear pulmonary blastoma, follicular and diffuse LBCL, sarcoma, prostate cancer, CLL, and NHL. Bristol has a Phase III trial underway in head and neck cancer with the majority of patients having squamous histology. MRK was thought to be in a leadership position in this tumor type, but BMY now appears well positioned. In May 2014, nivolumab received Breakthrough Therapy Designation for CLL, a surprising, but favorable event, given initial focus on lung and melanoma. Data in hematological malignancies will be presented at ASH in December.

Bristol still looks to be in the leading position in the PD-1 antibody race with U.S. filings for two indications (lung, melanoma) but the fact that competitors will have lung cancer studies completing just after BMY's, in tandem with toxicity issues (and resulting study drop outs) with the nivolumab/ipilimumab combo, have allowed competitors to narrow the gap and lessen Bristol's competitive advantage. We estimate Nivolumab sales of \$100MM in 2015, \$500MM in 2016, \$1B in 2017, \$2B in 2018, and \$5B in 2020.

Upcoming Data For Nivolumab

Indication	Phase	Trial Comments	Endpoints	Data Expected
squamous NSCLC 3L	II	n=100	ORR	at CMSTO late Oct. 2014
squamous NSCLC	III	n=265	OS, ORR	H2:2014
non-squamous NSCLC	III	n=575	OS	H2:2014
Lung	I	combo w/ ipilimumab; 14 arms		some data internal; more in H2:14; new trials in '14
Melanoma 1L	III	mono vs DTIC; n=400	OS	2015
Melanoma 2/3L	III	mono vs DTIC or carboplatin/paclitaxel n=400	OS, ORR	2016
Melanoma, untreated, advanced	III	mono vs combo w/ ipilimumab; n=917	OS	H1:2017
Hematologic tumors				ASH (early December '14)

Source: Company data

NSCLC: Rolling Submission Accepted In EU

Bristol's rolling BLA filing for nivolumab is underway in the U.S. based on a Phase II study in 3rd line NSCLC, although data will not be presented until October 31st at CMSTO. The filing was recently accepted in the EU. Our physicians expect the ORR in that study to be in the 19-20% range. Duration of benefit will be a key factor. While the ORR is expected to be quite low, it is more a reflection of the challenge of lung cancer rather than any deficiency in PD-1 antibody or Bristol's approach.

Upcoming Phase III Data May Factor Into Filing

Investors are focused on interim results, possibly available by YE, of the nivolumab Phase III squamous lung cancer trial (CheckMate 017) because the rolling filing is based on another squamous trial (3rd line, Phase II), and the Phase III data should be available while FDA is deciding on the Phase II submission. CheckMate 017 was recently changed to have OS as the primary endpoint (ORR dropped as considered not as important for 2nd line treatments). The non-squamous Phase III trial, CheckMate 057, has only an OS primary endpoint. 85% of lung cancer is NSCLC, and 30% of NSCLC is squamous.

A statistical analysis done by our biostatistician (discussed below) outlines the range of possible outcomes for the Phase III squamous and non-squamous trials at both the interim and final results. Across all scenarios tested, odds of success for the CheckMate 017 nivolumab arm averaged 65%, assuming each pair of medians was equally likely. The most optimistic pair of medians – from the OS standpoint – assumed nivolumab of 11 months and docetaxel of 8 months; here odds of statistical significance were 40%. Odds of success for CheckMate 057 are higher due to a larger sample size.

CheckMate 017: Probability Of Success Of Interim ORR Averages 66%

Although it is event-driven, Bristol could have interim data from the CheckMate 017 trial by YE 2014. 264 patients were enrolled between October 23, 2012 and November 26, 2013, and final data analysis is due in January 2016. We calculate that 244 events are expected at study conclusion, and 200-220 at the interim (assuming a median OS of 9 months for nivolumab). Should docetaxel be associated with ORR of 0.05-0.07 at the interim, there is a 75%+ chance that the trial will be statistically significant for ORR, assuming that nivolumab delivers an ORR of 0.2-0.23. If docetaxel delivers an

ORR of 0.1, then there is less than 70% chance the trial will be successful. Docetaxel median ORR is in the 0.1 range. Study 003 showed nivolumab ORR in the 0.17–0.23 range. Across all scenarios tested, odds of success average 66%, assuming each pair of medians is equally likely.

CheckMate 017: Probability Of Success Of Interim OS Averages 65%

Should docetaxel be associated with 5–6 months of median OS at the interim, there is an 84%+ chance the trial will be statistically significant for OS, assuming nivolumab delivers at least 9.5 months of median OS. If docetaxel delivers 8 months of OS, then there is less than 40% chance the trial will be successful, assuming that nivolumab has median OS no greater than 11 months. Across all scenarios tested, odds of success average 65%, assuming each pair of medians is equally likely. Other studies have shown docetaxel median OS to be in the 5–8 month range. Study 003 showed nivolumab OS in the 9–15 month range. Our analysis of nivolumab OS extends to a maximum of 11 months as we anticipate that data from Phase III may not be as strong as Phase I, although results are strong even at 11 months.

CheckMate 017: Probability Of Success Of Final OS Averages 78%

Should docetaxel be associated with 5–6 months of median OS in the final analysis, there is an 88%+ chance that the trial will be statistically significant, assuming that nivolumab delivers at least 9 months of median OS (Figure 5). If docetaxel delivers 8 months of OS, then there is less than 70% chance the trial will be successful. Across all scenarios tested, odds of success average 78%, assuming each pair of medians is equally likely.

CheckMate 057: Non-Squamous Trial More Likely To Achieve Endpoints

At the interim look, should docetaxel be associated with 5–6 months of median OS, there is an 98%+ chance that the trial will be statistically significant for OS, assuming that nivolumab delivers at least 9 months of median OS. If docetaxel delivers 8 months of OS, then there is less than 68% chance the trial will be successful, if nivolumab is associated with 10.5 months or less OS. Across all scenarios tested, odds of success at the interim average 83%, assuming each pair of medians is equally likely. At the final look, across all scenarios tested, odds of success average 89%.

Summary Of Probabilities Of Success*

	Squamous	Non-Squamous
OS		
Interim	65%	83%
Final	78%	89%
ORR		
Interim	66%	

*Assumes each pair of medians is equally likely.

Source: Cowen and Company

Investors Challenged Key Docetaxel Assumption – Our analysis assumed that docetaxel OS would range between 4–8 months, which was selected based on docetaxel's label. Our statistician shied away from assuming a more optimistic

outcome for docataxel and nivolumab, as we anticipate that Phase III results might not be as strong as Phase I, a dynamic that plays out frequently. However, the recently presented REVEL trial comparing LLY's ramucirumab to docataxel showed docataxel associated with 9.1 months of OS overall, 8.2 months for squamous patients and 9.7 months for non-squamous patients. Our statistician re-ran the analysis, including scenarios where docataxel delivers both 9 and 10 months of OS, but also scenarios where nivolumab is associated with 12-15 months of OS, to cover all reasonable scenarios. The conclusions are detailed below:

Probability Of Significant OS At Interim For Non-Squamous Trial (CheckMate 057)

Nivolumab Median	Docetaxel Median			
	5	6	7	8
9.0	1.000	0.979	0.630	0.133
9.5	1.000	0.996	0.805	0.297
10.0	1.000	0.999	0.921	0.481
10.5	1.000	1.000	0.967	0.676
11.0	1.000	1.000	0.989	0.802

Source: Cowen and Company

Probability Of Significant OS At Interim For Squamous Trial (CheckMate 017)

Nivolumab Median	Docetaxel Median			
	5	6	7	8
9.0	0.975	0.715	0.278	0.057
9.5	0.990	0.840	0.410	0.118
10.0	0.997	0.907	0.560	0.195
10.5	0.999	0.951	0.666	0.299
11.0	1.000	0.970	0.767	0.395

Source: Cowen and Company

Probability Of Significant OS At Final For Non-Squamous Trial (CheckMate 057)

Nivolumab Median	Docetaxel Median			
	5	6	7	8
9.0	1.000	0.995	0.791	0.251
9.5	1.000	0.999	0.917	0.483
10.0	1.000	1.000	0.976	0.685
10.5	1.000	1.000	0.993	0.849
11.0	1.000	1.000	0.998	0.927

Source: Cowen and Company

Probability Of Significant OS At Final For Squamous Trial (CheckMate 017)

Nivolumab Median	Docetaxel Median			
	5	6	7	8
9.0	0.996	0.884	0.495	0.149
9.5	0.999	0.953	0.654	0.273
10.0	1.000	0.979	0.794	0.409
10.5	1.000	0.992	0.876	0.564
11.0	1.000	0.996	0.933	0.678

Source: Cowen and Company

Updated Data At ASCO 2014 Less Impressive Than Expected For Combo In Lung But Phase III Trials Still Expected To Start By Year End

Updated data on the nivolumab plus Ipilimumab first-line NSCLC Phase I study was presented at ASCO 2014. Initial data from this study were presented in an abstract in mid May, and the 22% ORR reported at that time led to investor concern, given that nivolumab monotherapy is associated with a 17% ORR. Our physician experts expected the ORR presented at ASCO to be roughly similar to the 22% in the abstract. However, data presented in the poster at ASCO were even more modest at a 19% ORR in the PD-L1 + group and 14% in the PD-L1 - group. The low ORR seems explainable by a significant number of drop outs: of the 46 patients in the study, AEs were reported in 39, and led to discontinuation in 16. *Despite these seemingly tempered ORR results, Bristol maintains that it will determine a dose and regimen and enter Phase III with the combination of nivolumab plus ipilimumab in lung by YE.*

There were also concerns about the toxicity profile, especially pneumonitis. The lack of greater benefit from the nivolumab + ipilimumab combo leaves our physician experts eager to try other combos in lung. Since most of the benefit is from nivolumab, particularly at 3mg/kg, the docs do not expect an improved response from a lower dose combo (1+1) currently being studied.

Phase I 003 Monotherapy Study Demonstrated Strong OS

In late October 2013, Bristol announced nivolumab follow-up, top-line data (median 20.3 months) in squamous and non-squamous lung cancer cohort (n=129) from the Phase I 003 study. One- and two-year survival rates were 42% and 24% for all doses studied. This compares to 42% and 14% in the update provided at ASCO 2013. The new data represents an additional 6 months of follow-up compared to data presented at ASCO. The median overall survival (mOS) was 9.9 months vs. 9.6 months at the time of the ASCO presentation. The OS for the 3mg/kg dose was 14.9 months, same as at ASCO. The objective response rate (ORR) was 17%, as measured by RECIST criteria. This is identical to the ORR reported for all doses at ASCO. At ASCO, an ORR of 24% was reported at the 3mg/kg dose.

Bristol also presented data on PD-L1 expression and its relation to ORR in this same cohort of NSCLC patients (129 patients). The data was inconclusive as the PD-L1 positive patients showed an ORR of 16%, but the PD-L1 negative patients also reported a positive ORR, albeit at a slightly lower rate of 13%. Bristol has 2 large ongoing Phase 3 trials with nivolumab that will further evaluate the role of PD-L1 biomarker (secondary endpoint in these trials).

Nivolumab Responses In Combination With Chemotherapy Solid In NSCLC

At ASCO 2013, Bristol presented data from a Phase I trial of nivolumab in combination with different platinum-based doublet chemotherapeutic regimens for the treatment of chemotherapy-naïve NSCLC. ORRs >30% and PFS rates at 24 weeks were extremely impressive; results of the survival analysis are not yet available. No drug-related toxicities were observed at the maximum doses tested and there were no reported drug-related deaths. Frequencies of adverse events were similar to what would be anticipated with traditional platinum-based doublet therapy.

Best response and duration of response data are detailed below:

Nivolumab Best Response Rate In Chemotherapy-Naïve NSCLC

	Nivolumab 10mg/kg			Nivolumab 5mg/kg
	Gem/Cis (n=12)	Pem/Cis (n=15)	Pac/Carb (n=14)	Pac/Carb(n=14)
Best Overall Response (n, %)				
Complete Response	1 (8%)	0	0	0
Partial Response	3 (25%)	7 (47%)	7 (47%)	7 (50%)
Stable Disease	7 (58%)	7 (47%)	4 (27%)	6 (43%)
Progressive Disease	0	1 (7%)	3 (20%)	1 (7%)
Unable to determine	1 (8%)		1 (7%)	0

Source: ASCO 2013

Nivolumab Duration Of Response In Chemotherapy-Naïve NSCLC

	Nivolumab 10mg/kg			Nivolumab 5mg/kg
	Gem/Cis (n=12)	Pem/Cis (n=15)	Pac/Carb (n=14)	Pac/Carb(n=14)
Number of responders	4	7	7	7
Ongoing responders	2 (50%)	2 (29%)	2 (29%)	5 (71%)
Estimated duration of response (weeks)	NR	25	26	22
Response duration	12, 18, 33+, 36+	25, 32, 38	11+, 12, 14, 24, 27, 13, 14+, 18+, 18, 29, 39+	11, 12+, 16+, 17+, 22+, 24+

Source: ASCO 2013

The adverse event profile for nivolumab appears in-line with the expected toxicities of platinum-based chemotherapies.

AEs On Nivolumab In Chemotherapy-Naïve NSCLC

	Nivolumab 10mg/kg			Nivolumab 5mg/kg		Total	
	Gem/Cis (n=12) Grade 3/4	Pem/Cis (n=15) Grade 3/4	Pac/Carb (n=14) Grade 3/4	Pac/Carb (n=14) Grade 3/4	All Grades	n=56	Grade 3/4
Any AE	3 (25%)	7 (47%)	11 (73%)	4 (29%)	53 (95%)	24 (45%)	
Fatigue	0	1 (7%)	2 (13%)	0	40 (71%)	3 (5%)	
Nausea	0	1 (7%)	0	0	25 (45%)	1 (2%)	
Decreased Appetite	0	0	1 (7%)	0	20 (36%)	1 (2%)	
Alopecia	0	0	0	0	17 (30%)	0	
Anemia	1 (8%)	0	1 (7%)	0	16 (29%)	2 (4%)	
Rash	0	0	0	1 (7%)	13 (23%)	1 (2%)	
Arthralgia	0	0	0	0	11 (20%)	0	
Constipation	0	0	0	0	11 (20%)	0	
Diarrhea	0	0	1 (7%)	0	11 (20%)	1 (2%)	
Neuropathy (peripheral)	0	0	0	0	10 (18%)	0	
Dysgeusia	0	0	0	0	8 (14%)	0	
Pneumonitis	1 (8%)	2 (13%)	0	1 (7%)	8 (14%)	4 (7%)	
Vomiting	0	0	0	0	8 (14%)	0	
Hypersensitivity	0	1 (7%)	0	0	7 (13%)	1 (2%)	
Mucosal inflammation	0	0	0	0	7 (13%)	0	
Myalgia	0	0	0	0	7 (13%)	0	
Peripheral sensory neuropathy	0	0	0	0	7 (13%)	0	
Infusion-related reaction	0	0	0	0	6 (11%)	0	
Leukopenia	0	0	0	0	6 (11%)	0	
Lymphopenia	0	0	0	0	6 (11%)	0	
Pruritis	0	0	0	0	6 (11%)	0	

Source: ASCO 2013

Perhaps the most concerning toxicity associated with PD-1 blockade is pneumonitis. A detailed report of the incidence of pneumonitis in the Phase I trial is below:

Pneumonitis Cases On Nivolumab In Chemotherapy-Naïve NSCLC

Chemotherapy	Nivolumab Dose	AE Worst Grade	Day Of Onset	Therapy	Resolution	Final Outcome
Gem/Cis	10	3	117	Steroids, infliximab	No	Death due to PNA/PD
Gem/Cis	10	2	36	None	Yes	No sequelae
Pem/Cis	10	3	106	Steroids	Yes	No sequelae
Pem/Cis	10	2	266	Steroids	Yes	No sequelae
Pem/Cis	10	3	154	Steroids, infliximab	Yes	Death due to Aspergillus PNA
Pac/Carb	5	4	185	Steroids	no	Death due to FTT
Pac/Carb	5	2	109	Steroids	Yes	No sequelae
Pac/Carb	5	2	82	Steroids	NA	F/U bronch showed PD and not pneumonitis

Source: ASCO 2013

Phase I Results Demonstrated High Efficacy For Nivolumab

Bristol presented data from an abstract in solid tumors at ASCO 2012 with follow-up presentations at ASCO 2013. The primary endpoint of the study was the safety and tolerability of Nivolumab with anti-tumor activity stratified by biomarker status as the secondary endpoint. Two hundred ninety-six patients with heavily pretreated solid tumors initiated treatment with Nivolumab between October 2008 and February 2012: NSCLC (122), MEL (104), RCC (34), CRC (19), CPRC (19). 47% of patients had experience ≥ 3 systemic treatments. Patients were treated with 1-10mg/kg; the maximum tolerated dose was not reached in this study.

Nivolumab showed overall response rates (ORR, CR + PR) between 18-28% in melanoma, NSCLC, and renal cell carcinoma. 65% of responses were sustained for ≥ 1 year. No objective responses were observed in CRC or CRPC. Trial reviewers were

particularly impressed with the unprecedented activity of Nivolumab (18% ORR) compared to existing treatment options (low single-digit response rates). The clinical activity of Nivolumab is detailed below:

Clinical Activity of BMS-936558

Tumor Type	Dose (mg/kg)	No. Patients	ORR (CR/PR) No. pts (%)	SD >24wek No. pts (%)
MEL	0.1-10	94	26 (28)	6 (6)
NSCLC	1-10	76	14 (18)	5 (7)
RCC	1 or 10	33	9 (27)	9 (27)

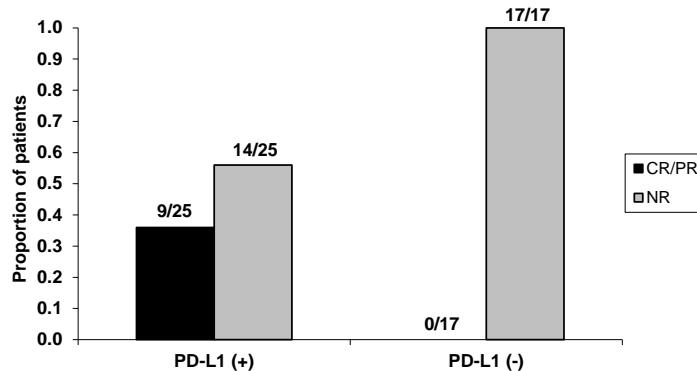
>236 patients starting therapy before 07/2011 were evaluated for response as of 2/24/2012; 20/31 responses lasted >1 year

No ORs were observed in 19 CRC or 13 CRPC patients

Source: ASCO 2012

Fifty-two patients had tumor biopsies available for histological analysis of PD-L1 expression. Nine of 25 patients whose tumors tested positive for PD-L1 expression showed a clinical response compared to 0/17 patients whose tumors did not express PD-L1. These data suggest that PD-L1 is a critical predictor of the clinical activity of Nivolumab; additional correlation studies between PD-L1 and Nivolumab will be conducted. The correlation is detailed below:

Response To BMS-936558 Stratified By PD-L1 Expression



Source: Cowen and Company, ASCO 2012

Nivolumab was also well tolerated as shown below.

Adverse Event Profile For Nivolumab

Adverse Event	All Grades (n, %)	Grade 3-4 (n, %)
Any Event	207 (70)	41 (14)
Fatigue	72 (24)	5 (2)
Rash	36 (12)	0
Diarrhea	33 (11)	3 (1)
Pruritis	28 (9)	1 (0.3)
Nausea	24 (8)	1 (0.3)
Appetite	24 (8)	0
Hemoglobin	19 (6)	1 (0.3)
Pyrexia	16 (5)	0

15 of 296 discontinued treatment due to AEs

Source: ASCO 2012

Nivolumab Monotherapy Demonstrates Impressive Survival Benefits

Overall Phase I survival data from 306 patients with either melanoma, mRCC, or NSCLC were presented at ASCO 2013. Of the 306 patients evaluated, 65 patients had an objective response. 46% of objective responses were evident at 8-weeks and 65% of responders had responses lasting >1 year. A summary by tumor type is below:

Nivolumab OS Summary

	Median OS (months)	1-Year Survival (%)	2-Year Survival (%)
NSCLC	9.6	42%	14%
MEL	16.8	62%	43%
RCC	>22	70%	50%

Source: ASCO 2013

Melanoma: Opdivo Filing Completed

Nivolumab Filing Based On Interim Look At Phase III Study

In melanoma, the FDA has accepted for priority review the BLA for Opdivo for previously treated advanced melanoma. The PDUFA date is March 30, 2015. The FDA also granted Opdivo Breakthrough Therapy status for this indication. In the EU, the filing in advanced melanoma has been validated for review by the MAA and has been granted accelerated assessment by the EMA's CHMP.

The filing is based on an interim look at the Phase III Checkmate 037 study (n=405) in advanced melanoma patients who have failed on ipilimumab. An ORR of 32% in the Opdivo arm (n=120) and 11% in the investigator's choice chemo arm (n=47) was reported. 95% of responses were ongoing in the Opdivo arm and the median duration of response was not reached. The majority of Opdivo treatment-related AEs were Grade 1/2. Grade 3/4 drug-related AEs were reported in 5% and 9% of patients treated with Opdivo and ICC. No Grade 3/4 pneumonitis was seen with Opdivo.

Ono's Nivolumab Approved For Melanoma In Japan

In July 2014, Ono Pharmaceutical received approval for nivolumab in Japan for the treatment of unresectable melanoma (trade name Opdivo). Chemotherapeutic agent dacarbazine is the only other approved agent for melanoma in Japan. The approved dose is 2mg/kg given every 2 weeks, which is less than the 3mg/kg utilized as the

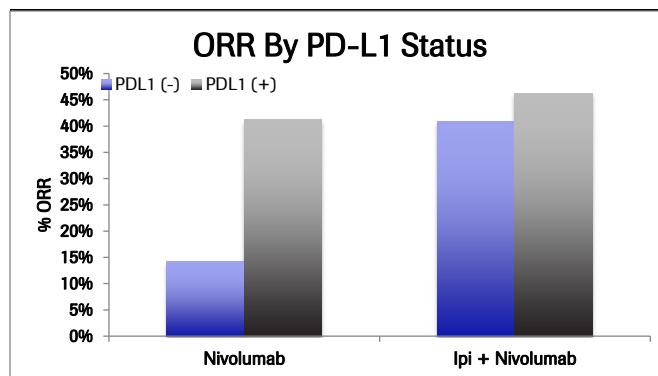
primary dose in ongoing BMY-sponsored trials. We read nothing into the differing doses. The approval was based on a small Phase II study run by Ono; post marketing studies are required due to the limited number of Japanese patients receiving the drug during clinical trials. Nonetheless, approval of nivolumab by a prominent regulatory body is important.

Reimbursement is also to be determined. Bristol will receive a royalty on nivo sales in Japan which we estimate to be in the single-digit range.

Nivolumab/Ipilimumab Combination Therapy Demonstrating Better Success In Melanoma Than Lung

Several studies have shown patients with elevated baseline PD-L1 expression to demonstrate a preferential response to PD-1 and PD-L1 antibodies. However, patients treated with the combination of ipilimumab and nivolumab demonstrated response rates similar to PD-L1 (+) patients regardless of PD-1 status.

ORR By PD-L1 Status



Source: ASCO 2013, Cowen and Company

Subanalyses of ipilimumab's Phase III trial have shown that patients with high absolute lymphocyte counts (ALC) have been shown to respond well to ipilimumab while patients with low baseline ALCs historically have not responded to Yervoy. A retrospective atoxinalysis of Phase I data from patients who received the ipilimumab/nivolumab combination demonstrated an improved response rate relative to high-ALC Ipilimumab monotherapy regardless of baseline ALC status.

Phase I Data On Nivolumab/Ipilimumab Combination In Melanoma Showed Excellent Results

BMY announced follow up results from Study -004 of the combination of nivolumab and Yervoy in advanced melanoma (n=127). After an additional year of follow up of the cohort receiving nivolumab 1 mg/kg plus Yervoy 3mg/kg (n=17), one-year OS was 94% and two-year OS was 88%. These are the doses used in the ongoing Phase II and Phase III trials, CheckMate -069 and -067 (these are registrational trials). No new safety signals were reported and grade 3-4 adverse events occurred in 62% of patients.

Data from a Phase I trial evaluating concurrent and sequential therapy with the combination of nivolumab and ipilimumab (Yervoy) in patients with advanced melanoma were presented at ASCO 2013. In the concurrent regimen, patients were dosed with nivolumab and ipilimumab every 3-weeks for 4 doses; the combined treatment was continued every 12-weeks for up to 8-doses. In the sequenced

regimen, patients previously treated with ipilimumab received nivolumab every 2-weeks for up to 48-doses. The 3mg/kg dose of nivolumab exceeded the maximum tolerated dose and patients were therefore dosed at 1mg/kg in combination with ipilimumab 10mg/kg. Results of this trial were simultaneously published in NEJM.

53% of patients on the concurrent 1mg/kg nivolumab regimen had an objective response with all of those patients experiencing tumor reduction >80% (by WHO criteria); the ORR for sequenced patients was 20%. 18% of patients on concurrent therapy experienced a complete response. Grade 3/4 AEs occurred in 53% of patients on concurrent treatment and in 18% of patients on sequenced therapy. While PD-L1 status (staining >5%) was positively correlated with outcomes, ORRs were observed in 9 of 22 patients with PD-L1 negative tumors in the concurrent treatment group.

Responses were rapid and generally occurred by first evaluation period. Such responses are significantly faster than have been observed with monotherapy and are similar to responses with targeted therapies (i.e., BRAF). Median survival has not yet been reached, but OS at 1-year is extremely impressive at 82%.

Monotherapy Nivolumab Also Solid In Melanoma

Also at ASCO 2013, Bristol presented updated data from a Phase I trial of nivolumab as monotherapy for the treatment of metastatic melanoma. 107 patients were randomized to receive 0.1-10mg/kg nivolumab every 2-weeks for 58 weeks or until disease progression; the study was amended to collect survival data. 68% of patients received >2 prior therapies and 25% of patients received >3 prior therapies (25% prior immunotherapy, 46% IL-2, 5% BRAF inhibitor). 78% of patients had visceral metastases and 36% of patients had elevated lactate dehydrogenase.

An ORR of 31% across all doses and 41% at the 3mg/kg dose were impressive and did not include patients whose tumors initially demonstrated progression followed by impressive regression. The mean duration of response was 104-weeks, which the presenter described as among the most impressive he has ever seen in melanoma.

Nivolumab Response Rates in Melanoma

Dose (mg/kg)	ORR (%)	Stable Disease >24week (%)	Duration of Response	
			Median (weeks)	Individual Responses (weeks)
All	31%	7%	104	--
0.1	35%	0%	NR	24.1, 24.1, 34.3, 44.1, 48.1, 48.7
0.3	28%	6%	NR	18.4, 44.4, 64.6, 65.1, 66.3
1	31%	14%	104	32.4, 32.4, 43.0, 64.1, 74.1, 80.1, 82.1, 99.4, 100.9+, 104.1, 108.1+
3	41%	6%	75	40.1, 40.4, 48.1, 56.1, 95.7, 106.7, 115.4+
10	20%	0%	112	73.9, 78.3+, 111.7, 117.0

Source: ASCO 2013

Treatment with nivolumab resulted in an impressive OS of 16.8 months. While 3.7 months is not overly impressive, high PFS rates at one- and two-years were extremely impressive; a trend consistent with the mechanism of action for immunotherapy.

Nivolumab Melanoma Survival Data

PFS	3.7 months
1-year PFS	36%
2-year PFS	27%
OS	16.8 months
1-year OS	62%
2-year OS	43%

Source: ASCO 2013

Collaborations Provide Combination Opportunities

Celldex – In May 2014, Bristol entered into a collaboration with Celldex to evaluate the combination of nivolumab with varilumab (CD27 antibody). The combo will be evaluated in NSCLC, melanoma, ovarian cancer, CRC, and SCHNC. Bristol paid \$5MM upfront and development costs will be shared. Bristol will have first rights to negotiate for out-licensing of varilumab. A Phase I/II study is expected to begin Q4:14.

Cellgene – In August 2014, Bristol announced a collaboration with Cellgene to evaluate Opdivo with Abraxane (paclitaxel) in a Phase I study in multiple tumor types including HER2- breast cancer, pancreatic cancer, and NSCLC. The study is expected to start Q4:14 and will be conducted by Cellgene.

CytomX – In May 2014, Bristol entered into a collaboration with CytomX to develop novel therapies against immune-oncology targets using CytomX's Probody Platform. Probodies are monoclonal antibodies that are selectively activated in the cancer microenvironment and focus activity on the tumor, leaving healthy tissue intact. Bristol will have exclusive WW rights to develop and commercialize up to four oncology targets including CTLA4. Bristol paid \$50MM upfront, will provide research funding, and pay up to \$298MM in future milestone payments for each target as well as royalties on future sales.

Incyte – In May 2014, Bristol entered into a collaboration with Incyte to evaluate nivolumab with Incyte's oral IDO1 inhibitor INCB24360 in multiple cancers including melanoma, NSCLC, ovarian cancer, CRC, SCCNH and DLBCL. A Phase I/II study is expected to begin in Q4:14 which will be co-founded by the two companies but conducted by Incyte.

Five Prime – In March 2013, Bristol signed an agreement with Five Prime Therapeutics for the development and commercialization of two undisclosed immune checkpoint pathway agents. Bristol paid \$20MM upfront, will pay \$9.5MM over the course of the research, will acquire 30% of FPRX stock for \$21MM (a 30% premium) and could potentially pay up to \$300MM in milestone payments. This agreement further broadens Bristol's portfolio of immune oncology drugs and expands the number of potential combination therapies.

Ono Pharmaceuticals – In July 2014, Bristol and Ono entered into a collaboration to develop and commercialize (in Japan, South Korea, and Taiwan) Opdivo and Yervoy across a broad range of tumor types, as well as early-stage IO agents lirilumab (anti-KIR), urelumab (CD137 agonist), and BMS-986016 (LAG3 inhibitor). Monotherapy and combination therapy will be evaluated.

Yervoy Melanoma Rollout Solid; New Indications And Combinations In Development

Bristol-Myers Squibb developed Yervoy (ipilimumab) for the treatment of metastatic melanoma. Yervoy is an anti-CTLA-4 mAb that blocks the effects of the negative T cell regulator CTLA-4, which may in turn augment T cell response to tumor cells. Data presented on Yervoy at the ASCO 2010 meeting demonstrated the first meaningful advance in metastatic melanoma treatment in years. In fact Yervoy's demonstration of a survival advantage in metastatic melanoma was the first ever Phase III trial to do so.

Yervoy was approved for the treatment of unresectable or metastatic melanoma on March 25, 2011. Importantly the label did not distinguish between the use of Yervoy as first or second line therapy. Yervoy was approved based on the Phase III second-line '020 study; however, the FDA review of positive top-line data from the first-line '024 trial may be partially reflected in the label. In November 2013, Yervoy gained EC approval for label extension to include first-line treatment in advanced melanoma.

Yervoy is priced at \$30,000 per infusion with an annual cap of \$120,000. Our physician consultants believe their initial use of Yervoy has been somewhat limited by concerns regarding reimbursement. We forecast Yervoy sales of \$1,250MM (+30%) in 2014, \$1,450MM in 2015, \$1,595MM in 2016, \$1,925MM in 2018, and \$2,275MM in 2020.

Our physician consultants believe Yervoy's mechanism of action is less likely to be specific and more likely to be a "shot gun" effect up-regulating the immune response. This is evidenced by a broad array of clinical side effects. The kinetics of Yervoy also are unique. Patient responses do not follow those of traditional chemotherapies in that the response to therapy may be significantly delayed. Patients on Yervoy may have worsening RECIST or mWHO response rates but actually demonstrate improved time to progression, median survival, and/or overall survival, suggesting a more durable response than with traditional therapy. The development of immune based therapies has therefore created a need to set new criteria for monitoring the efficacy of these drugs. As such, the immune-related response criterion (irRC) is now being adopted to predict more accurately overall survival with immune-based therapy.

Adjuvant Melanoma Data Impressive But Cost A Hurdle

BMY announced results from a Phase III study of Yervoy 10 mg/kg in adjuvant, stage 3 melanoma. Yervoy significantly improved recurrence-free survival (RFS, the length of time before recurrence or death) vs. placebo. A 25% reduction in the risk of recurrence or death was observed (HR = 0.75; p = 0.0013). At three years, 46.5% of patients treated with Yervoy were free of disease recurrence compared to 34.8% of patients on placebo. The question here is commercialization given that, at this dose and schedule, the regimen would cost roughly \$1MM; BMY indicated that it is exploring strategies to address this limitation. Perhaps for this reason, Bristol views high-risk patients as the initial opportunity.

IDO+Ipilimumab Continues To Demonstrate High Rates Of Tumor Control.

New data from the 50mg BID cohort of the Phase I/II study of INC024360 + ipilimumab was presented at ASCO 2014. The 50mg cohort (n=9 patients) contained 1 CR and 1 PR. These are in addition to the 3 PRs from the previously reported 8 person 25mg cohort. Incyte chose to segregate 50mg patients who were immunotherapy naïve (n=4) from those that were immunotherapy (CTLA4, PD-1/PD-L1, IL-2, IFN, IDO1) experienced (n=5). This was met with considerable debate as it represented the difference between an ORR of 50% versus 22% within the 50mg cohort (or a difference of 42% ORR versus 29% ORR in the combined 25mg+50mg cohorts). It should be noted that 2 patients with ocular melanoma (a notoriously difficult to treat

subset that was excluded from Yervoy's trials) were included in the combination trial, and that neither generated a response. Hence the efficacy of the combination relative to historical ipilimumab data may be somewhat understated.

Second Line Phase III Melanoma Study Demonstrated Impressive And Significant Survival Benefit

Data from ipilimumab's second-line Phase III study were presented at ASCO 2010 and subsequently published in the New England Journal of Medicine in August 2010. A total of 676 patients with unresectable stage III or IV melanoma, whose disease had progressed while they were receiving therapy for metastatic disease, were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus gp100 (403 patients), ipilimumab alone (137), or gp100 alone (136), a peptide vaccine. Ipilimumab, at a dose of 3 mg/kg, was administered with or without gp100, a vaccine directed towards a conserved extracellular melanoma antigen, every 3 weeks for up to four treatments (induction). Eligible patients could receive reinduction therapy. The primary endpoint was overall survival.

The median overall survival was 10.0 months among patients receiving ipilimumab plus gp100, as compared with 6.4 months among patients receiving gp100 alone (hazard ratio 0.68; $P < 0.001$). The median overall survival with ipilimumab alone was 10.1 months (hazard ratio for death in the comparison with gp100 alone, 0.66; $P = 0.003$). No difference in overall survival was detected between the ipilimumab groups (hazard ratio with ipilimumab plus gp100, 1.04; $P = 0.76$). There were no differences in PFS between the arms. Immune-related events occurred in ~60% of the ipi-treated patients. Diarrhea was the most common AE. Grade 3 or 4 immune-related adverse events occurred in 10 to 15% of patients treated with ipilimumab and in 3% treated with gp100 alone. There were 14 deaths related to the study drugs (2.1%), and 7 were associated with immune-related adverse events. Use of corticosteroids improved time to resolution of immune-related AEs.

The authors concluded that ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improves overall survival in patients with previously treated metastatic melanoma. They also noted that adverse events can be severe and long-lasting, but that most are reversible with appropriate treatment.

Ipilimumab Demonstrated Improved Survival In The First Line Compared To DTIC In '024 Trial

The '024 trial (NCT00324155) was designed to evaluate the safety and efficacy of ipilimumab + DTIC compared to DTIC alone in untreated, unresectable stage III/IV melanoma with the primary endpoint of OS. The trial enrolled 502 patients between August of 2006 and January 2008 with patients equally distributed between ipilimumab + DTIC and DTIC treatment arms. The trial was designed to detect a 37% increase in OS with a HR of 0.727 at a power of 90%.

Ipilimumab '024 First Line Trial Design

Arm	Intervention
Experimental (Ipi+DTIC)	Ipilimumab (10mg/kg) dosed i.v. every 3 weeks for 10 weeks then given every 12 weeks beginning at Week 24 + dacarbazine (850mg/m ²) once every 3 weeks for 22 weeks until disease progression, unacceptable toxicity or withdraw of consent
Active Comparator (DTIC)	Placebo (0mg) dosed i.v. every 3 weeks for 10 weeks then given every 12 weeks beginning at Week 24 + dacarbazine (850mg/m ²) once every 3 weeks for 22 weeks until disease progression, unacceptable toxicity or withdraw of consent

Inclusion: ECOG 0 or 1; negative for HIV/HepB,C; >18 years old; no prior therapy

Exclusion: pregnant/nursing; inadequate contraception; brain mets; prior melanoma

Source: Company data

The median number of doses received was 3 for the ipilimumab + DTIC arm compared to 4 in the DTIC arm with 37% and 66% receiving a 4th dose respectively. Only a small percentage of patients received greater than a single maintenance dose (17.4% in Ipilimumab + DTIC vs. 16% for DTIC alone) making maintenance data difficult to interpret.

Ipilimumab + DTIC met its primary OS endpoint when compared to DTIC alone (11.2 months for ipilimumab + DTIC vs. 9.1 months for DTIC alone, HR=0.72, p=0.0009). OS was greater for ipilimumab + DTIC at 1 year (47.4% for Ipi +DTIC vs. 36.8% for DTIC alone), 2 years (28.5% for Ipi + DTIC vs. 17.9% for DTIC alone), and 3 years (20.8% for Ipi +DTIC vs. 12.2% for DTIC alone). The addition of ipilimumab to DTIC demonstrated a modest increase in PFS compared to DTIC alone (2.8 months for ipilimumab +DTIC vs. 2.6 months for DTIC alone, HR=0.76, p=0.06); however, the durable response was 19.3 months in the ipilimumab + DTIC arm compared to 8.1 months with DTIC alone. The total number of adverse events was similar across treatment arms; however, significantly more SAEs occurred in the Ipilimumab + DTIC group compared to DTIC alone (50.6% vs. 11.6%) with dermatologic and GI events being the most common. Additionally, 33% of patients on Ipi + DTIC experienced increases in ALT/AST compared to 5.6% on DTIC alone (18.2% were grade 3 or 4 ALT/AST events in the Ipi + DTIC arm compared to 1.2% with DTIC alone). The majority of ADRs were easily managed when aggressively treated according to trial protocol. While the side effect profile for '024 was in-line with previous ipilimumab studies, the incidence of GI events were less frequent in '024 and the incidence of AST/ALT elevation was significantly higher than had been observed in previous trials. Reductions in colitis may be accounted for by physicians' increased awareness of the side effect profile for ipilimumab and improved management of ADRs. Interestingly, elevations in AST/ALTs are hypothesized to be the result of combination therapy with DTIC. Bristol speculates that ipilimumab's side effect profile may take on characteristics of concomitant chemotherapy. This idea was supported by a poster at ASCO where the addition of Avastin to Ipilimumab resulted in an amplified Avastin ADR profile.

As part of Bristol's post-marketing commitment to the approval of the 3mg/kg dose of ipilimumab, they are required to develop trials to compare 3mg/kg to 10mg/kg of ipilimumab as monotherapy. Given the durable response to ipilimumab, final results from this trial are not anticipated for at least 3 to 5 years. Management noted that CTLA4 saturation occurs at the 3mg/kg dose and higher. Bristol will continue to study ipilimumab in melanoma patients with brain metastases. Promising results from an

ASCO poster presentation suggest that ipilimumab may demonstrate a similar survival profile in patients with brain metastases.

Our physician consultants believe 85% of patients with metastatic disease will be eligible for Yervoy. This estimate excludes patients with autoimmune disease, brain metastasis, and patients who are in the final stages of life. Reimbursement is not anticipated to be limiting long-term, but daily reimbursement caps, and cumbersome approvals from private payors have been challenges to prescribing. While oncologists' prescribing practices are generally not influenced by pricing, our experts believe the 10mg/kg regimen will be priced in line with the 3mg/kg regimen, at near \$120,000 for four doses.

Ipilimumab Phase III Melanoma Program

Design	Study Population	Therapy	N	Primary End Point	Key Secondary End Points
A randomized, double-blind, multicenter study three arm study	Second line in HLA-A2*0201-positive patients with unresectable Stage III or IV melanoma	Ipilimumab 3mg/kg every 3 weeks for 4 doses, ipilimumab in combination MDX-1379, and MDX-1379 2mL (2 subcutaneous injections of 1mL each, to each thigh), every 3 weeks for 4 doses	676	BORR	OS; Most durable response rate; Duration of response; PFS; TTP
A multi-center, randomized, double-blind, two-arm study	First line Stage III (Unresectable) or IV melanoma	Dacarbazine 850 mg/m ² ± 10 mg/kg Ipilimumab	500	OS	PFS; DCR; BORR; Survival rate at Year 1; Duration of response; Time to response; Safety Profile
A randomized, double-blind placebo-controlled study	Adjuvant therapy after complete resection of high risk Stage III melanoma	Ipilimumab 10 mg/kg, 4x every 21 days, then starting from Week 24 every 12 weeks until Week 156 or progression, 3 years	950	Recurrence free survival	OS; Distant metastases-free survival; Safety profile

Source: Cowen and Company. clinicaltrials.gov

Primary Endpoint Not Reached In Advanced Stage Prostate Cancer Trial; Second Trial Ongoing

In September 2013, Bristol reported that Study 043, a Phase III randomized, double-blind clinical trial (n=399) comparing Yervoy to placebo in patients with advanced metastatic castration-resistant prostate cancer who received prior docetaxel treatment, did not reach its primary endpoint of statistically significant OS (HR = 0.85; 95% CI 0.72-1.00; p = 0.053). However, anti-tumor activity was observed in some secondary endpoints including PFS. Adverse effects were primarily immune related. A second Phase III study (095) evaluating Yervoy vs. placebo in mCRPC patients who have not received prior chemotherapy, is ongoing and expected to be completed in 2015.

Phase II Data In NSCLC Show Promise

The full Phase II data were presented at ASCO 2010. 203 patients with chemotherapy-naive, recurrent or stage IIIb/IV NSCLC were randomized 1:1:1 to receive either: ipilimumab (10 mg/kg IV q3wks) + concurrent (CON) IV paclitaxel/carboplatin (P/C; 175 mg/m² and AUC=6, q3wks); or IPI + sequential (SEQ) P/C, or P/C alone (PBO). After P/C, IPI was administered as continuation maintenance therapy q12 wks until toxicity or disease progression. Efficacy was assessed by mWHO and novel immune-related response criteria (irRC). Baseline characteristics were generally balanced between the arms. The table presents PFS and immature OS using the irRC and mWHO. IPI plus P/C was generally well tolerated. Grade (Gr) 3/4 AEs were 58%, 52% and 42% for CON, SEQ and PBO, respectively. Generally reversible and manageable Gr 3/4 immune-related AEs (pre-selected to reflect IPI mechanism of action) were 20%

and 15% for CON and SEQ, respectively. Safety results suggest a moderate added toxicity to the P/C regimen due to ipilimumab with no novel toxicities and rare and comparable drug-related death rates across all arms. Phase III data for NSCLC is expected in 2015. Phase II studies in non-small cell lung cancer (NSCLC) have shown a hint of efficacy that supported the move into ongoing Phase III trials. Our oncology expert is not concerned with Yervoy-related side effects in lung cancer as much of the toxicity is controlled via coadministration with high-dose steroids.

Phase II NSCLC Efficacy Summary

	IPI + P/C		P/C
	CON (n = 70)	SEQ (n = 68)	PBO (n = 66)
irPFS			
Median mo	5.52	5.68	4.63
95% CI	4.17, 6.74	4.76, 7.79	4.14, 5.52
p value	0.094	0.026	
HR	0.775	0.686	
95% CI	0.53, 1.13	0.47, 1.01	
PFS			
Median mo	4.11	5.13	4.21
95% CI	2.76, 5.32	4.17, 5.72	2.76, 5.32
p value	0.25	0.024	
HR	0.882	0.691	
95% CI	0.61, 1.27	0.48, 1.00	
OS			
Median mo	11.01	11.56	9.99
95% CI	8.38, 12.75	9.26, 14.39	6.97, 13.63
p value	0.429	0.104	
HR	0.962	0.748	
95% CI	0.63, 1.48	0.48, 1.18	

Source: Company data

Ipilimumab Promotes Durable Responses Post Progression On Prior Ipilimumab

Current treatment options are limited for patients whose melanoma progresses on immunotherapy such as ipilimumab. However, a study of patients with tumor progression on ipilimumab in Phase III trials suggested that re-treatment with ipilimumab is capable of producing durable responses in a portion of patients without new toxicities. Ipi-post Ipi resulted in a median survival of 21.12 months with 1-year OS of 81% and 2-year OS of 43%. The median OS for the overall population of 2,155 patients who received 3mg/kg on the expanded access program were 7.6 months and 38%; outcomes for the current analysis may reflect favorable characteristics of patients who had previously responded to ipilimumab and additional treatment. The benefits of ipilimumab retreatment on overall survival will be prospectively evaluated in a trial randomizing patients to either ipilimumab, vemurafenib, or physician preference post progression on ipilimumab.

A description of the adverse event profile during the initial and re-treatment periods is below:

SAEs Associated With Ipilimumab Re-treatment

	Initial Therapy + Retreatment (n, %)	Retreatment Only (n, %)
Any Gr 3/4 SAE	9 (8%)	5 (5%)
Dehydration	1 (1%)	1 (1%)
	1 (1%)	1 (1%)
Colitis	2 (2%)	2 (2%)
Diarrhea	1 (1%)	1 (1%)
GI Hemorrhage	1 (1%)	1 (1%)
Intestinal abscess	1 (1%)	0
Hypopituitarism	2 (2%)	0
Adrenal insufficiency	1 (1%)	0
Hypophysitis	1 (1%)	0
Hyponatremia	1 (1%)	0

Source: Cowen and Company

GM-CSF In Combination With Ipilimumab Improves OS And Mitigates Toxicities

Ipilimumab therapy has demonstrated unprecedented durability, but is associated with 10-25% high-grade adverse events. Given that GM-CSF-secreting tumor cell vaccines have demonstrated therapeutic synergies in preclinical animal models, a Phase II trial of ipilimumab plus GM-CSF versus ipilimumab (E1608) was designed to explore the potential of GM-CSF to improve outcomes and reduce ipilimumab-associated toxicities. 245 patients were randomized 1:1 to receive either ipi + GM-CSF or ipi alone with the primary endpoint of OS. Due to rapid accrual, 68.8% of events were reached within 24-months of initiating the trial. Interestingly, the addition of GM-CSF did not improve response rates or PFS, but was associated with a statistically significant improvement in OS. These data, while paradoxical, are consistent with immunotherapy's mechanism of action (i.e., sipuleucel-T in prostate cancer).

Response And Survival Data for Ipi+GM-CSF

	Ipi + GM-CSF (n=123)	Ipi (n=122)	HR	p-value
Complete response	2 (1.6%)	0 (0%)		
Partial response	17 (13.8%)	18 (14.8%)		
Stable disease	26 (21.1%)	23 (18.9%)		
Progressive disease	55 (44.7%)	52 (42.6%)		
ORR	19 (15.5%)	18 (14.8%)		0.88
PFS	3.1-months	3.1-months	0.92	0.589
OS	12.5-months	17.5-months	0.64	0.014

Source: Cowen and Company

The addition of GM-CSF to ipilimumab decreased the incidence of high-grade adverse events, specifically pulmonary and gastrointestinal SAEs. This is not to be unexpected as GM-CSF-/ mice develop significant lymphoid hyperplasia surrounding airways and lung vasculature and are associated with a GM-CSF reversible colitis. A comparison of SAEs between treatment arms is below:

Adverse Events On Ipi + GM-CSF

	Ipi + GM-CSF (n=118)	Ipi (n=120)	p-value
Diarrhea	15 (12.7%)	16 (13.3%)	
Rash	11 (9.3%)	11 (9.2%)	
Colitis	7 (5.9%)	10 (8.3%)	
Fatigue	7 (5.9%)	4 (3.3%)	
ALT elevation	6 (5.1%)	7 (5.8%)	
AST elevation	5 (4.2%)	9 (7.5%)	
Lipase increase	5 (4.2%)	6 (5.0%)	
Dehydration	5 (4.2%)	5 (4.2%)	
Hyponatremia	5 (4.2%)	3 (2.5%)	
Pruritis	3 (2.5%)	7 (5.8%)	
Endocrine disorder	3 (2.5%)	5 (4.2%)	
Nausea	3 (2.5%)	4 (3.3%)	
Colonic perforation	2 (1.7%)	7 (5.8%)	0.047
Muscle weakness	2 (1.7%)	4 (3.3%)	
Abdominal pain	1 (0.8%)	4 (3.3%)	
Autoimmune disorder	0	4 (3.3%)	
Blood bilirubin increase	0	4 (3.3%)	
Pulmonary	0	9 (7.5%)	0.03
Any toxicity	53 (44.9%)	70 (58.3%)	

Source: Cowen and Company

Cancer Immunotherapy The Next Frontier

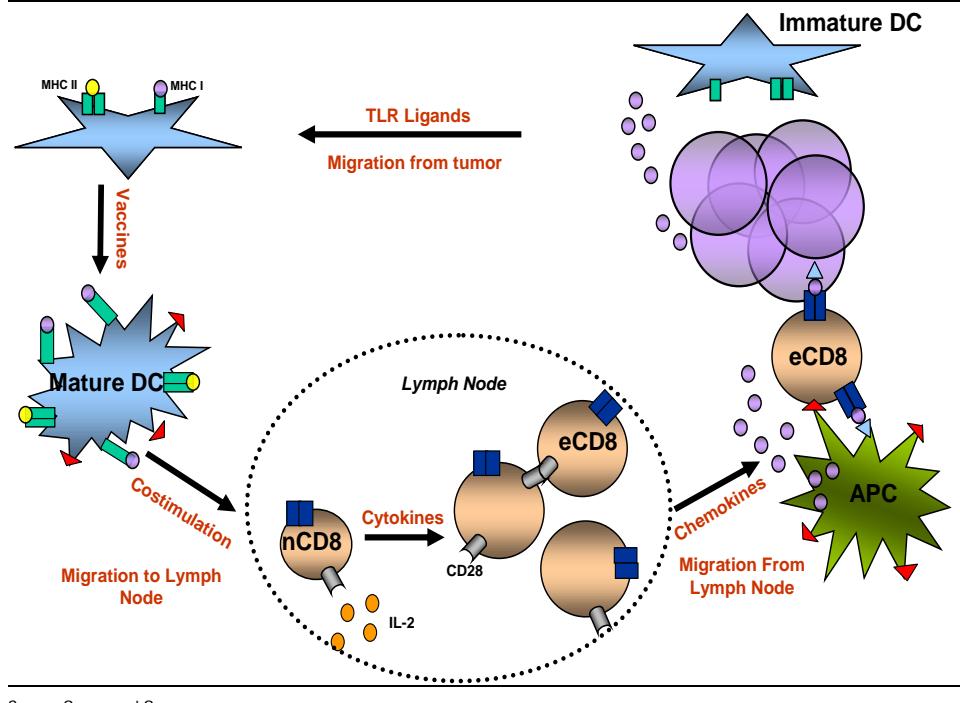
The immune system's ability to fight cancer is extremely powerful, but also extremely complex. Toll Like Receptors (TLR) were first identified in drosophila as receptors recognizing pathogens as part of the innate immune response. TLRs mediate the activation and maturation of antigen presenting cells to render them optimal for T-cell activation. Drugs targeting TLRs are therefore likely to be good candidates for use as cancer vaccine adjuvants.

A number of costimulatory antibodies, such as those blocking CTLA-4, are also in development. After migration to the lymph node, cytokines such as IL-2 are responsible for expanding relevant T-cell populations and supporting trafficking from the lymph node; exogenous IL-2 can be used to amplify this process.

Chemokines such as CD8, CCL2/4/5, CXCL9/10, and CCL19/21 define the inflammatory state of the tumor microenvironment and have been correlated with differential responses to immunotherapy. Efforts are being made to utilize chemokine gene signatures as predictive biomarkers. Expression of CXCR3-binding chemokines may also promote T-cell migration into tumors.

Inhibitory factors are often expressed on the tumor or in the tumor microenvironment and prevent immune-mediated destruction of the tumor. The inflammatory environment within tumors is known to induce the expression of PD-L1/2/3 and subsequently induce T-cell anergy.

Cancer Immunotherapy Summary



Source: Cowen and Company

Immunotherapy Could Be Used In 25% Of Cancers. Cancer immunotherapy is distinguished from traditional chemotherapy and other targeted therapies by its utility in multiple tumor types and curative potential. The largest barrier to prescribing immunotherapy is predicting which patients will respond. The identification of predictive biomarkers remains an active area of research. Until biomarkers to stratify patient risk/response are identified, immunotherapy is likely to be used in a sizable minority of patients (25%) within the next ten years. Should relevant biomarkers be identified, immunotherapy is likely to be broadly adopted.

Elotuzumab In Phase III For Multiple Myeloma

Bristol and AbbVie are jointly developing elotuzumab, an antibody targeting CS1 glycoprotein in multiple myeloma cells. CS1 is a glycoprotein that resides on the cell surface and is highly expressed in myeloma cells compared to normal cells. In a Phase II study presented at ASCO 2011, elotuzumab demonstrated a 92% ORR and only a 1% incidence of infusion reactions. The Phase II data were a good demonstration of clinical activity supporting the anti-CS1 mechanism in multiple myeloma. Despite the approval of Velcade for the treatment of multiple myeloma, our clinical consultants believe there is a need for multiple agents in the treatment armamentarium: 5-year survival rates for multiple myeloma patients are around 30% and 10-year survival rates are less than 5%.

Elotuzumab was also evaluated in combination with Velcade and Revlimid, which showed positive Phase I/II results: 82% of patients receiving elotuzumab achieved an objective response rate. Our consultants view the drug favorably, especially noting elotuzumab's ability to induce long median PFS when used in combination with Revlimid +dexamethasone. In May 2014, elotuzumab received Breakthrough Therapy designation from the FDA when used with Revlimid and dexamethasone in previously

treated multiple myeloma patients. We estimate elotuzumab sales recorded by Bristol of \$100MM in 2016, \$300MM in 2018 and \$500MM in 2020. Bristol records 70% of U.S. profits and pays a royalty ex U.S. to AbbVie.

Phase II Study Of Elotuzumab + Revlimid/dexamethasone Promising

A Phase II study in relapsed/refractory multiple myeloma (1-3 prior therapies) was presented at ASH 2012 and updated at EHA 2013. This study randomized patients either to 10 mg/kg or 20 mg/kg elotuzumab weekly, each in combination with Rev/dex. In the 10 mg/kg arm (n=36), ORR was 92% and PFS was 33 months. In the 20 mg/kg arm (n=37), ORR was 76% and median PFS was 18.7 months. Regarding safety, 78% of patients experienced at least one treatment-emergent Grade 3 or higher event. The most common of these were lymphopenia (26% on the 10mg arm and 9% on the 20mg arm), neutropenia (21% and 22%), thrombocytopenia (21% and 17%), anemia (13% and 12%), leukopenia (8% and 7%), hyperglycemia (5% and 12%), pneumonia (8% and 5%), diarrhea (10% and 5%), fatigue (8% and 9%), and hypokalemia (8% and 5%). Infusion reactions were experienced by 14% of patients.

Phase III Trials In Progress; Data Expected 2015

Two Phase III trials have been initiated: ELOQUENT-1 is evaluating 10mg/kg once daily dose of elotuzumab+Rev/dex vs. Rev/dex alone in first line, treatment naive multiple myeloma patients; enrollment is estimated at 750 patients with a primary completion date of May 2016. The primary endpoint is PFS, with OS and ORR as secondary endpoints. Data is not expected until at least late 2016.

ELOQUENT-2 has fully enrolled 640 relapsed/refractory patients (1-3 prior lines of therapy). The study arms are also 10mg/kg once daily elotuzumab+ Rev/dex vs, Rev/dex alone. The trial has primary endpoints of PFS and ORR; OS is a secondary endpoint. Primary completion is expected August 2017. Internal data may be available H1:15.

Erbitux Growth Modest

Erbitux (cetuximab), a chimeric monoclonal antibody directed against the extracellular domain of the epidermal growth factor receptor (EGFR), inhibits EGF-mediated cell growth by blocking the receptor from binding EGF. Erbitux has proven to be safe and effective in the treatment of irinotecan-refractory metastatic colorectal cancer (mCRC) patients, either in combination with irinotecan or as a monotherapy for those who are intolerant to chemotherapy. Erbitux rapidly penetrated the refractory colorectal cancer market and further benefited from a March 2006 label expansion into head and neck cancer. However, the expanding use of K-ras testing has clipped use in mCRC and other tumors. Those patients with K-ras mutations are unlikely to respond to Erbitux. In July 2009, FDA approved labeling revisions to include a modification which states that Erbitux is not recommended for patients whose tumors have K-ras mutations in codon 12 or 13. An estimated 40% of patients with mCRC have tumors with such K-ras mutations.

In July 2012, FDA approved Erbitux for use in combination with FOLFIRI as first-line treatment in patients with mCRC who have EGFR-expressing, and K-RAS wild-type tumors. The first-line approval was simultaneous with approval of a genetic test to evaluate KRAS mutation status (KRAS RGQ PCR Kit, Qiagen). A U.S. filing for adjuvant CRC appears unlikely given that CRYSTAL failed to demonstrate an overall survival advantage over standard of care in the ITT. Erbitux is also approved for use in SCCHN. We estimate Erbitux sales of \$735MM (+6%) in 2014, \$710MM in 2015, \$690MM in

2016, and \$580MM in 2018 (agreement with Lilly terminates 9/18). Post 2018, Bristol will record no sales of Erbitux.

Erbxitux Will Not Pursue Lung Cancer Indication

In May 2012, FDA issued a complete response letter for Erbitux's application to expand its label to include first-line NSCLC. The CRL requested an additional trial showing an improvement in OS as well as a validated diagnostic biomarker to predict patient response to Erbitux. Lilly and Bristol do not plan to resubmit the application. In September 2012, Lilly announced that it would no longer seek approval for first-line NSCLC in the E.U.

Colorectal Cancer Is Erbitux's Mainstay Market

Approximately 150,000 new cases of colorectal cancer are diagnosed in the U.S. annually, with roughly 30% of patients presenting with metastatic disease that cannot be surgically resected. Front-line treatment for such patients is the combination of 5-FU, leucovorin and Avastin plus either Sanofi's Eloxatin (oxaliplatin) or irinotecan. The majority of first-line patients receive oxaliplatin as a regimen termed FOLFOX or irinotecan as part of the FOLFIRI regimen. Despite the benefits provided by Avastin, close to 51K Americans are estimated to have died from colorectal cancer in 2013. Hence, there is a substantial need for a drug to treat refractory patients. Erbitux was initially developed to provide another treatment option for these patients. Results from a randomized, open-label Phase III study in mCRC (CALGB-C80405), n=290) comparing Erbitux to Avastin, both administered with combination chemotherapy, was presented at ASCO 2014.

Erbxitux Well Adopted By Third-Line Patients

Third-line patients were the first to adopt Erbitux. Conversations with oncologists indicate that anti-EGFR therapy (roughly 10% monotherapy response rate) is the preferred regimen versus chemotherapeutic options in third-line disease. Based upon third-party market data, we estimate that approximately 10-15K third-line colorectal cancer patients receive treatment in the U.S. each year. Although the company has lost some share to Amgen's Vectibix in the third-line setting, co-marketer Lilly believes that the overall size of the third-line market is still growing as newer drugs extend patients' life spans and increase the number of chemotherapy regimens to which patients are exposed. In October 2007, the FDA updated Erbitux's label to include a survival claim in refractory colorectal cancer. This label change had little commercial impact, as EGFR antibodies were already broadly used in the salvage setting and market share changes were therefore unlikely.

CALGB Study Show No Difference Between Avastin And Erbitux In mCRC

A Phase III randomized study (CALGB/SWOG 80405) comparing Avastin (Roche) to Erbitux when used with combination chemo in mCRC KRAS wild-type was presented at ASCO 2014. The study showed no significant difference between the two arms. Median OS for the Avastin arm was 29.0 months vs 29.9 months for Erbitux (HR=0.925, p= 0.34). Median PFS was 10.8 months for Avastin vs. 10.4 months for Erbitux (HR = 1.04, p=0.55). No new adverse events were seen with either agent.

Erbxitux Also Being Used In The Second-Line Market

We estimate that 25-30K patients are treated for second-line colorectal cancer in the U.S each year. While physicians were initially more inclined to give Avastin over Erbitux in Avastin-naïve patients, the Avastin naïve second-line market has contracted as Avastin's penetration into first-line disease has grown. Perhaps 30% of second-line colorectal cancer patients have been exposed to an irinotecan-containing regimen in

first-line. These patients are irinotecan failures and candidates for irinotecan plus Erbitux in second-line. ImClone/Lilly also believes that 20-30% of the second-line colorectal cancer market may be intolerant of chemotherapy and are therefore candidates for Erbitux monotherapy (Avastin has not shown monotherapy efficacy).

Use In First-Line Less Likely

In January 2007, ImClone and Bristol-Myers Squibb's E.U. partner Merck KGaA announced that the 1,200-patient CRYSTAL study comparing FOLFIRI vs. FOLFIRI + Erbitux in first-line colorectal cancer patients met the trial's primary endpoint of improved PFS. Specifics of the data reported at ASCO 2007 showed that the magnitude of the benefit was modest (8.0 months median PFS for chemotherapy vs. 8.9 months median for chemo + Erbitux), and the hazard ratio (HR= 0.85) for risk of progression (primary statistical endpoint) was barely statistically significant ($p=0.0479$). ImClone also released data showing an increase in resection rates in the Erbitux arm (more patients on Erbitux were able to have their tumors surgically removed following therapy (6% vs. 2.5%)). While some have suggested that this might make for a compelling reason to use Erbitux in first-line disease (despite modest improvements in PFS), we believe that there is little clinical benefit to a patient being resected if he/she does not live longer without disease. Overall survival data from this study were presented in September 2008. Erbitux failed to improve survival over FOLFIRI alone (19.9 months vs. 18.6 months, $p=0.305$).

Head & Neck Is A Meaningful Opportunity For Erbitux

Erbitux has also gained acceptance in head & neck cancer. In March 2006, the FDA approved an expanded label for use in combination with radiation for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN), and as a monotherapy for recurrent or metastatic SCCHN that are platinum-refractory. In April 2006, the EMEA approved Erbitux in combination with radiotherapy, for the treatment of locally advanced SCCHN. In the U.S., an estimated 55K new cases of HNC and 12K related deaths were estimated in 2013 (including laryngeal cancers).

Late-stage clinical data on Erbitux for treating head and neck cancer, either in combination with radiation (first-line disease) or as a monotherapy (refractory patients), have demonstrated a benefit in both treatment settings. Final results from a randomized, placebo-controlled first-line Phase III study of radiation therapy +/- Erbitux (IMCL-9815, n=424) were published in the *New England Journal of Medicine* in February 2006, and demonstrated a statistically significant improvement in locoregional control (primary endpoint) for Erbitux + radiation vs. radiation alone at one, two, and three years (63% vs. 55%, 50% vs. 41%, and 47% vs. 34% respectively, $p<0.01$), with a median duration of 24.4 months vs. 14.9 months ($p=0.005$). Progression-free survival (46% vs. 37% at two years, with a median duration of 17.1 months vs. 12.4 months, $p=0.006$) and overall median survival (55% vs. 45% at three years, with a median duration of 49.0 months vs. 29.3 months, $p=0.03$) also favored Erbitux with statistical significance. However, a subset analysis suggested that Erbitux may only benefit patients with oropharyngeal but not hypopharyngeal or laryngeal cancers.

Erbitux Approved For First-Line Recurrent Or Metastatic SCCHN

In November 2011, FDA approved Erbitux for first-line treatment of recurrent locoregional or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU. Given the longer duration of therapy in the recurrent and metastatic SCCHN disease setting, our consultants believe that this represents a more attractive market for Erbitux. Erbitux's sBLA was

based on the data from the EXTREME study. This trial randomized 440 first-line recurrent/metastatic SCCHN patients to platinum chemotherapy + 5-FU +/- Erbitux and demonstrated improved overall survival in Erbitux-treated patients (10.1 months vs. 7.4 months; HR= 0.797, p=0.036). Supporting Erbitux's label for recurrent/metastatic use are data from EMR-016, a 103-patient study which demonstrated a 12.6% response rate with time to progression of 85 days and a median survival time of 175 days. A second study in 53 recurrent/metastatic patients (EMR-008) testing Erbitux + 5FU + platinum produced a 36% response rate, 5.2 months' time to progression, and 9.9 months median survival (both studies were presented at ASCO 2004). However, a third trial (ECOG 5397) testing cisplatin +/- Erbitux failed to demonstrate a statistically significant survival benefit for Erbitux (response rate trends were positive, but the study may have been underpowered). Consultants believe that use of Erbitux in recurrent/metastatic disease is widespread in the community, although a reluctance to use Erbitux in patients who have failed the drug in the front-line setting might moderate penetration somewhat. With approximately 12,500 recurrent/metastatic patients treated at an average cost of \$40K/patient (\$10K/month for an average of 4 months) the recurrent/metastatic H&N market could be worth \$500MM for Erbitux.

Sprycel Continues To Make Inroads In CML

Sprycel (dasatinib), a dual SRC/ABL kinase inhibitor, continues to make inroads into the U.S. market for the treatment of chronic myelogenous leukemia (CML) and for acute Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Toxicities (pleural effusions and edema) associated with the initial dosage regimen -70mg bid- and Gleevec's (NVS) strangle-hold were the biggest reason for the tepid launch. Bristol has successfully expanded the dose and the label beyond refractory CML patients. In May 2009, FDA granted Sprycel full approval and also approved a new starting dosage of Sprycel 140 mg once daily for accelerated, myeloid blast and lymphoid blast Phase CML resistant or intolerant to prior therapy including Gleevec and Ph+ ALL resistant or intolerant to prior therapy. In September and November 2007, a 100mg once-daily dose was approved by the EMEA and FDA respectively for chronic Phase CML based on data from an open-label dose optimization Phase III study; this dose resulted in reduced side effects while retaining efficacy in Gleevec resistant patients. Bristol believes that potential in the E.U. is greater than that in the U.S. for two reasons: (1) 75% of Gleevec sales are ex-U.S., and (2) hematologists, who are more aggressive with therapy than oncologists, manage CML patients in the E.U.

Bristol is also pursuing NSCLC, head and neck cancer, and other solid tumors, but it failed in prostate. In December 2011, NICE guidance for the first-line treatment recommended Gleevec and Tasigna, but did not include Sprycel. This was in contrast to the February 2010 recommendation where neither Tasigna nor Sprycel were included. Sprycel was not recommended by NICE for second-line therapy. An uncontrolled single group interventional Phase II study to evaluate the patient response rates to Sprycel in Her2/Neu positive breast cancer was completed in late 2010. No patients elicited a complete response with 25 weeks of Sprycel treatment, suggesting that Sprycel will not be pursued in this area. We forecast Sprycel sales of \$1,485MM (+16%) in 2014, \$1,645MM in 2015, \$1,810MM in 2016, \$2,130MM in 2018, and \$2,450MM in 2020.

Sprycel Vs. Gleevec and Tasigna In CML Trials

The Phase III head-to-head study versus Gleevec in 518 newly diagnosed CML patients was presented at ASCO 2010. Data from the head-to-head study in 1st line

CML demonstrated that Sprycel was superior to Gleevec. In December 2009, Novartis filed for a first-line indication for Tasigna portended by the impressive results from its head-to-head study of Tasigna versus Gleevec in de novo CML patients. The Sprycel data did not outshine Tasigna's in the same setting. Sprycel may be more convenient given no food-drug interactions.

Comparison Of Twelve Month Efficacy In DASISION And ENESTnd

	Sprycel Vs. Gleevec			Tasigna Vs. Gleevec			P-value
	Sprycel (N = 258)	Gleevec (N = 258)	P-value	Tasigna 300mg (N=279)	Tasigna 400mg (N=277)	Gleevec (N=280)	
Complete cytogenetic response by 12 mo % (CI)	83 (78-88)	72 (66-77)	0.001‡	80	78	65	<0.001 for both comparisons
Major molecular response by 12 mo % (CI)	46 (40-52)	28 (23-34)	<0.0001‡	44	43	22	<0.001 for both comparisons

‡ This was a post hoc analysis; P values have not been adjusted for multiple comparisons.

Source: Cowen and Company

**Drug-Related Adverse Events That Occurred In At Least 10% Of Treated Patients In DASISION
And ENESTnd**

Event	Sprycel Vs. Gleevec		Tasigna Vs. Gleevec		
	Sprycel (N = 258)	Gleevec (N = 258)	Tasigna 300mg (N=279)	Tasigna 400mg (N=277)	Gleevec (N=280)
Cytopenia					
Neutropenia	65	58	43	38	68
Thrombocytopenia	70	62	48	49	56
Anemia	90	84	38	38	47
Nonhematologic adverse event					
Fluid retention	19	42	NG	NG	NG
Superficial edema	9	36	NG	NG	NG
Plueral effusion	10	0	NG	NG	NG
Other	5	8	NG	NG	NG
Peripheral edema	NG	NG	5	5	15
Eyelid edema	NG	NG	1	2	13
Periorbital edema	NG	NG	<1	1	12
Diarrhea	17	17	8	6	21
Nausea	8	20	11	19	31
Vomiting	5	10	NG	NG	NG
Myalgia	6	12	10	10	10
Muscle inflammation	4	17	NG	NG	NG
Musculoskeletal pain	11	14	NG	NG	NG
Rash	11	17	31	36	11
Headache	12	10	14	21	8
Fatigue	8	10	11	9	8
Alopecia	NG	NG	8	13	4
Pruritis	NG	NG	15	13	5

Source: Cowen and Company

Comparison Of Pivotal Head-To-Head Studies Of Tasigna Vs. Gleevec, Sprycel Vs. Gleevec, And Bosutinib Vs. Gleevec

	Tasigna Versus Gleevac	Sprycel Versus Gleevac	Bosutinib Versus Gleevac
Sponsor	Novartis	Bristol-Myers	Pfizer
Name	ENESTND	DASISION	
Name	771	518	412
Primary Endpoint	Rate of MMR after 12 months(degree of elimination of the cells that carry the Bcr-Abl protein in the marrow)	Best confirmed Complete Cytogenetic Response (CCyR) at 12 months	Cytogenic Response rate at 12 months
Dose	Tasigna 300,400mg BID Gleevac 400mg QD	Sprycel 50-180mg QD Gleevec 200-800mg QD	Bosutinib: 500mg start (increase to 600,700mg or decrease 300,400mg) Gleevec: 400mg start (increase to 500,600mg or decrease 300mg)
Status	Filed Q4:09	H1:10; ASCO	July 2010

Source: Cowen and Company, clinicaltrials.gov

In December 2013, Bristol provided updated data on the DASISION trial which showed that, at four years, 76% of Sprycel patients achieved a major molecular response (MMR) vs. 63% on Gleevec. Also at four years, 67% of Sprycel patients remained on treatment vs. 65% for Gleevec. Additionally, 53% of Sprycel patients achieved MR4 vs. 42% for Gleevec and 37% of Sprycel patients achieved MR4.5 vs. 30% for Gleevec. PFS at four years was 90% for both arms and OS was 93% for Sprycel and 92% for Gleevec. Adverse reactions occurring in 10% or greater of Sprycel patients included myelosuppression, fluid retention events, diarrhea, headache, musculoskeletal pain, rash, and nausea. Most grade 3-4 events were hematologic lab abnormalities and occurred in the first year.

Sprycel Patent Litigation Settled

Sprycel is covered by four Orange Book patents, three of which expire in 2020 and one that expires in 2026. In November 2010, Bristol filed a patent infringement lawsuit in the NJ District Court against Apotex for infringement of the four Orange Book listed patents covering Sprycel. In October 2011, Bristol received a Paragraph IV notice letter from Apotex stating that it was seeking approval of generic versions of the 80mg and 140mg dosage strengths of Sprycel and challenging the same four Orange Book patents. In November 2012, Bristol filed a patent infringement suit against Apotex on the 80mg and 140mg dosage strengths and the case was consolidated with the November 2010 suit. In September 2013, Bristol and Apotex reached an agreement and the patent litigation was dismissed, concluding the matter. No other settlement terms have been released.

Sprycel Failure In Prostate Cancer Not Meaningful To Franchise Value

In February 2013, Bristol reported that Sprycel failed to meet its primary OS endpoint in the Phase III READY trial in patients with metastatic castration-resistant prostate cancer (HR=0.99). Sprycel also failed to improve PFS, response rates, PSA progression, and pain, but was associated with a doubling in adverse events. Sprycel did demonstrate numerical improvement in time to first skeletal event (31.1 months for placebo vs. median time to 1st event not yet reached on Sprycel, p=0.077). The negative outcome in READY is not expected to impact Sprycel sales in CML.

Ixempra Has Modest Potential In Taxane-Refractory Breast Cancer

Ixempra (ixabepilone), a semi-synthetic epothilone B, was approved by FDA in October 2007 as a monotherapy or combination therapy with Xeloda for taxane-refractory locally advanced or metastatic breast cancer. Ixempra works via an antimitotic mechanism providing oncologists with a novel class for the treatment of metastatic disease. Ixempra suffers from significant toxicities including neuropathy, myelosuppression, and treatment related deaths. Ixempra is given intravenously every three weeks. Despite concern with the sequential, rather than cross-over design of the Phase III ('046) study, Ixempra has potential in taxane-refractory metastatic breast cancer. Ixempra's registration program included a study in combination with Xeloda versus Xeloda in taxane-refractory metastatic breast cancer and a monotherapy study in triple-refractory metastatic breast cancer. Data from the '046 open-label, multinational, Phase III study presented at ASCO 2007 demonstrated that Ixempra in combination with Xeloda in taxane and anthracycline refractory breast cancer patients prolonged PFS (5.8 months vs. 4.2 months) with a statistically significant reduction in disease free progression (HR, 0.75; 95.17% CI= 3.81 -4.50; p<0.0003). In December 2008, pooled data from the 046 and 048 studies presented at SABCS demonstrated a significant increase in PFS in triple negative receptor negative patients. The PFS of the combination group was a median of 4.2 months compared to a median of 1.7 months (Hazard Ratio 0.63, 95% CI: 0.52-0.77) for the Xeloda-treated group. Ixempra also is being studied for lung, prostate, pancreas and renal cancers. Ixempra is likely to remain a niche product given its side-effect profile. In November 2008, the CHMP recommended against the approval of Ixempra citing an unfavorable risk-benefit in light of the modest PFS and concerns about the neurotoxicity. In March 2009, Bristol withdrew its E.U. marketing authorization application for Ixempra. We forecast Ixempra sales of \$60MM (-9%) in 2014, \$50MM in 2015, \$40MM in 2016, \$20MM in 2018, and \$5MM in 2020.

Brivanib Failure In BRISK-FL Limits Opportunity In HCC

Brivanib is an oral once-daily dual inhibitor of VEGFR and FGFR tyrosine kinases. Upregulation of FGF signaling has been reported to be a primary mechanism for resistance to VEGFR inhibitors.

In July 2012, Bristol announced that the Phase III BRISK-FL head-to-head trial of brivanib versus Nexavar (ONXX) in front-line hepatocellular cancer (HCC) failed. According to the press release the "study did not meet its primary overall survival objective based upon a non-inferiority statistical design," which we interpret to mean Nexavar at least trended toward superior survival compared to brivanib. In April 2012, brivanib failed to meet its OS endpoint in a second-line HCC trial (BRISK-PS). However, significant improvements in PFS, disease control rate, and ORR in BRISK-PS suggested brivanib could be an active drug in HCC, leading us to believe that brivanib could achieve non-inferiority to Nexavar in the first-line setting. While failure in BRISK-FL is a disappointment, brivanib trials in HCC and other tumor types remain ongoing. Our brivanib sales estimates are \$25MM in 2015, \$50MM in 2016, \$100MM in 2018, and \$150MM in 2020.

Several Phase II/III Brivanib Trials Remain Ongoing

Ongoing Phase II/III Brivanib Studies

Study Title	Phase	Estimated Completion Date
2nd Line HCC (sorafenib failures) in Asian Subjects	3	Sep-14
Trans-Arterial Chemo-Embolization (TACE) Adjuvant HCC	3	Sep-14
Brivanib in Patients with Recurrent/Persistent Endometrial Cancer	2	Jan-14
1st Line HCC	3	Nov-13

Source: clinicaltrials.gov

Immunological

Orencia SQ Formulation Facilitating Market Penetration

Orencia (abatacept), an intravenous T-cell co-stimulator, was launched in the U.S. in 2006 for rheumatoid arthritis patients who have failed one or more DMARDs. In April 2008, the label was broadened to include all patients with moderate to severe RA and not only anti-TNF and methotrexate failures. In addition, it garnered approval for juvenile idiopathic arthritis. It can be used as monotherapy or in combination with other rheumatic agents (except for anti-TNFs and Amgen's Kineret). Differentiating features of Orencia are its mechanism of action (modulates T-cell activation), once-monthly administration, and its use in patients with congestive heart failure (relative contraindication for anti-TNFs). However, data also suggest that Orencia increases COPD flares and may be associated with more adverse events when combined with Arava. Orencia does not have a black-box warning for TB, which the anti-TNFs have, but it does have a warning for infection. In 2007, the E.U. approved a MAA for Orencia in the treatment of moderate-to-severe RA in those patients who have failed one or more DMARDs. In July 2010, the EMA label was broadened to include patients who have responded inadequately to one or more DMARDs, including methotrexate and anti-TNFs.

In January 2010, the European Commission approved Orencia in combination with methotrexate for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in pediatric patients six years of age and older who have had an insufficient response to other DMARDs including TNFs. Ono Pharmaceuticals has rights to co-develop and co-market Orencia in Japan.

Bristol has a series of patents covering Orencia and its method of use. A patent term extension has been granted for one of the composition-of-matter patents, extending the term of the patent to 2019. In the E.U., both the substance patent (which includes the SPC) and data protection expire in 2017. Data exclusivity in the E.U. expires in 2017. We forecast Orencia sales of \$1.635B (+13%) in 2014, \$1.83B in 2015, \$2.02B in 2016, \$2.36B in 2018, and \$2.7B in 2020.

SC Formulation Driving Growth

In August 2011, FDA approved the SubQ formulation of Orencia based on non-inferiority to the IV formulation in the AQUIRE trial. AQUIRE was a randomized, double-blind, double-dummy, multinational study. The primary goal of ACQUIRE was to evaluate non-inferiority of Orencia SC plus methotrexate (MTX) to Orencia IV plus MTX by difference in ACR 20 response at 6 months. The study consisted of 1,457 patients with moderately to severely active RA, of which most had an inadequate response to MTX. Patients were randomized to weekly injections of a 1 mL solution containing a 125 mg dose of Orencia SC plus MTX, followed by a single IV loading

dose (approximately 10 mg/kg) on Day 1, or Orencia IV (approximately 10 mg/kg) plus MTX on Days 1, 15, 29 and every 4 weeks thereafter, for 6 months. Both patient groups receiving SC injections plus MTX or IV infusions plus MTX at month 6 had a comparable ACR 20 response rate of 76%. ACR 50 and ACR 70 responses between Orencia SC and IV at 6 months were comparable as well as improvements in all patient-reported outcomes - pain, physical function and global assessment of disease activity. At month 6, high retention rates were seen in 94% of patients remaining in the study who received SC injections plus MTX and 94% of patients receiving Orencia IV plus MTX. The most common adverse effects discovered in more than 5% of patients in either the SC or IV Orencia groups were headache, nasopharyngitis, upper respiratory tract infection, diarrhea and nausea. 4.2% of patients in the Orencia SC plus MTX group and 4.9% of patients in the Orencia IV plus MTX group developed serious adverse effects. Serious infections developed in 0.7% of patients in the Orencia SC plus MTX group versus 1.4% of patients in the Orencia IV plus MTX group while malignancies appeared in 0.4% of patients in the Orencia SC plus MTX group versus 0.7% of patients in the Orencia IV plus MTX group.

Our physician consultants note that a majority of their patients have not requested to switch from i.v. to SQ Orencia, citing difficulties with reimbursement. However, the SQ formulation is growing and currently accounts for approximately 40% of Orencia sales.

18-Month ACQUIRE Extension Shows Durable Response For SQ Orencia

After 6-months in ACQUIRE, patients entered the open-label extension phase of the study. Of 1,372 patients who entered the extension study, 89.1% (1,222 patients) remained on therapy at the time of reporting. Median exposure to Orencia SQ was 22-months. ACR20/50/70, HAQ responses, and DAS improvements were maintained throughout the course of the extension phase and no differences in responses were noted between patients who began ACQUIRE on i.v. therapy compared to those who began the study on the SQ formulation. These data demonstrate a durable response for SQ Orencia, similar to what has been previously observed for the i.v. formulation.

Orencia SQ May Not Require I.V. Loading

I.V. loading may not be required to achieve timely and clinically meaningful efficacy with SQ Orencia. To address the utility of i.v. loading, Bristol compared the results of clinical trials where SQ Orencia was given with (ALLOW) and without (ACCOMPANY) i.v. loading. Baseline characteristics were similar across trials, although disease activity was slightly lower in ACCOMPANY than in ALLOW. When accounting for subtle difference across trials and considering the inherent variability associated with cross-trial comparisons, comparable improvements in clinical efficacy were observed over the course of the first three months of therapy with or without i.v. loading. Additionally, target PK values were achieved in both regimens, and the majority of patients achieved therapeutic Orencia concentrations (C_{min}) by Day 15 without i.v. loading. Our physician consultants are generally not loading their SQ Orencia patients, noting that adding an i.v. infusion is often difficult and not worth the one-to-two week efficacy advantage.

Efficacy Of Orencia SQ With Or Without IV Loading

Mean percentage change from baseline (95% CI)			
	ALLOW (SQ + IV)		ACCOMPANY (SQ Only)
	DAS-28 (CRP)	HAQ-DI	DAS-28 (CRP)
Month 1	-21.7 (-24.8, -18.7)	-27.3 (-32.6, -22.0)	-14.2 (-19.1, -9.3)
Month 2	-28.0 (-31.5, -24.6)	-37.7 (-44.7, -30.8)	-24 (-28.4, -19.6)
Month 3	-31.6 (-35.5, -27.7)	-44.6 (-51.8, -37.5)	-27.8 (-32.8, -22.9)

Source: Company data, ACR 2011

In addition to lupus (Phase III) and scleroderma (Phase II), Orencia is looking for other indications to tackle. These include Crohn's (Phase III), psoriatic arthritis (Phase II), Ankylosing spondylitis (Phase II), and vasculitis (ANCA positive, giant cell Arteritis, Takayasu's Arteritis, Wegner's Granulomatosis, Phase II).

AVERT Trial Supports Use In Early RA With Methotrexate

First data from the AVERT Phase IIIb trial in early RA (biologic and MTX-naïve; n=351) was released at EULAR 2014 showing that weekly Orencia + methotrexate (MTX) achieved significantly higher rates of DAS28 CRP <3.2 (low disease activity) at 12 months (of 60.9%) compared to weekly MTX alone (45.2%) and also weekly Orencia alone (42.5%). Greater benefits on MRI endpoints were also seen with the combo. The co-primary endpoint was also met with a small, but statistically significant, greater number of patients treated with Orencia + MTX for 12 months remaining in remission 6 months after all RA treatment was withdrawn (at 14.8% vs. 7.8% for MTX only and 12.4% for Orencia only). SAE's over the 12 months were reported in 6.7% of the combo arm, 12.1% for Orencia-only, and 7.8% for MTX only.

Orencia Phase III Data Robust But Considered Less Effective Than Anti-TNFs

Bristol-Myers conducted three Phase III studies in rheumatoid arthritis: (1) in combination with methotrexate; (2) in patients refractory to anti-TNF therapies; and (3) a large safety trial. Phase III results from AIM (Abatacept in Inadequate responders to Methotrexate) and ATTAIN (Abatacept Trial in Treatment of Anti-TNF INadequate responders) concluded that Orencia is effective and safe when dosed at 10mg/kg in combination with methotrexate, and in combination with DMARDs in anti-TNF non-responders. Phase III results of ASSURE, a one-year safety trial of Orencia with or without biologic therapy vs. biologic therapy alone, were presented at the EULAR meeting in June 2005. These data did not include efficacy results. The combination of Orencia with biologic therapy was relatively safe and well tolerated, but there was a higher rate of infections with Orencia + biologic vs. biologics alone (5.8% or 6 patients vs. 1.6% or 1 patient). Other trials combining biologics (Enbrel + IL-1ra) have shown a higher rate of infections (7% vs. 0%) with no incremental efficacy. Current FDA guidelines do not permit Orencia to be used in combination with anti-TNFs and recommend that it not be used with Kineret. Of the 1,955 patients treated in placebo-controlled clinical trials, 4 were diagnosed with lung cancer vs. 0 for the placebo. Although many rheumatologists take precautions when prescribing Orencia in patients with an extensive history of smoking or chest x-ray abnormalities, they do not view this as a major drawback.

ATTAIN Phase III RA Efficacy Data At Six Months

Response Criteria at 52 weeks	DMARD + placebo (n=130)	Abatacept 10mg/kg + DMARD (n=261)
ACR-20	19.5%	50.4%
ACR-50	3.8	20.3
ACR-70	1.5	10.2

Source: Cowen and Company/ACR 2004 Abstracts

AIM Phase III Data At Six Months And One Year

Response Criteria	Methotrexate (n=219)	6 months	12 months	
		Abatacept 10mg/kg + methotrexate (n=433)	Methotrexate (n=162)	Abatacept 10mg/kg + methotrexate (n=385)
ACR-20	39.7%	67.9%	39.7%	73.1%
ACR-50	16.8	39.9	18.2	48.3
ACR-70	6.5	19.8	6.1	28.8

Source: Cowen and Company/ACR 2004 Abstracts

Bristol estimates that 250,000 U.S. RA patients are treated with anti-TNF biologics each year and that 15-25% are inadequate responders or treatment failures, although our physician experts believe these estimates are too high. In June 2005, Bristol entered into a manufacturing agreement with South Korean contract manufacturer, Celltrion, to ensure sufficient long-term supply for biologics including Orencia and Belatacept (LEA29Y). Orencia is priced (WAC) at \$595/vial with an average of 3 vials per infusion. The cost of the first year of treatment is estimated at \$27,000 (15 infusions) and \$23,000 in each subsequent year (13 infusions). Pricing is in line with anti-TNFs.

Orencia Plus Methotrexate Beneficial In Early Erosive RA

In a Phase IIIb study presented at ACR 2008, 509 MTX-naïve individuals with early erosive RA who had evidence of joint erosion in hands, wrists or feet, were randomized to receive either combination therapy of Orencia plus MTX (n=256) or MTX plus placebo (MTX alone, n=253). The primary endpoints were DAS28 (CRP)-defined remission [DAS28 (CRP) less than 2.6] and joint damage progression measured using the Genant-modified Total Sharp Score, which uses X-ray to measure change at Year 1. Significantly more patients taking Orencia plus MTX reached an ACR 50 score compared to those taking MTX alone (57.4% versus 42.3%; p-value <0.001). In addition, there was a significant difference between the patients taking Orencia plus MTX versus those taking MTX alone who achieved a major clinical response (27.3% versus 11.9%, respectively; p-value <0.001). The mean change in the Genant-modified Total Sharp Score from baseline was 0.63 for patients receiving Orencia plus MTX, compared to 1.06 for those receiving MTX alone (p-value = 0.04).

Orencia Data In Early RA Interesting

At EULAR in June 2014, Bristol announced results from a Phase IIIb trial (AVERT) in 351 adult patients with early stage RA (biologic and MTX-naïve) in which once weekly 125mg SC Orencia + methotrexate (MTX) demonstrated significantly higher rates of DAS-defined remission at 12 months compared to MTX alone (60.9% vs. 45.2%). Similar results were seen using more stringent efficiency measures including Boolean, CDAI and SDAI remission. The Orencia + MTX combo also demonstrated a small, but

statistically significant, greater number of patients maintained remission 6 months after all RA treatment was withdrawn (14.8% vs. 7.8%).

Lupus Nephritis Phase III Trial Under Way

Phase II data in Lupus flares were presented at ACR 2008. The top-line results demonstrate that Orencia missed both the primary and secondary endpoints. Bristol initiated a 400-patient Phase III trial in lupus nephritis in January 2013. The primary completion date is February 2017. The primary endpoint is a composite of renal function, proteinuria, urine sediment, and corticosteroid dose.

Nulojix A Niche Product For Kidney Transplant

Nulojix (belatacept) is an optimized CTLA4-Ig fusion protein, differing from Orencia by only 2 amino acids, for the treatment of transplant rejection. In June 2011, FDA approved Nulojix to prevent acute rejection in adult patients who have had a kidney transplant. The drug is approved for use with other immunosuppressants specifically basiliximab, mycophenolate mofetil, and corticosteroids. We forecast Nulojix sales of \$40MM (+54%) in 2014, \$55MM in 2015, \$45MM in 2016, \$65MM in 2018 and \$85MM in 2020.

Label Warns Against Increased Risk Of Post-Transplant Lymphoproliferative Disorder, Other Cancers, And Infections

The Nulojix label warns against an increased risk of developing post-transplant lymphoproliferative disorder (PTLD). PTLD is the result of the unregulated production of B-cells during immunosuppression which increases the likelihood of developing mutations within the B-cell population; dominant mutations may prevail resulting in a malignancy that is similar to a Burkitt lymphoma. The label particularly warns against PTLD, predominantly involving the CNS, in patients who have not been exposed to Epstein-Barr virus (risk 9-times greater in EBV seronegative patients). Given that EBV is carried up to 80% of donated organs, it is recommended that patients be tested for EBV and should only receive Nulojix if the test shows they have already been exposed to the virus. Our physician consultants are concerned with the high acute rejection and PTLD rates versus cyclosporine in the BENEFIT and BENEFIT-EXT studies, as acute rejection rates are associated with graft failure. However, the transplant consultants believe acute rejection can be managed in some cases. The physicians were moderately impressed with belatacept's benefit on glomerular filtration rates (GFR) and kidney function. Improved GFR should translate into long-term graft survival although this has yet to be demonstrated. However, one physician consultant believes that, had belatacept been compared to tacrolimus (vs. cyclosporine), the GFR benefit may not have been seen. Tacrolimus is used more widely in the U.S. and has been shown less detrimental to kidney function than cyclosporine. Another Boxed Warning on the Nulojix label, as well as labels of other immunosuppressants, warns of an increased risk of serious infections, progressive multifocal leukoencephalopathy (PML), and other cancers. The use of Nulojix is liver transplant is not recommended as the administration of belatacept was associated with higher rates of graft loss and death when compared to tacrolimus.

The market opportunity for conversion is approximately 4x that of the new patient market. Switching to a belatacept-based regimen from a calcineurin inhibitor was safe, associated with low rates of acute rejection, and resulted in improved renal function. Monthly i.v. infusions may limit use of belatacept given that the alternative (cyclosporine) is given orally. The Organ Procurement and Transplantation Network suggest that as many as 89,000 patients are currently waiting for a kidney transplant

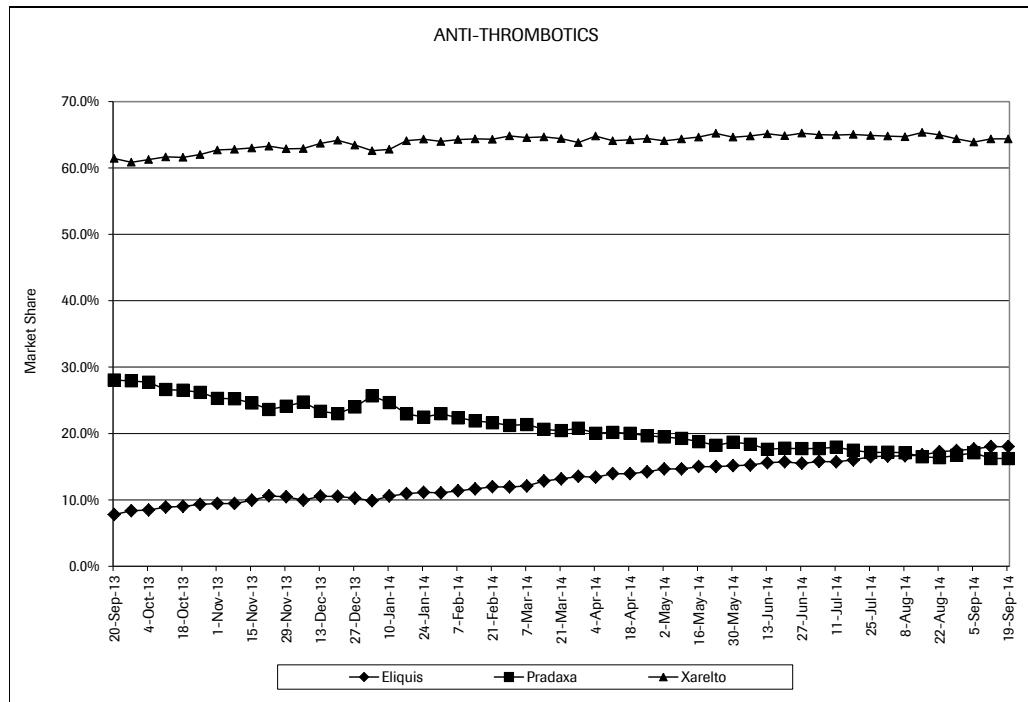
in the United States. Phase III data presented at the 2009 American Transplant Meeting underwhelmed our physician consultants.

Cardiovascular

Eliquis Rollout Gaining Momentum

In late 2012, FDA and EMA approved Eliquis (apixaban) for stroke prevention in atrial fibrillation with strong labels that accurately reflect data from the ARISTOTLE and AVERROES trials. Eliquis is a selective, oral direct Factor Xa inhibitor that offers good oral bioavailability, no food effect, a half-life of 12 hours with a low peak to trough ratio, and no organ toxicity or raised LFTs seen in animal toxicity studies. Apixaban is excreted predominantly via the liver but also by the kidney (25%), may not require monitoring, and has a superior bleeding profile when compared to warfarin. Bristol-Myers/Pfizer have pursued additional indications including DVT prevention which was FDA approved in March 2014 (EU approved May 2011). Eliquis also received EU (July 2014) and U.S. (August 2014) approval for the treatment of DVTs and PEs, and prevention of recurrent DVTs and PEs following initial therapy. Eliquis continues to build momentum with a 20.4% share as of August 2014, showing increased share each month. JNJ's Xarelto continues to perform well, likely due to its once-daily dosing format, multiple indications, and second to market position. However, we believe superior data ultimately will make Eliquis the leader among the newer agents. In addition, BMY initiated DTC advertising in the U.S. in Q3:13, and has launched Eliquis in all major markets. We estimate Eliquis sales of \$680MM in 2014, \$1,080MM in 2015, \$1.4B in 2016, \$1.9B in 2018, and \$2.4B in 2020.

Anti-Thrombotics



Source: IMS America

Phase IV Study Initiated In Patients With NVAF Undergoing Cardioversion

In July 2014, Bristol/Pfizer announced enrollment of the first patient in the EMANATE Phase IV trial ($n = 1,500$) to evaluate Eliquis in patients with nonvalvular atrial fibrillation (NVAF) undergoing cardioversion. Eliquis is currently approved to decrease the risk of stroke/systemic embolism in patients with NVAF. EMANATE is a randomized, open label trial which will evaluate Eliquis vs. usual care (heparin and/or oral anticoagulant + vitamin K antagonist) in NVAF patients expected to undergo cardioversion after short-term anti-coagulation. All patients will receive Eliquis or usual care prior to cardioversion and for up to 30 days post-conversion. The primary efficacy endpoints are the occurrence of acute stroke, systemic embolism, and all-cause death. The primary completion date is January 2016 (per clinicaltrials.gov).

European SPAF Labeling As Expected

In November 2012, the EMA approved Eliquis for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors (prior stroke/TIA, age ≥ 75 years, hypertension, diabetes, NYHA Class ≥ 2 HF). The label reflects the data from ARISTOTLE and AVERROES, defining Eliquis as providing superior efficacy, superior safety (bleeding), and improved mortality relative to warfarin. The label does not contain a black box warning for bleeding risk. Eliquis is recommended for use in patients with normal renal function and mild-to-moderate renal impairment, but is not recommended for use in patients with $\text{SCr} < 15 \text{ mL/min}$ (Xarelto dose adjusted for $\text{SCr} < 50 \text{ mL/min}$). The label does not contain any reference to an increase in events when stopping therapy (this is a boxed warning for Xarelto).

U.S SPAF Labeling Is Best In Class

On December 28, 2012, FDA approved Eliquis to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Eliquis was approved with a strong label, including superiority to warfarin for stroke prevention, bleeding, and all cause death. The label includes a box black warning citing a higher incidence of thromboembolic events in patients who discontinue Eliquis (Xarelto's label also has a black box warning). In the event that a patient discontinues Eliquis for a reason other than pathological bleeding, coverage with another anticoagulant is recommended. Eliquis is priced at \$9.72 per day, at parity to Pradaxa (Bd; \$9.72 per day) and Xarelto (JNJ; \$9.55 per day). Bristol/Pfizer launched Eliquis in Q1:13.

Eliquis Offers Superior Clinical Profile Relative To Competition At Similar Price

Both Eliquis and Pradaxa have demonstrated superiority to warfarin in reducing strokes in patients with nonvalvular atrial fibrillation; Xarelto demonstrated non-inferiority. Eliquis is the only novel anticoagulant to demonstrate a reduction in major and clinically relevant non-major bleeding relative to warfarin and is the only novel anticoagulant to improve overall mortality. Given the superior clinical profile of and pricing of Eliquis, we believe there is no compelling reason to prescribe any other anticoagulant for SPAF.

Comparison Of Novel Anticoagulants

	Eliquis (BMY/PFE)	Pradaxa (BI)	Xarelto (JNJ)
FDA Indication	SPAF	SPAF	SPAF, DVT treatment and prevention
Superiority to warfarin (SPAF)	Yes	Yes	No
Superior bleeding to warfarin	Yes	No	No
Mortality benefit	Yes	No	No
Black box warning	Increased event rate in patients discontinuing Eliquis	NA	Increased event rate in patients discontinuing Xarelto; increased risk of spinal/epidural hematoma with spinal puncture
Price	\$9.72/day	\$9.72/day	\$9.55/day

Source: Product labels, PriceRx.com

SPAF:

Two studies in stroke prevention in atrial fibrillation (SPAF) were initiated: ARISTOTLE and AVERROES. ARISTOTLE enrolled 18,183 patients to evaluate Apixaban in SPAF; data was presented at ESC 2011. Absolute and relative risk reductions for apixaban in ARISTOTLE were in line with our expectations. Consistent with previously released top-line data, apixaban demonstrated superiority over warfarin for stroke prevention with an improved bleeding profile. Apixaban also met its secondary all-cause mortality endpoint versus warfarin, although the magnitude of the mortality benefit in ARISTOTLE was similar to what has been observed in trials for other novel anticoagulants. Nonetheless, ARISTOTLE is the first trial to demonstrate a statistically significant mortality benefit. AVERROES was stopped early because a predefined interim analysis by the independent Data Monitoring Committee revealed clear evidence of a clinically important reduction in stroke and systemic embolism. This interim analysis also demonstrated an acceptable safety profile for Apixaban compared to aspirin. The AVERROES study included 5,600 patients with atrial fibrillation at risk for stroke who were considered intolerant of or unsuitable for therapy with a vitamin K antagonist such as warfarin; as many as 40% of patients enrolled in AVERROES had previously failed therapy with a vitamin K antagonist. Patients were randomized to receive either Apixaban 5mg twice daily or aspirin 81mg to 324mg once daily. In February 2011 the complete results from AVERROES were published in the NEJM. 51 patients on apixaban (1.6% per year) experienced a stroke during the course of the study versus 113 patients (3.7% per year) on aspirin (HR 0.45, CI 0.32-0.62, p<0.001). Rates of death were 3.5% per year with apixaban versus 4.4% in the aspirin group (HR 0.79, CI 0.74-1.02, p=0.07). There were 44 major bleeds in the apixaban group (11 intracranial) compared to 39 on aspirin (13 intracranial) (HR=1.13, CI 0.74-1.75, p=0.57). Apixaban also significantly reduced the risk for hospitalization in these patients. No differences were noted between important patient subgroups.

VTE Prevention:

Data from the Phase III U.S. VTE prevention study, ADVANCE-1, released in August 2008 revealed that it had missed the primary endpoint. This delayed the U.S. VTE prevention filing. However, BMY filed for this indication in mid-2013, and also indicated they plan to file for VTE Treatment later this year. The data from the Phase III, European DVT prevention study in knee surgery appear robust, with superior efficacy and less bleeding than Lovenox. The full data were presented at ISTH 2009. Bristol submitted the VTE filing in March 2010 in the E.U. based on the positive results of ADVANCE-2 and -3. On March 20, 2011, apixaban was approved in the E.U. for the prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery.

ACS:

In March 2009, Bristol and Pfizer initiated the 10,848 patient ACS study, APPRAISE-2. However in November 2010, APPRAISE-2 was stopped early due to excessive bleeding in patients on apixaban plus dual antiplatelet therapy. Bristol has stated that the opportunity for the orthopedic indications is 5% of the potential market, with the ACS and atrial fibrillation indications making up the remainder.

Apixaban Phase III Program

Study	Clinical Setting	Apixaban Dose	Comparator	Number of Patients	Status
Surgical VTE Prophylaxis					
ADVANCE-1	Knee replacement surgery	2.5mg BID	Lovenox 30mg BID	3,200	Failed to show non-inferiority
ADVANCE-2	Knee replacement surgery	2.5mg BID	Lovenox 40mg QD	3,100	Superior results in major VTE and clinically relevant bleeding AEs
ADVANCE-3	Hip replacement surgery	2.5mg BID	Lovenox 40mg QD	5,400	Superior to enoxaparin in prevention of symptomatic/asymptomatic DVT, PE, and all-cause death. No difference in bleeding or clinically relevant bleeding compared to enoxaparin alone
Medical Prophylaxis					
AVERROES	Stroke prevention in atrial fibrillation	5mg BID; 2.5mg BID in selected patients	Aspirin in warfarin ineligible patients	5,600	Stopped early for efficacy
ARISTOTLE	Stroke prevention in atrial fibrillation who VKA ineligible	5mg BID	Warfarin	18,183	Superior efficacy and bleeding profile compared to warfarin. Statistically significant mortality benefit demonstrated
ADOPT	Acute medical illness	2.5mg BID	Lovenox 40mg QD	6,524	Did not show differentiation from Lovenox
APPRAISE-2	Prevent MACE in recent ACS	5mg BID	Placebo	10,848	Stopped for safety; no path forward
VTE Treatment					
AMPLIFY	Acute DVT/PE	10mg BID for 7 days; 5mg BID for 6 months	Lovenox + warfarin	5,395	Non-inferior to standard of care
AMPLIFY-EXT	Long-term treatment of VTE/PE	2.5mg or 5mg BID	Placebo	2,486	Superiority vs. placebo in reduction of recurrent VTE/all cause death

Source: Company data, clinicaltrials.gov

Infectious Diseases

Bristol HIV Franchise Facing New Competition

Flat Reyataz Trend Through 2015

Reyataz (atazanavir) has been a big success in the protease inhibitor market since being approved in treatment-resistant HIV, claiming 20.2% new prescription share in August 2014; NRxs were down 13% year-on-year. Ritonavir-boosted Reyataz offers improved dosing (two capsules once daily) and virtually no impact on lipids, its major advantage over Abbott's Kaletra. In November 2008, FDA approved Reyataz as part of combination therapy in treatment-naïve patients. The approval was based on the 48-week CASTLE study, presented at CROI 2008, which demonstrated non-inferiority to twice daily Kaletra (lopinavir)/ritonavir. The CASTLE study confirmed Reyataz's favorable safety profile, especially its low impact on cholesterol. Ninety-six week data from CASTLE, presented at ICAAC 2008, demonstrated that 74% of the patients in the Reyataz arm had undetectable HIV levels versus 68% in the Kaletra arm; discontinuation rates were 16% versus 21%, respectively. In November 2009 FDA approved a label update to include the 96-week data.

Competition has increased: JNJ's once-daily Prezista (darunavir) offers a very competitive profile and is approved in both indications, and its ARTEMIS study in treatment-naïve patients demonstrated superiority over Kaletra. However, Prezista results in increased cholesterol versus Kaletra, has been associated with liver toxicity, and has a Pregnancy C warning for women. Merck's Isentress, ViiV's Tivicay, integrase inhibitors approved for treatment-naïve HIV patients, are competitors in the front-line. The basic patent expires in the U.S. in 2017 and an SPC filed in the U.K. and Denmark, if granted, will extend the patent to March 2019 in these countries; for the remainder of Europe, data exclusivity is to expire in 2014 but the patent expires in March 2017. In April 2014, Bristol filed an NDA for a Reyataz + cobicistat (investigational boosting agent from Gilead) fixed dose combination to improve dosing convenience. We forecast Reyataz sales of \$1,410MM (-9%) in 2014, \$1,335MM in 2015, \$1,250MM in 2016, \$500MM in 2018, and \$100MM in 2020, post its 6/17 patent expiration.

Atripla (Sustiva/Truvada) Offers Modest Advantage But Convenience Is Key

Sustiva (efavirenz), a non-nucleoside reverse transcriptase inhibitor, had 10.6% new prescription share of the non-nucleoside reverse transcriptase inhibitor (NNRTI) market in May 2014. This share has been declining (-7% Y/Y), due to the success of Atripla, which has 23.1% share; NRxs -4% Y/Y. Our physician experts believe Atripla, a once-daily Sustiva/Truvada (emtricitabine + tenofovir) fixed-dose combination pill marketed by Gilead, offers only a modest convenience advantage.

Bristol has a joint venture with Gilead to develop and commercialize Atripla in the U.S., Canada and Europe. Bristol and Gilead share responsibility for commercializing Atripla in the U.S., Canada, throughout the E.U. and certain other European countries, and both provide funding and field-based sales representatives in support of promotional efforts for Atripla. Gilead recognizes 100% of Atripla revenues in the U.S., Canada and most countries in Europe. Bristol records revenue for the bulk efavirenz component of Atripla upon sales of that product to third parties. In a limited number of E.U. countries, Bristol records revenue for Atripla where it agreed to purchase the product from Gilead and distribute it to third-party customers. The JV is operated essentially at breakeven.

The JV continues until terminated by mutual agreement or a material breach by one party. In the latter instance, the non-breaching party may terminate the joint venture only if both parties agree that it is both desirable and practicable to withdraw the combination product from the markets where it is commercialized. If one or more generic versions of either party's component product(s) appear on the market in the U.S., the other party will have the right to terminate the joint venture and thereby acquire all of the rights to the combination product, both in the U.S. and Canada. However, for three years the terminated party will continue to receive a percentage of the net sales based on the contribution of bulk component(s) to Atripla, and otherwise retains all rights to its own product(s).

The composition-of-matter patent for Sustiva in the U.S. expired in 2013; a method-of-use patent for the treatment of HIV infection expires in 2014; a six month pediatric extension has been granted. Sustiva is also covered by polymorph patents which expire in June 2019. In April 2009, Teva filed an ANDA to manufacture and market a generic version of Atripla. The Paragraph IV challenged two of the fifteen Orange Book-listed patents for Atripla. In May 2009, Gilead filed a patent infringement action against Teva in the District Court for the Southern District of New York. In January 2010, Bristol received a notice that Teva has amended its ANDA and was now challenging eight additional Orange Book-listed patents for Atripla. In March 2010,

Bristol filed a patent infringement suit against Teva relating to two patents relating to the crystalline or polymorph form of efavirenz; in August 2013, a settlement was reached. In April 2013, Gilead and Teva reached a settlement on the tenofovir patents and in February 2014 Gilead and Teva reached a settlement in principle on the emtricitabine patents. Atripla/Sustiva franchise sales are forecast to be \$1.4B (-13%) in 2014, \$685MM in 2015, \$135MM in 2016, \$60MM in 2018, and \$10MM in 2020.

BMS-663068 May Provide New Option For HIV Treatment Experienced Patients

BMS-663068 is a prodrug, which is converted into BMS-626529, a novel attachment inhibitor that prevents initial viral attachment to the host CD4+ T cell and entry into the host immune cell. By targeting the virus at an earlier stage, BMS-663068 may provide another method of suppressing the virus in patients who have failed a prior HIV treatment regimen. Phase IIb studies, released in March 2014, showed similar viral suppression in a 24-week regimen of BMS-663068 compared to boosted Reyatz (HIV-1 RNA levels <50c/ml in 80% vs. 75%). The drug was well tolerated with no discontinuations from side effects.

New Regimens Led By Gilead's Stribild (QUAD) Threaten Bristol's HIV Franchise Growth

The biggest potential threat to Sustiva is Gilead's quad combination pill, known as Stribild. The pill combines Truvada (tenofovir + emtricitabine) with an integrase inhibitor, as well as a boosting agent, which increases potency and allows the inhibitor to be used in a once-daily formulation. In September 2011, Gilead announced that Stribild met its primary non-inferiority end points in a head-to-head Phase III trial against ritonavir-boosted atazanavir plus Truvada. The Quad demonstrated a strong trend toward superiority (90% of Quad patients versus 87% of atazanavir maintained suppression), although this trend did not reach statistical significance (95% CI -1.9% to 7.8%). The discontinuation rate due to adverse events was lower in the Quad arm (3.1%) than the ritonavir-boosted atazanavir arm (5.1%), driven primarily by elevated bilirubin levels observed in the atazanavir arm. The rate of other Grade 3 or 4 adverse events was similar between the arms, although the release did not provide detailed data. Key adverse event data for the Quad include its GI side effects and effects on the kidney. Cobicistat, the quad boosting agent, met its Phase III (Study 114) primary endpoint of non-inferiority compared to ritonavir.

In August 2012, FDA approved Stribild for the treatment of HIV-1 infection in treatment naïve adults. Our physician experts believe Stribild could garner significant market share.

Glaxo's once-daily integrase inhibitor, Tivicay, does not require boosting and appears to offer a superior tolerability and resistance profile when compared to existing regimens. Dolutegravir demonstrated statistically superior viral suppression compared to Atripla, driven by improved tolerability translating to fewer dropouts in the dolutegravir-containing arm. At 48 weeks, 88% of patients on the dolutegravir regimen were virologically suppressed compared to 81% of patients on Atripla; the difference in treatment effect was statistically significant ($p=0.003$). Differences in efficacy were driven by improved tolerability and a lower dropout rate in the dolutegravir-containing arm (2% of patients dropped out in dolutegravir arm vs. 10% in Atripla arm). The most frequent adverse events in the Atripla arm were CNS-related (41%). CNS-related events occurred in only 15% of patients in the dolutegravir-containing arm. The rates of GI-related adverse events were similar between treatment groups (22% in both dolutegravir and Atripla arms).

Baraclude: Good Choice For First-Line HBV, But U.S. Patent Ruled Invalid; Generic Approved

Baraclude (entecavir), approved in March 2005, induces significant viral load reduction compared with lamivudine (80% vs. 39% of patients demonstrated undetectable HBV DNA at two years) and has shown <1% resistance after four years of therapy. It is believed that Baraclude is one of the best choices for front-line treatment, especially for patients with high baseline viral loads. That said, Baraclude is not ideal for lamivudine-refractory patients due to the cross-resistance. Specifically, 42% of lamivudine-refractory patients experience virologic breakthrough after four years on Baraclude therapy. Separately, Baraclude's preclinical carcinogenicity data remain a source of debate in the infectious disease community.

Baraclude's composition of matter patent was set to expire in the U.S. in 2015 and in October 2016 ex-U.S.; however, in February 2013 the Delaware District Court ruled that Baraclude's composition of matter patent was invalid. Bristol appealed the Court's decision but in June 2014, the appeal was denied. Bristol has requested an en banc hearing.

In October 2013, Teva's ANDA for its generic version of entecavir was tentatively approved by the FDA and in August 2014, FDA granted full approval. On September 4, 2014, Teva launched its generic version in two doses. 80% of Baraclude use is ex-U.S. Generics already exist in China; however, branded Baraclude maintains preferential placement on China's national formulary while generics do not. Bristol has therefore continued to grow Baraclude in China. We forecast Baraclude sales of \$1.595B (+4%) in 2014, \$1.67B in 2015, \$1.725B in 2016, \$1.8B in 2018, and \$1.85B in 2020. Our 2015 estimate includes \$50MM of U.S. sales.

Bristol's HCV Portfolio Targeting Range Of Therapies

Bristol is targeting HCV disease via several approaches. It has a NS5a inhibitor (daclatasvir/DCV) that received EU approval in August 2014 for use in combo therapy; a NS3 inhibitor (asunaprevir/ASV) that has been filed in the U.S. as combo therapy with DCV (combo approved in Japan in July); a Phase III peg-interferon lambda; and a non-nucleoside polymerase inhibitor (BMS-791325) which is part of a 3DAA combo in Phase III.

In July 2014, Bristol received approval in Japan for the all-oral HCV dual combo regimen of daclatasvir (trade name Daklinza; NS5A inhibitor), and asunaprevir (trade name Sunvepra; NS3/4A protease inhibitor) for patients who are interferon ineligible/intolerant or non-responders. This is the first all-oral interferon and ribavirin free regimen to be approved in Japan for genotype-1 HCV patients, including those with cirrhosis. Bristol estimates that of the 1.2MM people in Japan with HCV, 70% have genotype-1b. While the Hep C population in Japan is older, Bristol notes that they do not tolerate interferon-based therapy well, so there is a ready market for a non-interferon-based regimen. The Japanese government is being proactive in these efforts in part due to tainted blood being a common vector for transmission. The 24-week regimen will be priced at roughly \$25,000 in Japan.

In February 2014, the daclatasvir + asunaprevir combo received Breakthrough Therapy designation from the FDA for its use in treatment of genotype 1b HCV patients. Bristol filed daclatasvir + asunaprevir combo in the U.S. in April 2014 with a PDUFA of November 30, 2014.

We estimate Asunaprevir sales of \$100MM in 2014, \$500MM in 2015, \$500MM in 2016, \$300MM in 2018 and \$100MM in 2020 as we believe Bristol will capture share in Japan, but competition will follow quickly. In August 2014, the EC approved daclatasvir for use in combination with other agents (including sofosbuvir). Our sales forecasts for Daclatasvir of \$100MM in 2014, \$500MM in 2015, \$500MM in 2016, \$300MM in 2018, and \$100MM in 2020 are based on similar market assumptions as asunaprevir.

Phase III Dual Regimen Data Solid Across Sub-Groups

At EASL 2014, Bristol presented data from the Phase III HALLMARK-Dual data for daclatasvir + asunaprevir (DCV+ASN) oral combo (24 week regimen) in GT-1b treatment-naïve patients. Results showed an SVR12 of 90%, and SVR12 of 82% in both null responders and in pegRBV-intolerant patients, and an SVR12 of 84% in cirrhotic patients.

At AASLD 2013, Bristol presented data from a Phase III confirmatory study of the all-oral combination of daclatasvir (NS5A inhibitor) and asunaprevir (NS3 PI) in Japanese patients with HCV genotype 1b who were ineligible/intolerant to interferon-based therapies. The combo therapy achieved SVR24 in 87.4% of interferon intolerant/ineligible patients and 80.5% of non-responders. The drugs were well tolerated with few discontinuations.

Daclatasvir And Asunaprevir Deliver Impressive Phase II Data

Daclatasvir (BMS-790052) is a first-in-class, highly selective, oral HCV NS5A inhibitor. 12-week data from a Phase IIa multiple ascending dose trial were presented at EASL 2010. The study evaluated 3, 10, and 60mg of daclatasvir on top of standard of care for 48 weeks. Participants in all three arms receiving daclatasvir had a significantly higher response rate than placebo recipients. The two higher daclatasvir doses (10 and 60) were more effective than the 3 mg dose. RVR rates at week 4 were 42% in the 3 mg daclatasvir arm, 92% in the 10 mg arm, and 83% in the 60 mg arm, compared with 8% in the placebo arm. Complete EVR rates at week 12 were 58%, 83%, 83%, and 42%, respectively. Extended RVR rates (undetectable at both week 4 and 12) were 42%, 83%, 75%, and 8%, respectively. Confirmed viral breakthrough did not occur in the 10 mg or 60 mg daclatasvir arms through week 12. Adverse events were similar across the study arms and were consistent with those typically seen with pegylated interferon/ribavirin. One person in each of the three daclatasvir dose arms experienced serious adverse events. One person in the two lower dose daclatasvir arms and three people in the 60 mg arm developed skin rash.

The function of NS5a is not well understood, although it has been identified as an essential component of the HCV replicase and associates with a number of viral and host cell proteins to accommodate viral entry and replication. NS3/4 are viral proteases that are necessary for virus entry, replication, and suppression of host immune responses. NS3a cleaves NS5a to its active form which is why NS3a inhibitors are used in combination with NS5a's; hypothetically they are synergistic. However, neither the protease inhibitors nor the NS5a inhibitors directly target viral replication machinery the way the nucs do; the nucs target an entirely different mechanism and in combination with other antivirals seem to be more effective at reducing viral load and preventing resistance/breakthrough.

A Phase II treatment-experience study evaluated daclatasvir (60mg QD) and asunaprevir (BMS-650032), 600mg BID, in combination for 24 and 48 weeks and together with Peg/ribavirin for 24 weeks. Data from this study, presented at the 2010 AASLD, showed 6/11 patients achieving cEVR by week 4 with asunaprevir and daclatasvir alone with viral breakthrough in 6 of those patients at later time points and

9/10 patients achieving a sustained cEVR by week 12 with the addition of Peg/rivavirin. It should be noted that of the 9/10 patients achieving cEVR on the 65032/79005/Peg/Rib combination that the single patient who did not achieve cEVR was retested and found to have an undetectable viral load at that time. Bristol presented Phase II data from a clinical trial of 48 treatment-naïve genotype 1 hepatitis C patients at ICAAC 2011. Daclatasvir plus pegIFNalfa/RBV achieved higher rates of SVR24 compared to pegIFNalfa/RBV alone across all daclatasvir treatment groups (daclatasvir: 60 mg: 83%, 10 mg: 83%, 3 mg: 42% (5/12); control: 25%). Adverse events (AEs) leading to discontinuation with daclatasvir plus pegIFNalfa/RBV were comparable with treatment with pegIFNalfa/RBV plus placebo. One patient (8.3%) in each of the 3 mg and 10 mg groups and four patients (33.3%) in the 60 mg group discontinued due to AEs, compared with two patients (16.7%) in the control group. Reasons for discontinuation were a diverse set of AEs sometimes associated with the use of pegIFNalfa/RBV. Serious adverse events (SAEs) and overall AEs were comparable across study arms.

The addition of daclatasvir to pegIFNalfa/RBV therapy did not result in any apparent incremental hematologic, hepatic or dermatologic adverse events. One patient (8.3%) in each of the BMS-790052 treatment groups experienced a SAE during therapy compared with zero patients in the control group. On-treatment Grade 3-4 AEs were: daclatasvir 60 mg: 33.0%, 10 mg: 25.0%, 3 mg: 8.3%; control: 41.7%. One patient (8.3%) in each of the daclatasvir 3 mg and 60 mg groups experienced hemoglobin <10 g/dL, compared with zero patients in the 10 mg and control groups. AEs occurring in at least four patients (33.3%) in any cohort were consistent across BMS-790052 treatment arms and the placebo arm, and included the following events of interest: anemia (daclatasvir: 60 mg: 50.0%, 10 mg: 41.7%, 3 mg: 25.0%; control: 41.7%), nausea (daclatasvir: 60 mg: 33.3%, 10 mg: 33.3%, 3 mg: 41.7%; control: 50.0%), vomiting (daclatasvir 60 mg: 33.3%, 10 mg: 8.3%, 3 mg: 16.7%; control: 0%), neutropenia (daclatasvir: 60 mg: 16.7%, 10 mg: 33.3%, 3 mg: 25.0%; control: 41.7%), and rash (daclatasvir: 60 mg: 16.7%, 10 mg: 33.3%, 3 mg: 33.3%; control: 25.0%). Erythropoietin use was comparable across all study arms. Three patients (25.0%) in each of the BMS-790052 10 mg and 60 mg groups and one patient (8.3%) in the 3 mg group required erythropoietin, compared with two patients (16.7%) in the control group. The use of filgrastim (G-CSF) in the study groups was: daclatasvir 60 mg: 0%, 10 mg: 25.0%, 3 mg: 16.7%; control: 16.7%.

Interferon-Free Asunaprevir/Daclatasvir Combination Achieves 90% SVR In Genotype 1b Prior Null-Responders

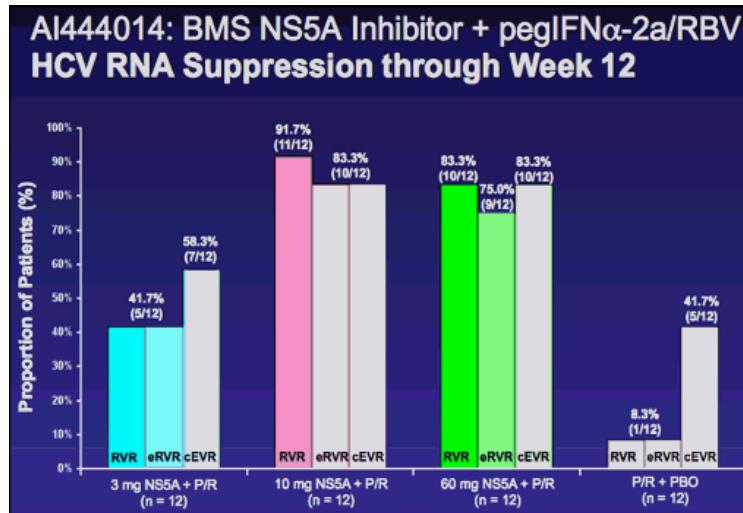
Historically, patients who failed to respond to previous interferon- α monotherapy have roughly a 10-15% chance of achieving SVR with interferon- α plus ribavirin, a 25-35% chance of achieving SVR with pegylated interferon plus ribavirin, and a >50% chance of achieving SVR in a regimen that includes a protease inhibitor. Boceprevir and Incivek achieved 65-66% SVR in prior null responders in their Peg/Riba-containing RECORD-2 and REALIZE trials. A 90% SVR in the absence of interferon is therefore an impressive milestone. While these 24-week data are impressive, 6 /11 genotype 1a patients experienced viral breakthrough on the asunaprevir/daclatasvir combination in the absence of Peg/Riba in an abstract at AASLD 2010.

The abstract at AASLD, entitled "Dual Oral Combination Therapy with the NS5A Inhibitor daclatasvir and the NS3 Protease Inhibitor asunaprevir Achieved 90% Sustained Virologic Response (SVR12) in HCV Genotype 1b-Infected Null Responders," was a 24-week analysis of a sentinel cohort of 10 patients in a Phase II combination trial of asunaprevir and daclatasvir. The trial is enrolling 50 HCV infected patients who are null responders to prior interferon-based therapy. The trial is open-

label, and patients are randomized into one of two arms: 60mg daclatasvir QD and 600mg asunaprevir BID for 24 weeks, or 60mg daclatasvirQD, 600mg asunaprevir BID, PEG-IFN, and RBV for 24 weeks. Endpoints include safety, pharmacokinetics, RVR, EVR, and SVR.

Of the 10 patients analyzed, the mean baseline HCV RNA was 6.8 log₁₀ IU/mL with a median age of 62 years. 9/10 patients completed 24 weeks of therapy with a single patient discontinuing after 2 weeks of treatment. In all 9 patients completing therapy, HCV RNA was undetectable at week 8 through post-treatment week 12 (SVR12). No viral breakthrough was observed. Polymorphisms associated with daclatasvir resistance were detected at baseline in several patients, although they did not impact virologic outcomes. The most common adverse events were diarrhea and headache. Three patients experienced grade 1/2 elevations in transaminases and 2 patients experienced serious adverse events (possibly related to treatments for infectious gastroenteritis that lead to discontinuation and pyrexia).

HCV RNA Suppression Through Week 12



Source: Company data, Cowen and Company

3DAA Regimen Anticipated To Be Filed Early 2015

Bristol's all-oral 3DAA regimen of daclatasvir+asunaprevir+BMS-791325 received Breakthrough designation from the FDA in 2013. Bristol expects to file this 3DAA combo in the U.S. in Q1:15. Phase III data from BMY's 3DAA combo, which has a 12 week regimen, will be available internally by year-end. Bristol is also evaluating DCV in other all-oral combinations, including sofosbuvir. In August 2014, one of four 3DAA studies ongoing in Japan (and in several other countries OUS) was halted but is expected to re-start post an adjustment in the study protocol.

At AASLD 2013, Bristol presented results from the Phase IIb study. In a 12 week interferon and ribavirin free study of daclatasvir, asunaprevir, and BMS-791325 (NS5B inhibitor), 90%+ of 166 patients achieved SVR12, even with a high prevalence of tougher-to-treat patients (those with GT 1a, advanced fibrosis/cirrhosis, and IL28B non CCgenotypes.) The regimen was well tolerated with few discontinuations, regardless of dose, although the higher dose (150mg) BMS-791325 arm did show 2 serious AEs (vs. 1 at lower dose). Based on these results, Phase III trials will be initiated for this triple-combo including BMS-791325 at the 75mg dose.

At AASLD 2012, Bristol presented results from a 12-week Phase IIa HCV trial with its all oral regimen of daclatasvir 60mg, asunaprevir 200mg (NS3), and BMS-791325 75mg (non-nuc NS5B) in treatment naïve patients with genotype 1a/b (75% 1a). Bristol's three drug regimen lowered HCV RNA below detectable levels in 100% of patients at week 4 and in 88-94% of patients at week 12. Had data been available for all patients, it appears likely that HCV RNA below the lower limits of quantification (LLOQ) may have been reached in 100% of patients at week 12. The most commonly observed adverse events ($\geq 10\%$) were headache, diarrhea, and asthenia. No grade 3/4 elevations in ALT/AST were observed.

Results presented at EASI 2012 included a Phase IIa study of 32 GT1 (a/b) patients who were randomized 1:1 to receive DCV/ASV/BMS-791325 for 12 (Group 1) or 24 (Group 2) weeks. All patients had HCV RNA < LLOQ at week 4 without virologic breakthrough or relapse. In Group 1, 94% (15/16) of patients achieved HCV RNA < LLOQ at week 12; 1 patient discontinued with undetectable HCV RNA prior to week 12. In Group 2, 88% (14/16) of patients achieved HCV RNA < LLOQ; 2 patients did not have week 12 results (both achieved SVR4). 24-week data are not yet available.

Details of reported data from the Phase IIa trial are below:

Week 12 Efficacy Summary

	Group 1 (24-weeks, n=16)	Group 2 (12-weeks, n=16)
HCV GT1a	12 (75%)	12 (75%)
HCV RNA < LLOQ		
Week 4	16 (100%)	16 (100%)
Week 12	15 (94%) ^a	14 (88%)
EOT/Last on Treatment	--	16 (100%)
SVR4	--	15 (94%)
Virologic breakthrough	0	0
Relapse	--	0

Source: Company data, AASLD 2012

Peg-Interferon Lambda A Niche Player

In January 2009, Bristol licensed a novel type 3 interferon (interferon lambda) for the treatment of hepatitis C from ZymoGenetics. In September 2010, Bristol announced it was acquiring ZymoGenetics for \$885MM. While there are similarities in terms of activation of immune system response, intracellular pathway, and anti-viral activity between lambda and alpha interferons, the key difference is lower presence of lambda interferon receptors throughout the body to potentially improve safety and efficacy. This could result in absent flu-like symptoms and fewer effects on neutrophils and platelets.

Rates of ADRs commonly associated with interferon therapy were lower with PEG-Interferon lambda compared to PEG-Interferon alpha including flu-like symptoms (lambda 240 μ g, 9.7%; lambda 180 μ g, 9.9%; lambda 120 μ g, 12.5% vs. alpha, 42.9%), musculoskeletal symptoms (lambda 240 μ g, 14.2%, lambda 180 μ g, 14.5%; lambda 120 μ g, 18% vs. alpha, 46.6%), neutropenia <750/mm³ (lambda, 0.08% vs. alpha, 15.2%), anemia with hemoglobin <10mg/dl (lambda 240 μ g, 12.9%; lambda 180 μ g, 15.4%, lambda 120 μ g, 20.5% vs. alpha, 43.9%), thrombocytopenia <50K/mm³ (lambda, 0% vs. alpha, 14.4%). Rates of other serious adverse events were similar between all treatment groups with higher rates of ALT elevation and direct bilirubin elevation in the 240 μ g PEG-Interferon lambda group compared to alpha. We estimate Peg-

Interferon Lambda sales of \$25MM in 2015, \$50MM in 2016, \$100MM in 2018, and \$150MM in 2020.

CNS

Abilify Alliance Revenue Contribution To Decline In 2014-18, And Reach Zero In 2019

Abilify is indicated for long-term maintenance of schizophrenia, acute bipolar mania, bipolar maintenance, add-on treatment of MDD, adolescent schizophrenia, and for adjunctive therapy for manic and mixed episodes associated with Bipolar I disorder. In August 2014, Abilify achieved 16% share of the U.S. antipsychotic new prescription market; NRxs were flat year on year. Abilify is viewed as the drug of choice for long-term treatment of schizophrenia given a tolerable side-effect profile. However, Abilify also is viewed as less effective than alternative agents.

Bristol Has Exclusive Rights In International Markets Ex Japan

Abilify has been launched for the treatment of schizophrenia in all major E.U. markets, and is available in an intramuscular formulation. In April 2009, Bristol announced an agreement with Otsuka to extend the U.S. portion of the companies' agreement for the development and commercialization of Abilify from the scheduled end date of November 2012 until the expected loss of exclusivity in April 2015. In addition, the companies established an oncology collaboration for Sprycel and Ixempra. For the entire E.U., the agreement remained unchanged and will expire in June 2014. In other countries where Bristol has the exclusive right to sell Abilify, the agreement expires on the later of the 10th anniversary of the first commercial sale in each country or expiration of the applicable patent in each country.

We forecast a decline in Abilify revenues beginning in 2014. Otsuka records revenue in major markets while Bristol recorded approximately 52% in 2012, but substantially lower thereafter, as alliance revenue in major markets. Bristol records end-market sales in certain other countries.

Bristol-Myers Squibb Alliance Revenue Analysis (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Abilify*	\$5,795	\$4,340	\$850	\$0	\$0	\$0	\$0	\$0
Estimated share to BMY	Tiered	Tiered	50%	50%	50%	50%	50%	50%
Alliance revenue to BMY	\$1,814	\$1,595	\$425	\$0	\$0	\$0	\$0	\$0
Abilify sales recorded by BMY**	475	300	0	0	0	0	0	0
Abilify total revenue to BMY	\$2,289	\$1,895	\$425	\$0	\$0	\$0	\$0	\$0

* Copromoted territories: U.S.; Germany and Spain

** Territories where BMY is the exclusive distributor and/ or sole promoter including U.K., France and Italy

Source: Cowen and Company

Bristol Increases Focus On Genetic Diseases With iPierian Acquisition

In April 2014, Bristol acquired iPierian, a privately-held biotech company which is focused on treatment for Tauopathies, which are neurodegenerative diseases associated with aggregation of Tau protein in the brain. The lead asset is IPN007, a preclinical mAb for treatment of the genetic disease progressive supranuclear palsy

(PSP) and other Tauopathies. Phase I clinicals could potentially start in 2015. Bristol paid \$175MM in cash with additional potential milestone payments of \$500MM.

Bristol Diabetes Assets Sold To Alliance Partner AstraZeneca; Bristol Gains Royalty Stream

In January 2014, Bristol finalized the sale of its portion of its diabetes collaboration to AstraZeneca for \$2.7B and up to \$1.4B in regulatory, launch, and sales-related payments. BMY received \$3.4B cash in Q1:14, which includes \$0.6B for Farxiga's U.S. approval (January 2014) and \$0.1B for Japan approval (March 2014). BMY had paid about \$7B in total for Amylin, and then AZN paid 50% of that to enter the collaboration. The elimination of the diabetes franchise reduces BMY's primary care footprint and enables greater focus on targeted specialty areas. We estimate BMY's diabetes royalties at \$280MM in 2014, \$315MM in 2015, \$320MM in 2016, \$575MM in 2018, and \$880MM in 2020.

BMY Diabetes Royalty Buildup (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	CGR		Comments
									2014-20	2019-20	
WW Sales											
Bydureon	\$298	\$600	\$1,000	\$1,300	\$1,600	\$1,900	\$2,200	\$2,500	27%	36%	- Synthetic exendin-4
Byetta	400	525	575	625	675	725	775	825	8%	11%	
Total GLP1 franchise	698	1,125	1,575	1,925	2,275	2,625	2,975	3,325	20%	25%	
Onglyza	877	1,100	1,300	1,450	1,600	1,750	1,900	2,050	11%	13%	- Saxagliptin; DPP-IV inhibitor; 1% share 6/14
Forxiga	23	100	200	300	400	500	600	700	38%	63%	- Dapagliflozin; SGLT2 inhibitor; rolling out in EU and U.S.
Metreleptin		20	40	60	80	100	120	140	38%	NM	- Lipodystrophy
Symtrel	83	90	95	100	105	110	115	120	5%	5%	
Royalties											
Bydureon		\$6.0	\$10.0	\$32.5	\$80.00	\$114.0	\$132.0		- Assumes 50/50 U.S./EU		
Byetta		5.3	5.8	15.6	33.8	43.5	46.5		- 2% in 2015-16; 5% in 2017; 10% in 2018; 12% in 2019-20		
Total GLP1 franchise		11.3	15.8	48.1	113.8	157.5	178.5		- 2% in 2015-16; 5% in 2017; 10% in 2018; 12% in 2019-20		
Onglyza		238.0	231.0	220.5	192.0	350.0	418.0	512.5	- Below \$500MM/above \$500MM: 44%/3% in 2014, 35%/7% in 2015, 27%/9% in 2016; 12%/12% in 2017; 20%/20% in 2018; 22%/22% in 2019; 25%/25% in 2020		
Forxiga		44.0	70.0	81.0	48.0	100.0	132.0	175.0	- Below \$500MM/above \$500MM: 44%/3% in 2014, 35%/7% in 2015, 27%/9% in 2016; 12%/12% in 2017; 20%/20% in 2018; 22%/22% in 2019; 25%/25% in 2020		
Metreleptin		0.2	0.4	1.5	4.0	6.0	7.2		- 2% in 2015-16; 5% in 2017; 10% in 2018; 12% in 2019-20		
Symtrel		0.9	1.0	2.5	5.3	6.6	6.9		- 2% in 2015-16; 5% in 2017; 10% in 2018; 12% in 2019-20		
Total Royalties	280	315	320	290	575	720	880		- To "other" line in P&L		

Source: Cowen and Company

Bristol Faces Significant Exclusivity Lapses

Bristol faced significant exclusivity lapses in 2012 when Plavix (5/12 with pedi exclusivity) and Avapro lost protection. In 2014, Bristol will lose E.U. exclusivity on Abilify. During 2014-20, 65% of EPS is at risk, versus the average exposure of 41%.

BMY Patent Vulnerability

Company	Drug	Territory	Patent Exp.	Date	U.S. Sales		Estimated U.S. Sales (\$MM)*	Non-U.S. Sales As % Of Total Sales	Estimated Non-U.S. Sales (\$MM)*	% Total Sales	% Total EPS (#)	
					Estimated WW Sales (\$MM)	As % Of Total Sales					EPS (#)	EPS
BMY	Abilify	E.U.	2014	2014	\$2,289					32%	\$730	5%
	Abilify	U.S.		Apr-15	1,895	68%	1,291				9%	0.19
	Baraclude	U.S.		2015	1,510	23%	344				2%	0.05
	Baraclude	E.U.		Oct-16	1,385			77%	1,070		7%	0.16
	Erbitux	U.S.		Jan-17	690	96%	660				4%	0.10
	Reyataz	U.S.		Jun-17	1,250	46%	580				4%	0.09
	Orencia	E.U.		2017	2,020			37%	744		5%	0.11
	Ixempra	U.S.		May-17	40	100%	40				0%	0.01
	Reyataz	E.U.		Mar-19	500			54%	268		1%	0.00
	Orencia	U.S.		2019	2,360	63%	1,491				8%	0.22
	Sprycel	E.U.		Apr-20	2,290			56%	1,276		6%	0.19
	Sprycel	U.S.		Jun-20	2,290	44%	1,014				5%	0.15

*Estimated sales in year prior to patent expiration

**Estimated sales in the year generic competition is expected

#Assumes 25% net margin

Source: Cowen and Company, Thomson Pharma, Company data, FDA Orange Book

New Products Drive Growth Long Term

Bristol has a good new product portfolio that should be the primary driver of the top line. New drugs have combined estimated sales potential of \$6.8B in 2014, \$10B in 2016, \$13.4B in 2018, and \$18.3B in 2020. During 2014-20, new products could contribute an incremental \$2.14 to EPS.

Bristol-Myers Squibb New Pharmaceutical Product Sales (\$MM)/EPS Contribution

2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	'14-'20 CGR		'15-'20 CGR		Comments
								'14-'20 CGR	'15-'20 CGR	'14-'20 CGR	'15-'20 CGR	
Opdivo		\$100	\$500	\$1,000	\$2,000	\$3,500	\$5,000	NM	NM	- Nivolumab: PD1 antibody; melanoma, lung and renal cancer in Phase III; numerous data points in next 1-3 years		
Orencia	1,444	1,635	1,830	2,020	2,190	2,360	2,530	2,700	9%	9%	9%	- Abatacept: rheumatoid arthritis; SLE flares (P10), PS (P10), Crohn's/UC (P10); sub Q marketed
Sprycel	1,280	1,485	1,645	1,810	1,970	2,130	2,290	2,450	9%	10%	10%	- 10.2% share 6/14; patent litigation settled with Apotex
Eliquis	146	680	1,080	1,400	1,650	1,900	2,150	2,400	23%	49%	49%	- Approved for SPAF in U.S.; DVT treatment and prophylaxis filed; 19% market share 6/14
Yervoy	960	1,250	1,450	1,595	1,750	1,925	2,100	2,275	10%	13%	13%	- Ipilimumab: monoclonal AB for melanoma, prostate, other tumors; immune oncology combination trials
Baraclude	1,527	1,510	1,385	1,410	1,485	1,535	1,585	1,635	1%	1%	1%	- U.S. patent expires 2015 but adverse Court decision; en banc rehearing requested 7/14 but Teva launched; new competitors
Elotuzumab			100	200	300	400	500	NM	NM	- Anti-CS1: multiple myeloma; Phase III; breakthrough designation; with PDL, BioPharma		
BMS-791325			25	50	100	150	200	NM	NM	- Hepatitis C: non-nuc NS5b; Phase II		
Peg-Interferon Lambda		25	50	75	100	125	150	NM	NM	- Hepatitis C; safety advantages over other interferons; Phase III data in 2014; ZymoGenetics		
Briavab		25	50	75	100	125	150	NM	NM	- VEGFR/GFRR inhibitor; adjutant liver; advanced colorectal, advanced or metastatic solid tumors Phase III; sarcoma Phase II		
Daklinza	100	500	500	400	300	200	100	NM	NM	- Daclatasvir; hepatitis C; NS5A + GS-7977 (NS5B) 100% SVR in GT1 patients; 1, 5, 10mg; approved in Japan; CHMP pos opinion; filed in U.S. 4/14; PDUFA 11/30/14		
Sunrevra	100	500	500	400	300	200	100	NM	NM	- Asunaprevir; hepatitis C; NS3; approved in Japan; CHMP positive opinion; filed in U.S. 4/14; PDUFA 11/30/14		
CCR2 antagonist			25	50	75	100	125	NM	NM	- Pan Her+VEGFR kinase inhibitor; wide range of tumors including lung; Phase II		
Anti-IP10 (MDX)			25	50	75	100	125	NM	NM	- Ulcerative colitis; Phase II		
BMS-896268			25	50	75	100	125	NM	NM	- Pan Her+VEGFR kinase inhibitor; wide range of tumors including lung; Phase II		
BMS-986202			25	50	75	100	125	NM	NM	- Lupus; Phase II		
Anti-IFN alpha (MDX)			25	50	75	100	125	NM	NM	- Multiple myeloma as monotherapy/combo with Velcade; HER2+ mBC in combo with Herceptin; Phase II		
Tanespimycin			25	50	75	100	125	NM	NM	- Belatacept; blocks T-cell activation; marketed for renal transplant rejection; Islet transplantation Phase I/II		
Nulojix - U.S.	26	40	55	45	55	65	75	85	13%	18%	18%	- Belatacept; blocks T-cell activation; marketed for renal transplant rejection; Islet transplantation Phase I/II
TOTAL New Drugs	\$6,869	\$8,800	\$8,896	\$10,005	\$11,460	\$18,415	\$16,800	\$18,845	18%	19%	19%	
% Chg	25%	26%	26%	16%	14%	17%	18%	16%				
% BMY Sales	33%	44%	59%	68%	72%	78%	86%	88%				
Estimated Net P.M.	25.3%	25.5%	25.8%	26.0%	26.3%	26.5%	26.8%	27.0%				
EPS Contribution	\$0.82	\$1.04	\$1.38	\$1.56	\$1.80	\$2.18	\$2.54	\$2.98	19%	20%	20%	
% BMY EPS	44%	57%	73%	83%	89%	96%	101%	101%				

Source: Company data, Cowen and Company

New Products Should Drive Substantial EPS Acceleration EPS Flat In 2014-15 On Lower Sales

We forecast 2014 revenue of \$15.48B, reflecting the sale of the diabetes assets, and EPS of \$1.80 (-1%) as higher spending on new products limits gains. We estimate 2014 GPM of 75.0%, 1pp ahead of 2013, on mix shift away from diabetes and

annualization of the pressure from Plavix's patent expiration. SG&A of \$4,510MM is down 8% y/y and down slightly to 29.1% as a percentage of sales vs. 30.0% in 2013; we estimate R&D of \$3,900MM (+5%), 25.2% of sales, a 2.5pp uptick from 22.7% in 2013. We estimate 2014 other income of \$315MM, boosted by the diabetes royalty from AstraZeneca (\$280MM), tax rate at 18.1%, and share count up modestly to 1,667MM.

Bristol-Myers Squibb 2014 Guidance

	BMY Guidance #	Cowen Forecasts
Sales	\$15.2-15.8B	\$15.48B
Gross P.M.	75-76%	75.0%
A&P	Mid-teens decrease	-15%
MS&A	Mid-single decrease	-7%
R&D	Mid-single growth	+5%
Tax Rate	18%*	18.1%
EPS	\$1.70-1.80	\$1.80

Bold=revised

*Assumes R&D tax credit # Assumes Baraclude retained exclusivity

Source: Cowen and Company

For 2015, we forecast another flattish year with revenues of \$14,540MM (-6%) and EPS of \$1.80 (flat), pressured by the expiration of the Abilify agreement in the U.S. We forecast Abilify total revenue of \$425MM (-77%) in 2015. We estimate GPM to move up 1.5pp to 76.5%, SG&A/sales to decline 2pp to 27.1%, and R&D/sales to increase 3pp to 28.2%. Other income is estimated to increase to \$455MM in 2015 (from \$315MM in 2014), tax rate stable at 18.0% and share count flat.

Improved EPS Performance In 2016-20

New products should continue to gain traction and drive top- and bottom-line growth in 2016-20. We forecast total revenues of \$14.81B (+2%) and EPS of \$1.85 (+3%) in 2016, growing to \$17.1B and \$2.20 in 2018, and \$20.74B and \$2.90 in 2020. This implies 3% sales and 7% EPS growth during 2013-20. We look for gross profit margin to trend up, but only modestly, as Eliquis payments to Pfizer are reflected in COGS and offset higher margin new drugs, 3% compound growth in SG&A, 5% compound growth in R&D, significant expansion in total other income, a flat tax rate (at 18%), and share count up modestly to 1,673MM in 2020.

Bristol-Myers Squibb 2013-15 P&L Buildup (\$MM)

	2013			2014E			2015E			
	Sales	Op. Pft.	P.M.	Sales	Op. Pft.	P.M.	Sales	Op. Pft.	P.M.	
Total Sales	\$16,385	\$3,482	21.3%	\$15,480	\$3,203	20.7%	\$14,540	\$3,079	21.2%	
Equity Income From Affiliates		148			140				125	
Interest Income		\$104			\$115				\$150	
Interest Expense		(199)			(190)				(150)	
SG&A		<u>96</u>			<u>110</u>				<u>140</u>	
Other Inc./Exp.)		\$1			\$315				\$455	
Pretax Income		\$3,631	22.2%		\$3,658	23.6%			\$3,659	25.2%
Tax Rate		15.4%				18.1%				18.0%
Minority Interest		29			0				0	
Net Income		\$3,043	18.6%		\$2,996	19.4%			\$3,001	20.6%
EPS - Diluted		\$1.82			\$1.80				\$1.80	
Shares (MM) - Diluted		1660			1667				1668	
EPS - Basic		\$1.85			\$1.81				\$1.81	
Shares (MM) - Basic		1644			1655				1655	

Source: Cowen and Company

Speculation On 2013-20 EPS Outcomes

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	'13-16 CGR	'13-20 CGR	'14-20 CGR	Comments
Nivolumab	\$0.00	\$0.00	\$0.02	\$0.08	\$0.16	\$0.32	\$0.56	\$0.81	NM	NM	NM	NM - Nivolumab; PD1 antibody; melanoma, lung and renal cancer in Phase III; numerous datapoints in next 1-3 years
Orencia	0.22	0.25	0.28	0.31	0.34	0.37	0.40	0.44	13%	10%	10%	10% - Abatacept; rheumatoid arthritis; SLE flares (PIII), PS (PII), Crohn's/UC (PIII); sub Q marketed
Sprycel	0.19	0.23	0.25	0.28	0.31	0.34	0.37	0.40	13%	11%	10%	10% - 10.2% share 6/14; patent litigation settled with Apotex
Yervoy	0.15	0.19	0.22	0.25	0.28	0.31	0.34	0.37	19%	14%	11%	11% - Ipilimumab; monoclonal AB for melanoma, prostate, other tumors; immune oncology combination trials
Eliquis	0.02	0.10	0.17	0.22	0.26	0.30	0.34	0.39	NM	50%	25%	25% - Approved for SPAF in U.S.; DVT treatment and prophylaxis filed; 19% market share 6/14
Bracleude	0.23	0.23	0.21	0.22	0.23	0.24	0.25	0.26	-2%	2%	2%	2% - U.S. patent expires 2015 but adverse Court decision; en banc rehearing requested 7/14 but Teva launched; new competitors
Hepatitis C franchise	0.00	0.03	0.16	0.17	0.15	0.13	0.11	0.09	NM	NM	19%	19% - Daclatasvir (NS5A), Asunaprevir (NS3), '325 (NS5B), Peg-Interferon Lambda
Reyataz	0.24	0.22	0.21	0.19	0.16	0.08	0.04	0.02	-6%	-32%	-35%	-21% share 6/14; pat. exp. 6/17
Other New Drugs	0.00	0.01	0.01	0.03	0.08	0.12	0.17	0.22	97%	NM	NM	NM - Eliquis, elotuzumab, brivanib, many others
Diabetes franchise	0.26	0.14	0.15	0.16	0.14	0.28	0.35	0.43	-15%	8%	21%	21% - Sale to AZN finalized 1/31/14, royalty from AZN thereafter
In-Line Drugs	0.51	0.40	0.11	-0.06	-0.10	-0.29	-0.44	-0.51	NM	NM	NM	NM - \$2.4B 2020, \$8.7B 2014, \$11B in 2013 vs. \$12.6B 2012
BMY EPS - Diluted	\$1.82	\$1.80	\$1.80	\$1.85	\$2.00	\$2.20	\$2.50	\$2.80	1%	7%	8%	- Versus +4%, +6% and +8% industry averages
% Change	-9%	-1%	0%	3%	8%	10%	13%	16%				

Source: Cowen and Company

Bristol-Myers Squibb Quarterly EPS Buildup 2013-20 (\$MM)

	Total Sales	% Chg.	Gross	SG&A		R&D		Oper.	Other	Pretax	Tax	Net			Shares
				\$MM	P.M.	\$MM	% SIs					Inc.	P.M.	Rate	Inc.
Q1	\$3,831	-27%	74.9%	\$1,182	30.9%	\$930	24.3%	19.8%	\$2	20.8%	11.0%	\$695	\$0.42	-35%	1655
Q2	4,048	-9%	74.5%	1,259	31.1%	951	23.5%	19.9%	22	21.3%	13.8%	736	0.44	-8%	1660
Q3	4,065	9%	72.9%	1,170	28.8%	893	22.0%	22.1%	(4)	23.1%	17.8%	771	0.46	12%	1662
Q4	4,441	6%	73.6%	1,312	29.5%	941	21.2%	22.9%	(19)	23.3%	17.9%	841	0.51	8%	1662
2013	\$16,385	-7%	74.0%	\$4,923	30.0%	\$3,715	22.7%	21.3%	\$1	22.2%	15.4%	\$3,043	\$1.82	-9%	1,660
Q1	\$3,811	NM	75.3%	\$1,117	29.3%	\$898	23.6%	22.4%	\$84	25.6%	22.9%	\$752	\$0.45	8%	1666
Q2	3,889	NM	75.5%	1,135	29.2%	958	24.6%	21.7%	138	26.1%	21.3%	800	0.48	9%	1669
Q3E	3,775	NM	74.6%	1,095	29.2%	985	26.1%	19.5%	40	21.5%	18.0%	664	0.40	-14%	1667
Q4E	4,005	NM	74.7%	1,163	29.0%	1,059	26.4%	19.2%	53	21.4%	9.0%	779	0.47	-8%	1667
2014E	\$15,480	NM	75.0%	\$4,510	29.1%	\$3,900	25.2%	20.7%	\$315	23.6%	18.1%	\$2,996	\$1.80	-1%	1,667
Q1E	\$3,780	-1%	76.8%	\$1,040	27.5%	\$945	25.0%	24.3%	\$120	28.3%	18.0%	\$877	\$0.53	16%	1668
Q2E	3,545	-9%	76.7%	955	26.9%	1,010	28.5%	21.2%	120	25.5%	18.0%	740	0.44	-7%	1668
Q3E	3,555	-6%	76.2%	935	26.3%	1,035	29.1%	20.7%	105	24.5%	18.0%	715	0.43	8%	1668
Q4E	3,660	-9%	76.2%	1,010	27.6%	1,110	30.3%	18.3%	110	22.3%	18.0%	669	0.40	-14%	1668
2015E	\$14,540	-6%	76.5%	\$3,940	27.1%	\$4,100	28.2%	21.2%	\$455	25.2%	18.0%	\$3,001	\$1.80	0%	1,668
2016P	\$14,810	2%	76.0%	\$3,785	25.6%	\$4,300	29.0%	21.4%	\$505	25.4%	18.0%	\$3,091	\$1.85	3%	1,669
2017P	\$15,815	7%	75.8%	\$4,015	25.4%	\$4,525	28.6%	21.8%	\$520	25.8%	18.0%	\$3,340	\$2.00	8%	1,670
2018P	\$17,110	8%	75.8%	\$4,730	27.6%	\$4,725	27.6%	20.6%	\$865	26.2%	18.0%	\$3,676	\$2.20	10%	1,671
2019P	\$18,510	8%	75.9%	\$5,170	27.9%	\$4,950	26.7%	21.2%	\$1,060	27.5%	18.0%	\$4,173	\$2.50	13%	1,672
2020P	\$20,740	12%	76.2%	\$6,050	29.2%	\$5,200	25.1%	21.9%	\$1,270	28.5%	18.0%	\$4,851	\$2.90	16%	1,673

Source: Cowen reports, Cowen and Company

Bristol-Myers Squibb Quarterly Sales Buildup (\$MM)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
ANTI-INFECTIVES															
Baraclude - U.S.	\$68	\$73	\$67	\$81	\$289	\$70	\$84	\$50	\$25	\$230	\$20	\$15	\$10	\$5	\$50
Baraclude - ROW	<u>298</u>	<u>298</u>	<u>311</u>	<u>331</u>	<u>1,238</u>	<u>336</u>	<u>285</u>	<u>325</u>	<u>335</u>	<u>1,280</u>	<u>345</u>	<u>300</u>	<u>340</u>	<u>350</u>	<u>1,335</u>
Baraclude - Worldwide	\$366	\$371	\$378	\$412	\$1,527	\$406	\$369	\$375	\$360	\$1,510	\$365	\$315	\$350	\$355	\$1,385
BMS-791325															
Peg-Interferon Lambda											5	5	5	10	25
Daklinza								50	50	100	125	125	125	125	500
Sunvepra								50	50	100	125	125	125	125	500
Reyataz - U.S.	\$193	\$200	\$189	\$187	\$769	\$176	\$168	\$170	\$165	\$680	\$165	\$160	\$160	\$155	\$640
Reyataz - ROW	<u>168</u>	<u>231</u>	<u>186</u>	<u>197</u>	<u>782</u>	<u>168</u>	<u>194</u>	<u>180</u>	<u>190</u>	<u>730</u>	<u>160</u>	<u>185</u>	<u>170</u>	<u>180</u>	<u>695</u>
Reyataz - Worldwide	\$361	\$431	\$375	\$384	\$1,551	\$344	\$362	\$350	\$355	\$1,410	\$325	\$345	\$330	\$335	\$1,335
Azactam Line	20	18	19	13	70	18	13	15	15	60	15	15	15	15	60
Atripla/Sustiva Franchise - U.S.	\$251	\$275	\$259	\$307	\$1,092	\$228	\$266	\$245	\$295	\$1,035	\$200	\$100	\$75	\$50	\$425
Atripla/Sustiva Franchise - ROW	<u>136</u>	<u>136</u>	<u>130</u>	<u>120</u>	<u>522</u>	<u>91</u>	<u>95</u>	<u>90</u>	<u>90</u>	<u>365</u>	<u>80</u>	<u>70</u>	<u>60</u>	<u>50</u>	<u>260</u>
Atripla/Sustiva Franchise - Worldwide	\$387	\$411	\$389	\$427	\$1,614	\$319	\$361	\$335	\$385	\$1,400	\$280	\$170	\$135	\$100	\$685
Maxipime	15	15	14	14	58	14	12	10	10	45	5	5	5	5	20
Videx	5	10	7	5	27	6	4	0	5	15	0	5	0	5	10
Amiken	3	2	2	2	9	2	2	0	0	5	5	0	0	0	5
Duricef/Ultracet	5	4	4	4	17	4	6	0	5	15	0	5	0	5	10
Cefzil	2	3	1	2	8	2	2	5	0	10	0	0	5	0	5
Zerit	1	2	1	2	6	2	1	5	0	10	0	0	5	0	5
Other	20	10	10	10	50	18	10	10	10	50	20	10	10	10	50
ANTI-INFECTIVES TOTAL	\$1,185	\$1,277	\$1,200	\$1,275	\$4,937	\$1,135	\$1,142	\$1,205	\$1,245	4,725	\$1,270	\$1,125	\$1,110	\$1,090	4,595
% Chg.	3%	4%	5%	6%	5%	-4%	-11%	0%	-2%	-4%	12%	-1%	-8%	-12%	-3%

Source: Cowen and Company

Bristol-Myers Squibb Quarterly Sales Buildup (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
CANCER/IMMUNOLOGICAL															
Opdivo														\$50	\$50
Orencia - U.S.	\$214	\$238	\$246	\$256	\$954	\$229	\$254	\$270	\$280	\$1,035	\$250	\$280	\$295	\$305	\$1,130
Orencia - ROW	106	114	129	141	490	134	148	155	165	600	160	170	180	190	700
Orencia - Worldwide	\$320	\$352	\$375	\$397	\$1,444	\$363	\$402	\$425	\$445	\$1,635	\$410	\$450	\$475	\$495	\$1,830
Sprycel - U.S.	\$115	\$135	\$134	\$157	\$541	\$145	\$163	\$160	\$175	\$645	\$160	\$180	\$175	\$190	\$705
Sprycel - ROW	172	177	182	208	739	197	205	205	235	840	220	230	230	260	940
Sprycel - Worldwide	\$287	\$312	\$316	\$365	\$1,280	\$342	\$368	\$365	\$410	\$1,485	\$380	\$410	\$405	\$450	\$1,645
Yervoy - U.S.	\$159	\$140	\$130	\$148	\$577	\$146	\$173	\$160	\$180	\$660	\$165	\$195	\$180	\$200	\$740
Yervoy - ROW	70	93	108	112	383	125	148	155	165	595	170	175	180	185	710
Yervoy - Worldwide	\$229	\$233	\$238	\$260	\$960	\$271	\$321	\$315	\$345	\$1,250	\$335	\$370	\$360	\$385	\$1,450
Elotuzumab															
Orzel	30	30	30	35	125	30	30	35	35	130	30	35	35	35	135
Brivanib											5	5	5	10	25
Anti-IP10 (MDX)															
BMS-599626															
BMS-986202															
Anti-IFN alpha (MDX)															
Tanespimycin															
Nulojix - U.S.	\$4	\$4	\$5	\$7	\$20	\$8	\$9	\$10	\$10	\$35	\$10	\$10	\$11	\$11	\$40
Nulojix - ROW	1	2	2	1	6	1	1	1	2	5	2	2	2	5	10
Nulojix - Worldwide	\$5	\$6	\$7	\$8	\$26	\$9	\$10	\$11	\$12	\$40	\$12	\$12	\$13	\$16	\$55
Taxol	37	37	32	36	142	29	31	30	30	120	25	25	25	25	\$100
Ixempra	17	17	17	15	66	14	15	15	15	60	15	15	10	10	50
Paraplatin	9	8	8	7	32	6	6	5	5	20	5	5	5	0	15
VePesid & Analogs	5	5	0	5	15	0	5	0	5	10	0	5	0	5	10
Platinol	0	0	0	5	5	0	0	0	5	5	0	0	0	5	5
Erbritux - U.S.	\$158	\$168	\$180	\$176	\$682	\$158	\$178	\$185	\$185	\$705	\$150	\$170	\$180	\$180	\$680
Erbritux - ROW	4	3	3	4	14	11	8	5	5	30	5	5	10	10	30
Erbritux - Worldwide	\$162	\$171	\$183	\$180	\$696	\$169	\$186	\$190	\$190	\$735	\$155	\$175	\$190	\$190	\$710
Other	5	5	5	5	20	7	5	5	5	20	8	3	7	4	20
CANCER TOTAL	\$1,106	\$1,176	\$1,211	\$1,318	\$4,811	\$1,240	\$1,379	\$1,396	\$1,502	\$5,515	\$1,380	\$1,510	\$1,580	\$1,680	\$6,150
% Chg.	18%	18%	16%	18%	18%	12%	17%	15%	14%	15%	11%	9%	13%	12%	12%

Source: Cowen and Company

Bristol-Myers Squibb Quarterly Sales Buildup (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
CARDIOVASCULAR															
Eliquis - U.S.	\$17	\$5	\$27	\$48	\$97	\$61	\$94	\$110	\$120	\$385	\$130	\$140	\$150	\$160	\$580
Eliquis - ROW	5	7	14	23	49	30	77	90	100	295	110	120	130	140	500
Eliquis - Worldwide	\$22	\$12	\$41	\$71	\$146	\$91	\$171	\$200	\$220	\$680	\$240	\$260	\$280	\$300	\$1,080
Recothrom	18	24	21	19	82	17	17	20	20	75	20	20	20	20	80
Pravachol	20	15	16	19	70	9	8	10	10	35	10	10	5	5	30
Capoten	6	6	7	8	27	5	7	5	5	20	5	0	5	5	15
Monopril	20	19	17	14	70	17	18	15	15	65	15	15	10	10	50
Coumadin	29	32	30	35	126	27	26	25	25	105	20	20	20	20	80
Questran Line	4	4	4	4	16	4	5	5	5	20	5	0	5	5	15
Plavix - U.S.	\$66	\$18	\$18	\$51	\$153	\$23	\$20	\$20	\$20	\$85	\$15	\$15	\$15	\$10	\$55
Plavix - ROW	25	26	24	30	105	25	25	20	20	90	15	15	10	10	50
Plavix - Worldwide	\$91	\$44	\$42	\$81	\$258	\$48	\$45	\$40	\$40	\$175	\$30	\$30	\$25	\$20	\$105
Avapro - U.S.	\$0	\$9	\$0	\$2	\$7	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Avapro - ROW	46	65	71	56	238	56	59	50	45	210	40	40	35	35	150
Avapro - Worldwide	\$46	\$56	\$71	\$58	\$231	\$56	\$59	\$50	\$45	\$210	\$40	\$40	\$35	\$35	\$150
Other	15	10	10	10	45	16	10	10	10	45	15	10	10	10	45
CARDIOVAS. TOTAL	\$271	\$222	\$259	\$319	\$1,071	\$290	\$366	\$380	\$395	\$1,430	\$400	\$405	\$415	\$430	\$1,650
% Chg.	-87%	-77%	-4%	30%	-69%	7%	65%	47%	24%	34%	38%	11%	9%	9%	15%
CNS															
APAP/Paracetemol	\$161	\$145	\$137	\$159	\$602	\$144	\$150	\$140	\$140	\$575	\$140	\$140	\$130	\$130	\$540
Psychotropics	2	2	3	3	10	0	2	5	5	10	0	0	5	5	10
Abilify Total Revenue - U.S.	\$328	\$378	\$378	\$435	\$1,519	\$325	\$417	\$350	\$400	\$1,490	\$275	\$50	\$0	\$0	\$325
Abilify Total Revenue - ROW	194	185	191	200	770	215	138	25	25	405	25	25	25	25	100
Abilify Total Revenue - Worldwide	\$522	\$563	\$569	\$635	\$2,289	\$540	\$555	\$375	\$425	\$1,895	\$300	\$75	\$25	\$25	\$425
Other	10	5	5	5	25	6	5	5	5	20	10	5	5	5	25
CNS TOTAL	\$695	\$715	\$714	\$802	\$2,926	\$690	\$712	\$525	\$575	\$2,500	\$450	\$220	\$165	\$165	\$1,000
% Chg.	-12%	-18%	-15%	-19%	-16%	-1%	0%	-26%	-28%	-15%	-35%	-69%	-69%	-71%	-60%

Source: Cowen and Company

Bristol-Myers Squibb Quarterly Sales Buildup (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
DERMATOLOGICALS															
Kenalog	\$46	\$57	\$43	\$49	\$195	\$48	\$55	\$45	\$50	\$200	\$50	\$55	\$50	\$50	\$205
Topical Antifungals	16	16	16	15	63	18	15	15	15	65	15	15	15	10	55
Other	0	0	0	5	5	0	0	0	5	5	0	0	0	5	5
DERMS. TOTAL	\$62	\$73	\$59	\$69	\$263	\$66	\$70	\$60	\$70	265	\$65	\$70	\$65	\$65	\$265
% Chg.	-3%	12%	-9%	-1%	0%	6%	-4%	2%	1%	1%	-2%	0%	8%	-7%	0%
DIABETES															
Bydureon - U.S.	\$52	\$57	\$73	\$81	\$263	\$45	\$0	\$0	\$0	\$45					
Bydureon - ROW	0	9	14	12	35	10				10					
Bydureon - Worldwide	\$52	\$66	\$87	\$93	\$298	\$55				\$55					
Byetta - U.S.	\$84	\$74	\$76	\$70	\$304	\$35				\$35					
Byetta - ROW	1	30	30	35	96	20				20					
Byetta - Worldwide	\$85	\$104	\$106	\$105	\$400	\$55				\$55					
Total GLP1 franchise	\$137	\$170	\$193	\$198	\$698	\$110				\$110					
Onglyza/Kombiglyze- U.S.	\$140	\$167	\$138	\$146	\$591	\$25				\$25					
Onglyza/Kombiglyze - ROW	62	73	73	78	286	30				30					
Onglyza/Kombiglyze - Worldwide	\$202	\$240	\$211	\$224	\$877	\$55				\$55					
Forxiga - U.S.	\$0	\$0	\$0	\$0	\$0	\$4				\$5					
Forxiga - ROW	3	5	7	8	23	5				5					
Forxiga - Worldwide	\$3	\$5	\$7	\$8	\$23	\$9				\$10					
Metreleptin						0				0					
Symlin	16	21	22	24	83	5				5					
CCR2 antagonist															
Glucophage	42	43	44	40	169	47	51	50	50	200	55	55	55	55	220
Glucovance	0	0	0	5	5	0	0	0	5	5	0	0	0	5	5
Glucophage XR	0	0	0	4	4	0	0	0	5	5	0	0	0	5	5
Glucophage Franchise	42	43	44	49	178	47	51	50	60	210	55	55	55	65	230
Other	36	86	93	98	313	109	120	99	98	425	100	100	100	100	400
TOTAL DRUGS	\$3,755	\$4,028	\$4,013	\$4,384	\$16,180	\$3,756	\$3,840	\$3,715	\$3,945	\$15,255	\$3,720	\$3,485	\$3,490	\$3,595	\$14,290
% Chg.					-7%					-6%					-6%
OTC Brands															
OTC Brands	\$76	\$20	\$52	\$57	\$205	\$55	\$49	\$60	\$60	\$225	\$60	\$60	\$65	\$65	\$250
TOTAL OTC	\$76	\$20	\$52	\$57	\$205	\$55	\$49	\$60	\$60	\$225	\$60	\$60	\$65	\$65	\$250
% Chg.	4%	-73%	-29%	-22%	-30%	-28%	145%	15%	5%	10%	9%	22%	8%	8%	11%
TOTAL MEDICINES	\$3,831	\$4,048	\$4,065	\$4,441	\$16,385	\$3,811	\$3,889	\$3,775	\$4,005	\$15,480	\$3,780	\$3,545	\$3,555	\$3,660	\$14,540
% Chg.	-27%	-9%	8%	7%	-7%	-1%	-4%	-7%	-10%	-6%	-1%	-9%	-6%	-9%	-6%

Source: Cowen and Company

Bristol-Myers Squibb Annual Sales Buildup (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	CGR 2014-20	CGR 2013-20	Comments
ANTI-INFECTIVES											
Baraclude - U.S.	\$289	\$230	\$50	\$10	\$10	\$10	\$10	\$10	-41%	-38%	- U.S. patent expires 2015 but adverse Court decision; en banc rehearing requested 7/14 but Teva launched; new competitors
Baraclude - ROW	1,238	1,280	1,335	1,400	1,475	1,525	1,575	1,625	4%	4%	- Marketed EU, Japan (65-68% share), generics to launch in China
Baraclude - Worldwide	\$1,527	\$1,510	\$1,385	\$1,410	\$1,485	\$1,535	\$1,585	\$1,635	1%	1%	- Entecavir; hepatitis B
BMS-791325			25	50	100	150	200	NM	NM	NM	- Hepatitis C; non-nuc NS5b; Phase II
Peg-Interferon Lambda			25	50	75	100	125	150	NM	NM	- Hepatitis C; safety advantages over other interferons; Phase III data in 2014; ZymoGenetics
Daklinza	100	500	500	400	300	200	100	NM	NM	NM	- Daclatasvir; hepatitis C, NS5A + GS-7977 (NS5B) 100% SVR4 in GT1 patients; 1, 5, 10mg; approved in Japan; CHMP pos opinion; filed in U.S. 4/14; PDUFA 11/30/14
Sunvepra	100	500	500	400	300	200	100	NM	NM	NM	- Asunaprevir; hepatitis C; NS3; approved in Japan; CHMP positive opinion; filed in U.S. 4/14; PDUFA 11/30/14
Reyataz - U.S.	\$769	\$680	\$640	\$600	\$500	\$250	\$125	\$50	-35%	-32%	- 21% share 6/14; pat. exp.: 6/17
Reyataz - ROW	782	730	695	650	500	250	125	50	-36%	-32%	
Reyataz - Worldwide	\$1,551	\$1,410	\$1,335	\$1,250	\$1,000	\$500	\$250	\$100	-36%	-32%	- Atazanavir; once-daily protease inhibitor
Azactam Line	70	60	60	60	60	60	60	60	0%	-2%	- Monobactam; U.S. rights sold to Dura
Atripla/Sustiva Franchise - U.S.	\$1,092	\$1,035	\$425	\$100	\$75	\$50	\$25	\$10	-54%	-49%	- Sustiva patent exp. in 5/13 but use patent until 3/15; QUAD competition clips
Atripla/Sustiva Franchise - ROW	522	365	260	35	15	10	5	0	NM	NM	- EU patent expires 11/13
Atripla/Sustiva Franchise - Worldwide	\$1,614	\$1,400	\$685	\$135	\$90	\$60	\$30	\$10	-56%	-52%	- Sustiva portion of Sustiva/Truvada; qD; with Gilead
Maxipime	58	45	20	10	5	5	5	5	-31%	-30%	- Inj, broad spec.; ceftipime; U.S. rights sold to Dura
Videx	27	15	10	5	5	5	5	5	-17%	-21%	- HIV; EC dominates but generic competition from Barr Labs
Amiken	9	5	5	5	5	5	5	5	NM	-8%	- Top aminoglycoside in decline
Duricef/Ultracef	17	15	10	5	5	5	5	5	-17%	-16%	- Certain rights sold
Cefzil	8	10	5	5	5	5	5	5	-11%	-6%	- Broad spectrum/dosing regimen; patent expired 12/05
Zerit	6	10	5	5	5	5	5	5	-11%	-3%	- Anti-HIV therapy; 1st line
Other	50	50	50	50	50	50	50	50	0%	0%	- Bulk penicillins, mostly international; other
ANTI-INFECTIVES TOTAL	\$4,937	4,725	4,595	\$4,015	\$3,640	\$3,035	\$2,680	\$2,435	-10%	-10%	
% Chg.	5%	-4%	-3%	-13%	-9%	-17%	-12%	-9%			

Source: Company data, Cowen and Company estimates

Bristol-Myers Squibb Annual Sales Buildup (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	CGR 2014-20	CGR 2013-20	Comments
CANCER/IMMUNOLOGICAL											
Opdivo			\$100	\$500	\$1,000	\$2,000	\$3,500	\$5,000	NM	NM	- Nivolumab; PD1 antibody; melanoma, lung and renal cancer in Phase III; numerous datapoints in next 1-3 years
Orencia - U.S.	\$954	\$1,035	\$1,130	\$1,250	\$1,350	\$1,450	\$1,550	\$1,650	8%	8%	
Orencia - ROW	490	600	700	770	840	910	980	1,050	10%	12%	
Orencia - Worldwide	\$1,444	\$1,635	\$1,830	\$2,020	\$2,190	\$2,360	\$2,530	\$2,700	9%	9%	- Abatacept; rheumatoid arthritis; SLE flares (PIII), PS (PII), Crohn's/UC (PIII); sub Q marketed
Sprycel - U.S.	\$541	\$645	\$705	\$760	\$820	\$880	\$940	\$1,000	8%	9%	- 10.2% share 6/14; patent litigation settled with Apotex
Sprycel - ROW	739	840	940	1,050	1,150	1,250	1,350	1,450	10%	10%	
Sprycel - Worldwide	\$1,280	\$1,485	\$1,645	\$1,810	\$1,970	\$2,130	\$2,290	\$2,450	9%	10%	- SRC/ABL kinase inhib.; resistant CML, GI, lung, stromal; READY trial in prostate did not meet endpoint
Yervoy - U.S.	\$577	\$660	\$740	\$820	\$900	\$1,000	\$1,100	\$1,200	10%	11%	
Yervoy - ROW	383	595	710	775	850	925	1,000	1,075	10%	16%	
Yervoy - Worldwide	\$960	\$1,250	\$1,450	\$1,595	\$1,750	\$1,925	\$2,100	\$2,275	10%	13%	- Ipilimumab; monoclonal AB for melanoma, prostate, other tumors; immune oncology combination trials
Elotuzumab			100	200	300	400	500	NM	NM	NM	- Anti-CS1; multiple myeloma; Phase III; breakthrough designation; with PDL BioPharma
Orzel	125	130	135	140	145	150	155	160	4%	4%	- Uracil+tegafur+leucovorin; colon cancer; foreign markets only
Brivanib			25	50	75	100	125	150	NM	NM	- VEGFR/FGFR inhibitor; adjuvant liver, advanced colorectal, advanced or metastatic solid tumors Phase III; sarcoma Phase II
Anti-IP10 (MDX)					25	50	75	100	NM	NM	- Ulcerative colitis; Phase II
BMS-599626					25	50	75	100	NM	NM	- Pan Her-VEGF kinase inhibitor; wide range of tumors including lung; Phase II
BMS-986202					25	50	75	100	NM	NM	- Lysophospholipid receptor antagonist, signals through S1P1; treatment of idiopathic pulmonary fibrosis; Phase II
Anti-IFN alpha (MDX)					25	50	75	100	NM	NM	- Lupus; Phase II
Tanespimycin					25	50	75	100	NM	NM	- Multiple myeloma as monotherapy/combo with Velcade; HER2+ mBC in combo with Herceptin; Phase II
Nulojix - U.S.	\$20	\$35	\$40	\$35	\$40	\$45	\$50	\$55	8%	16%	
Nulojix - ROW	6	5	10	10	15	20	25	30	35%	26%	
Nulojix - Worldwide	\$26	\$40	\$55	\$45	\$55	\$65	\$75	\$85	13%	18%	- Belatacept; blocks T-cell activation; marketed for renal transplant rejection; Islet transplantation Phase I/II
Taxol	142	120	\$100	80	60	40	20	10	-34%	-32%	- Generics pressure in U.S. and foreign markets
Ixempra	66	60	50	40	30	20	10	5	-34%	-31%	- Epothilone; non-taxane; rolling out for metastatic or locally advanced breast cancer; adjuvant breast Phase III
Paraplatin	32	20	15	10	5	5	5	5	-21%	-23%	- Better toxicity profile than Platinol; generics
VePesid & Analogs	15	10	10	5	5	5	5	5	-11%	-15%	- Patent expired; phosphate launched
Platinol	5	5	5	5	5	5	5	5	0%	0%	- Patent expired 12/12; licensed from RTC
Erbritux - U.S.	\$682	\$705	\$680	\$650	\$600	\$550	\$0	\$0	NM	NM	- Agreement ends 9/18
Erbritux - ROW	14	30	30	40	50	30	0	0	NM	NM	- Japan
Erbritux - Worldwide	\$696	\$735	\$710	\$690	\$650	\$580	\$0	\$0	NM	NM	- EGF receptor antagonist; assumes approval in NSCLC and H&N cancer; via ImClone/Lilly
Other	20	20	20	20	20	20	20	20	0%	0%	- Miscellaneous products and generics
CANCER TOTAL	\$4,811	\$5,515	\$6,150	\$7,110	\$8,285	\$9,955	\$11,615	\$13,870	17%	16%	
% Chg.	18%	15%	12%	16%	17%	20%	17%	19%			

Source: Cowen and Company

Bristol-Myers Squibb Annual Sales Buildup (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	CGR 2014-20	CGR 2013-20	Comments
CARDIOVASCULAR											
Eliquis - U.S.	\$97	\$385	\$580	\$800	\$950	\$1,100	\$1,250	\$1,400	24%	46%	- Approved for SPAF in U.S.; DVT treatment and prophylaxis filed; 19% market share 6/14
Eliquis - ROW	49	295	500	600	700	800	900	1000	23%	54%	- Approved for SPAF in EU and Japan; DVT treatment and prophylaxis CHMP positive opinion
Eliquis - Worldwide	\$146	\$680	\$1,080	\$1,400	\$1,650	\$1,900	\$2,150	\$2,400	23%	49%	- Apixaban; oral factor Xa inhibitor; with Pfizer
Recothrom	82	75	80	85	90	95	100	105	6%	4%	- Thrombin for use during surgery; from ZymoGenetics
Pravachol	70	35	30	20	15	10	5	5	-28%	-31%	
Capoten	27	20	15	10	5	5	5	5	-21%	-21%	
Monopril	70	65	50	45	40	35	30	25	-15%	-14%	- Patent expired 6/03
Coumadin	126	105	80	60	50	40	30	10	-32%	-30%	- Anticoagulant; generic competition clips
Questran Line	16	20	15	15	15	15	15	15	-5%	-1%	- Older resin cholesterol reducer; OTC outlook unclear
Plavix - U.S.	\$153	\$85	\$55	\$30	\$15	\$10	\$5	\$0	NM	NM	- Exclusivity ended 5/12 in U.S. with pediatric extension
Plavix - ROW	105	90	50	25	10	5	5	5			- Generics in EU
Plavix - Worldwide	\$258	\$175	\$105	\$55	\$25	\$15	\$10	\$5	-45%	-43%	
Avapro - U.S.	\$7	\$0	\$0	\$0	\$0	\$0	\$0	\$0	NM	NM	- Patent expired 3/12
Avapro - ROW	238	210	150	125	100	75	50	25			- Patent expired 3/12 in Canada, Mexico, Argentina, P.R.
Avapro - Worldwide	\$231	\$210	\$150	\$125	\$100	\$75	\$50	\$25			- ARB; hypertension
Other	45	45	45	45	45	45	45	45	0%	0%	- Generic products
CARDIOVAS. TOTAL	\$1,071	\$1,430	\$1,650	\$1,860	\$2,035	\$2,235	\$2,440	\$2,640	11%	14%	
% Chg.	-69%	34%	15%	13%	9%	10%	9%	8%			
CNS											
APAP/Paracetemol	\$602	\$575	\$540	\$500	\$460	\$420	\$380	\$340	-8%	-8%	
Psychotropics	10	10	10	10	10	10	10	10	0%	0%	- Older Squibb products
Abilify Total Revenue - U.S.	\$1,519	\$1,490	\$325	0	0	0	0	0	NM	NM	- Agreement expires 4/15 U.S.
Abilify Total Revenue - ROW	770	405	100	110	120	130	0	0	NM	NM	- Agreement expires 6/14 EU, 2018 Canada
Abilify Total Revenue - Worldwide	\$2,289	\$1,895	\$425	\$110	\$120	\$130	0	0	NM	NM	- Schizophrenia and bipolar
Other	25	20	25	25	25	25	25	25	4%	0%	- Miscellaneous products and generics
CNS TOTAL	\$2,926	\$2,500	\$1,000	\$645	\$615	\$585	\$415	\$375	-27%	-25%	
% Chg.	-16%	-15%	-60%	-36%	-5%	-5%	-29%	-10%			

Source: Cowen and Company

Bristol-Myers Squibb Annual Sales Buildup (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	CGR 2014-20	CGR 2013-20	Comments
DERMATOLOGICALS											
Kenalog	\$195	\$200	\$205	\$210	\$215	\$220	\$225	\$230	2%	2%	
Topical Antifungals	63	65	55	50	45	40	35	30	-12%	-10%	- Potential OTC switch candidates
Other	5	5	5	5	5	5	5	5	0%	0%	- Older products; negative sales suggest heavy discounts
DERMS. TOTAL	\$263	265	\$265	\$265	\$265	\$265	\$265	\$265	0%	0%	
% Chg.	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	
DIABETES											
Bydureon - U.S.	\$263	\$45							NM	NM	
Bydureon - ROW	35	10									
Bydureon - Worldwide	\$298	\$55									
Byetta - U.S.	\$304	\$35							NM	NM	
Byetta - ROW	96	20									
Byetta - Worldwide	\$400	\$55									
Total GLP1 franchise	\$698	\$110							NM	NM	- Sale to Amylin finalized 1/31/14
Onglyza/Kombiglyze- U.S.	\$591	\$25							NM	NM	- Sale to Amylin finalized 1/31/14
Onglyza/Kombiglyze - ROW	286	30									
Onglyza/Kombiglyze - Worldwide	\$877	\$55									
Forxiga - U.S.	\$0	\$5							NM	NM	- Sale to Amylin finalized 1/31/14
Forxiga - ROW	23	5									
Forxiga - Worldwide	\$23	\$10									
Metreleptin		0							NM	NM	- Sale to Amylin finalized 1/31/14
Symlin	83	5							NM	NM	- Sale to Amylin finalized 1/31/14
CCR2 antagonist			25	50	75	100			NM	NM	- Diabetes; Phase II
Glucophage	169	200	220	250	280	310	340	370	11%	12%	- Generic competition
Glucovance	5	5	5	5	5	5	5	5	0%	0%	- Exclusivity ended 2/1/04 with pediatric extension
Glucophage XR	4	5	5	5	5	5	5	5	0%	3%	- Exclusivity ended 10/03
Glucophage Franchise	178	210	230	260	290	320	350	380	10%	11%	
Other	313	425	400	380	360	340	320	300	-6%	-1%	- Medarex, Apothecon, DuPont, other
TOTAL DRUGS	\$16,180	\$15,255	\$14,290	\$14,535	\$15,515	\$16,785	\$18,160	\$20,365	5%	3%	- Industry average growth
% Chg.	-7%	-6%	-6%	2%	7%	8%	8%	12%			
OTC Brands											
OTC Brands	\$205	\$225	\$250	\$275	\$300	\$325	\$350	\$375	9%	9%	- Clipped by Fervex (cold and flu prep in EU)
TOTAL OTC	\$205	\$225	\$250	\$275	\$300	\$325	\$350	\$375	9%	9%	- U.S./Canadian franchise sold to Novartis; BMY retained certain international markets
% Chg.	-30%	10%	11%	10%	9%	8%	8%	7%			
TOTAL MEDICINES	\$16,385	\$15,480	\$14,540	\$14,810	\$15,815	\$17,110	\$18,510	\$20,740	5%	3%	- New pharmaceuticals drive growth in 2014-20
% Chg.	-7%	-6%	-6%	2%	7%	8%	8%	12%			

Source: Cowen and Company

Bristol-Myers Squibb Estimated 2013-20 Summary Balance Sheet (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Assets:								
Cash & Equivalents	\$3,586	\$6,790	\$6,730	\$7,090	\$7,540	\$8,240	\$9,310	\$10,850
Marketable securities	939	2,500	1,000	1,000	1,000	1,000	1,000	1,000
Receivables	3,360	3,200	3,000	3,050	3,250	3,500	3,800	4,200
Inventories	1,498	1,550	1,300	1,300	1,400	1,500	1,600	1,750
Other Current Assets	<u>9,533</u>	<u>1,950</u>	<u>1,750</u>	<u>1,800</u>	<u>1,900</u>	<u>2,050</u>	<u>2,200</u>	<u>2,500</u>
Total Current Assets	\$18,916	\$15,990	\$13,780	\$14,240	\$15,090	\$16,290	\$17,910	\$20,300
Property, Plant & Equipment	4,579	4,650	4,350	4,450	4,750	5,150	5,550	5,800
Intangibles	9,414	10,000	10,000	10,000	10,000	10,000	9,750	9,500
Other Long-Term Assets	<u>5,683</u>	<u>5,000</u>	<u>5,000</u>	<u>5,000</u>	<u>5,000</u>	<u>4,500</u>	<u>4,500</u>	<u>4,500</u>
Total Long-Term Assets	\$19,676	\$19,650	\$19,350	\$19,450	\$19,750	\$19,650	\$19,800	\$19,800
Total Assets	\$38,592	\$35,640	\$33,130	\$33,690	\$34,840	\$35,940	\$37,710	\$40,100
Liabilities:								
Short-Term Debt	\$359	\$400	\$400	\$400	\$400	\$400	\$400	\$400
Accounts Payable	2,559	2,350	2,000	2,000	2,100	2,250	2,400	2,650
Other Current Liabilities	<u>9,522</u>	<u>4,800</u>	<u>4,050</u>	<u>4,100</u>	<u>4,300</u>	<u>4,600</u>	<u>4,950</u>	<u>5,450</u>
Total Current Liabilities	\$12,440	\$7,550	\$6,450	\$6,500	\$6,800	\$7,250	\$7,750	\$8,500
Long-Term Debt	\$7,981	\$7,500	\$7,000	\$7,250	\$7,250	\$7,500	\$7,750	\$8,000
Other Long-Term Liabilities	<u>2,935</u>	<u>3,000</u>						
Total Liabilities	\$23,356	\$18,050	\$16,450	\$16,750	\$17,050	\$17,750	\$18,500	\$19,500
Net Equity	\$15,236	\$17,590	\$16,680	\$16,940	\$17,790	\$18,190	\$19,210	\$20,600

Source: Company data, Cowen and Company estimates

Bristol-Myers Squibb Estimated 2013-20 Working Capital Analysis (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Inventories	\$1,498	\$1,550	\$1,300	\$1,300	\$1,400	\$1,500	\$1,600	\$1,750
COGS	3,581	3,546	3,017	3,036	3,203	3,422	3,656	4,044
Inventory Turns	2.4	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Months	5.0	5.2	5.2	5.2	5.2	5.2	5.2	5.2
Accounts Receivable	\$3,360	\$3,200	\$3,000	\$3,050	\$3,250	\$3,500	\$3,800	\$4,200
Sales	16,385	15,480	14,540	14,810	15,815	17,110	18,510	20,740
Receivables Days	74.8	75.0	75.0	75.0	75.0	75.0	75.0	74.0
Other Current Assets	\$9,533	\$1,950	\$1,750	\$1,800	\$1,900	\$2,050	\$2,200	\$2,500
% of Sales	58.2%	12.5%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%
Accounts Payable	\$2,559	\$2,350	\$2,000	\$2,000	\$2,100	\$2,250	\$2,400	\$2,650
COGS	3,581	3,546	3,017	3,036	3,203	3,422	3,656	4,044
Payables Days	260.8	240.0	240.0	240.0	240.0	240.0	240.0	240.0
Other Current Liabilities	\$9,522	\$4,800	\$4,050	\$4,100	\$4,300	\$4,600	\$4,950	\$5,450
% of COGS	265.9%	135.0%	135.0%	135.0%	135.0%	135.0%	135.0%	135.0%
Net Working Capital (Ex. Cash, Debt)	\$2,310	(\$450)	\$0	\$50	\$150	\$200	\$250	\$350

Source: Company data, Cowen and Company estimates

Bristol-Myers Squibb Estimated 2013-20 Cash Flow Analysis (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Operating Activities								
Net Income (Continuing Operations)	\$3,043	\$2,996	\$3,001	\$3,091	\$3,340	\$3,676	\$4,173	\$4,851
Depreciation & Amort.	763	700	725	750	775	800	825	850
Change in Working Capital	(3071)	2760	(450)	(50)	(100)	(50)	(50)	(100)
Other/Liability	<u>2810</u>	<u>0</u>						
Net Cash Provided By Operations	\$3,545	\$6,456	\$3,276	\$3,791	\$4,015	\$4,426	\$4,948	\$5,601
Investing Activities								
Capital Expenditures	(537)	(\$550)	(\$600)	(\$625)	(\$675)	(\$700)	(\$725)	(\$750)
Asset Sales (net)	9	3,200	0	0	0	0	0	0
Acquisitions	0	0	0	0	0	0	0	0
Other, net	(44)	(3,000)	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
Net Cash Provided By Investing	(\$572)	(\$350)	(\$600)	(\$625)	(\$675)	(\$700)	(\$725)	(\$750)
Financing Activities								
Long-Term Debt Financings	\$1,489	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Equity Financings	564	0	0	0	0	0	0	0
Net Debt Payments	(399)	(500)	(250)	(250)	(250)	(250)	(250)	(250)
Dividend Payments	(2,309)	(2,410)	(2,480)	(2,560)	(2,640)	(2,770)	(2,910)	(3,060)
Share Repurchase	(433)	0	0	0	0	0	0	0
Other, net	<u>20</u>	<u>0</u>						
Net Cash Provided By Financing	(\$1,068)	(\$2,910)	(\$2,730)	(\$2,810)	(\$2,890)	(\$3,020)	(\$3,160)	(\$3,310)
Net Change in Cash & Equivalents	\$1,930	\$3,196	(\$54)	\$356	\$450	\$706	\$1,063	\$1,541
Ending Cash & Equivalents	\$3,586	\$6,782	\$6,727	\$7,083	\$7,532	\$8,239	\$9,302	\$10,843

Source: Company data, Cowen and Company estimates

BMY DCF Analysis

9/26/14											
Assumptions:											
Share Price	\$51		Output								
			Equity Value								
				\$95,877							
					Estimated Share Price						
						\$58					
Discount Rate	6.0%		Net Cash								
				(\$3,815)							
Shares Outstanding (000)	1,667		Enterprise Value								
				\$99,692							

BMY DCF

	2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021P	2022P	2023P	2024P	2025P	Terminal
Total Revenues	\$16,385	\$15,480	\$14,540	\$14,810	\$15,815	\$17,110	\$18,510	\$20,740	\$22,814	\$25,095	\$27,605	\$30,365	\$33,402	
% Change	-7%	-6%	-6%	+2%	+7%	+8%	+8%	+12%	+10%	+10%	+10%	+10%	+10%	+10%
Cost of Goods	\$4,265	\$3,867	\$3,421	\$3,561	\$3,822	\$4,137	\$4,461	\$4,944	\$5,293	\$5,822	\$6,404	\$6,984	\$7,515	
Gross Profit	\$12,120	\$11,613	\$11,119	\$11,249	\$11,993	\$12,974	\$14,049	\$15,796	\$17,521	\$19,273	\$21,201	\$23,381	\$25,887	
Gross Margin - Total	74.0%	75.0%	76.5%	76.0%	75.8%	75.8%	75.9%	76.2%	76.8%	76.8%	76.8%	77.0%	77.5%	
SG&A	\$4,923	\$4,510	\$3,940	\$3,785	\$4,015	\$4,730	\$5,170	\$6,050	\$6,616	\$7,152	\$7,812	\$8,442	\$9,019	
% of Revs	30.0%	29.1%	27.1%	25.6%	25.4%	27.6%	27.9%	29.2%	29.0%	28.5%	28.3%	27.8%	27.0%	
R&D	\$3,715	\$3,900	\$4,100	\$4,300	\$4,525	\$4,725	\$4,950	\$5,200	\$5,704	\$6,274	\$6,763	\$7,440	\$8,016	
% of Revs	22.7%	25.2%	28.2%	29.0%	28.6%	27.6%	26.7%	25.1%	25.0%	25.0%	24.5%	24.5%	24.0%	
Operating Expenses	\$8,638	\$8,410	\$8,040	\$8,085	\$8,540	\$9,455	\$10,120	\$11,250	\$12,320	\$13,426	\$14,575	\$15,881	\$17,035	
% of Revenues	52.7%	54.3%	55.3%	54.6%	54.0%	55.3%	54.7%	54.2%	54.0%	53.5%	52.8%	52.3%	51.0%	
Operating Income	\$3,482	\$3,203	\$3,079	\$3,164	\$3,453	\$3,519	\$3,929	\$4,546	\$5,202	\$5,847	\$6,625	\$7,500	\$8,852	
% Operating Margin	21.3%	20.7%	21.2%	21.4%	21.8%	20.6%	21.2%	21.9%	22.8%	23.3%	24.0%	24.7%	26.5%	
Equity income	\$148	\$140	\$125	\$100	\$100	\$100	\$100	\$100	\$100	\$100	\$100	\$100	\$100	
Non-operating income	96	110	140	145	150	170	180	190	200	210	220	230	250	
EBIT	\$3,726	\$3,453	\$3,344	\$3,409	\$3,703	\$3,789	\$4,209	\$4,836	\$5,502	\$6,157	\$6,945	\$7,830	\$9,202	
% of Revs	22.7%	22.3%	23.0%	23.0%	23.4%	22.1%	22.7%	23.3%	24.1%	24.5%	25.2%	25.8%	27.5%	
D&A	\$763	\$700	\$725	\$750	\$775	\$800	\$825	\$850	\$875	\$900	\$925	\$950	\$1,000	
EBITDA	\$4,489	\$4,153	\$4,069	\$4,159	\$4,478	\$4,589	\$5,034	\$5,686	\$6,377	\$7,057	\$7,870	\$8,780	\$10,202	
% of Revs	27.4%	26.8%	28.0%	28.1%	28.3%	26.8%	27.2%	27.4%	28.0%	28.1%	28.5%	28.9%	30.5%	
Net Interest Income (Expense)	(\$95)	(\$75)	\$0	\$40	\$80	\$120	\$160	\$200	\$250	\$300	\$350	\$400	\$450	
Pre-Tax Income	\$3,631	\$3,378	\$3,344	\$3,449	\$3,783	\$3,909	\$4,369	\$5,036	\$5,752	\$6,457	\$7,295	\$8,230	\$9,652	
Taxes	\$559	\$662	\$659	\$678	\$733	\$807	\$916	\$1,065	\$1,210	\$1,355	\$1,528	\$1,723	\$2,024	
Income Tax Rate	15.0%	19.2%	19.7%	19.9%	19.8%	21.3%	21.8%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	
Minority Interest	\$29	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	
Net Income	\$3,043	\$2,716	\$2,686	\$2,771	\$3,050	\$3,101	\$3,453	\$3,971	\$4,541	\$5,103	\$5,767	\$6,508	\$7,627	
% of Revs	18.6%	17.5%	18.5%	18.7%	19.3%	18.1%	18.7%	19.1%	19.9%	20.3%	20.9%	21.4%	22.8%	
% Change	-10%	-11%	-1%	+3%	+10%	+2%	+11%	+15%	+14%	+12%	+13%	+13%	+17%	
NOPAT	\$3,167	\$2,791	\$2,686	\$2,781	\$2,970	\$2,981	\$3,293	\$3,771	\$4,291	\$4,803	\$5,417	\$6,108	\$7,177	
<u>Adjustments:</u>														
Capex	(\$537)	(\$550)	(\$600)	(\$625)	(\$675)	(\$700)	(\$725)	(\$750)	(\$750)	(\$775)	(\$775)	(\$775)	(\$775)	
Depreciation & Amortization	\$763	\$700	\$725	\$750	\$775	\$800	\$825	\$850	\$875	\$900	\$925	\$950	\$1,000	
Change In Working Capital	(\$3,071)	\$2,760	(\$450)	(\$50)	(\$100)	(\$50)	(\$100)	\$0	\$0	\$50	\$50	\$100		
Operating Free Cash Flow	\$198	\$5,626	\$2,381	\$2,848	\$3,050	\$3,151	\$3,803	\$3,971	\$4,886	\$5,228	\$5,987	\$8,733	\$7,952	\$133,850

Source: Cowen and Company.

Bristol-Myers Squibb Key Upcoming Events

Time Frame	Event Type	Product	Event
2014	Clinical	Opdivo	Squamous NSCLC, 3rd line, Phase II, ORR endpoint; to be presented at CMSTO (Multidisciplinary Symposium In Thoracic Oncology) Oct. 30 - Nov. 1 in Chicago
		Opdivo	Presentation of '066; SMR Nov. 13-16, Zurich
		Opdivo	Squamous NSCLC, interim Phase III, OS endpoint; H2:14 (registrational trial)
		Opdivo	Non-squamous NSCLC, interim Phase III; OS endpoint; H2:14 (registrational trial)
		Opdivo	Additional data from Checkmate 012
		Opdivo	Phase I data in hematologic tumors at ASH
		Triple DAA regimen	Phase III data at AASLD (UNITY 1 and 2)
Regulatory	Asunaprevir +Dacalatbsvir combo		U.S. decision; PDUFA 11/30/14

Source: Company data

BRISTOL-MYERS SQUIBB R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Arthritis/Inflammation							
Orencia			.	.			PII for sclerodoma; PIII for systemic lupus erythematosus
Cancer/Oncology/Hematology							
Elotuzumab			.				Anti-CS1 antibody; PIII for 1st line multiple myeloma and 2nd line relapsed/refractory multiple myeloma; received FDA Breakthrough Therapy Designation in May, 2014; with PDL BioPharma
Elotuzumab/Revlimid combo			.				1st-line and relapsed/refractory multiple myeloma
Erbitux			.				Additional indication for esophageal cancer
Yervoy (Ipilimumab)		.	.				MDX-010; monoclonal antibody; approved for advanced melanoma; PII/III for adjuvant melanoma, prostate cancer, NSCLC, small cell lung cancer; various PII indications
Opdivo		.	.		H2:14		Nivolumab; anti-PD1; PIII for NSCLC, melanoma and RCC; PII for NHL (FL, DBLCL); PI for HCC, hematologic malignancies; other solid tumors; BLA for advanced melanoma Q3:14
Sprycel		.	.				Dasatinib; oral multi-targeted kinase inhibitor; solid tumors (breast); multiple myeloma; CLL; pediatric indications
Elotuzumab/Velcade combo		.					2nd-line multiple myeloma
Anti-CXCR4		.					Ulocuplumab; hematologic malignancies
Anti-LAG3 + Opdivo		.					Solid tumors
BMS-986016	⇒	.					Anti-LAG3; cancer
Denenicokin		.					IL-21; metastatic melanoma; renal cell carcinoma (RCC), in combination with chemotherapy
Denenicokin + Opdivo		.					Solid tumors
JAK2 inhibitor		.					Hematologic malignancies
Lirilumab		.					Anti-KIR; cancer
Lirilumab + Opdivo		.					Solid tumors
Lirilumab + Yervoy		.					Solid tumors
Notch inhibitors		.					Cancer
Opdivo + Sprycel		.					CML
Opdivo + Yervoy		.					NSCLC, RCC, solid tumors
Urelumab		.					Anti-CD137 antibody; cancer
Cardiovascular							
CCR2/CCR5 Dual Antagonist		.	.				Cardiovascular
BMS-962476		.					PCSK9 apolipoprotein B inhibitor; prevention and treatment of cardiovascular disease; from Isis
Factor Xia Inhibitor (oral)		.					Cardiovascular
Ikur Antagonists		.					Cardiovascular
PAR4 Antagonist		.					Antithrombotic
Endocrine/Metabolic/Hormones							
PEG-FGF21		.					Metabolics; management of lipids in diabetes
Immunological							
BMS-936557		.					Elidelumab; anti-IP10; ulcerative colitis
LPA1 Antagonist		.					Treatment of idiopathic pulmonary fibrosis (PI); preclinical for treatment of systemic sclerosis
Sifalimumab		.					Anti-IFNa; lupus; with MedImmune/AstraZeneca
Nulojix		.	.				Belatacept; immunosuppressant; solid organ rejection (liver, heart, islet cell); approved for renal transplant
Anti-CD28		.					Multiple sclerosis
Anti-CD40L		.					Immunology
Anti-IL31		.					Immunology

BRISTOL-MYERS SQUIBB R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Infectious Disease							
Daklinza					Apr-14		Daclatasvir; hepatitis C; NS5A; novel mechanism; add-on to interferon/ribavirin; 3-4 log drop; positive CHMP opinion June 2014; approved in EU
Reyataz					Apr-14		Boosted naïve pediatric; FDC with cobicistat
Sunvera					Apr-14		Asunaprevir; hepatitis C; HCV NS3 Protease Inhibitor; approved in EU
BMS-791325				.			Non-nucleoside NS5B inhibitor; hepatitis C
PEG-Interferon lambda				.			Type 3 interferon; hepatitis C; with ZymoGenetics
Sustiva				.			Pediatric
Baraclude			.				Prevention of the recurrence of hepatitis B virus in subjects who receive an orthotopic liver transplant (OLT); treatment of HBV/HIV co-infection; pediatric indication
BMS-663068			.				HIV attachment inhibitor; novel mechanism; acts against viral targets; useful in any treatment stage and combination; no cross resistance; oral
BMS-791325			.				HCV NS5B replicase inhibitor; hepatitis C
Festinavir		.					NRTI; HIV, AIDS
HIV Program		.					HIV; mechanism of action not disclosed
NRT Inhibitor		.					HIV
Anti-PD-L1		.					Virology; with Ono Pharmaceutical
Respiratory							
BMS-986202			.				Treatment of idiopathic pulmonary fibrosis; lysophospholipid RA signals through S1P1
Total Drugs In Development	0	22	13	10	3		48

Progress since last update in bold; movement marked by arrow

Investor Relations Contact: John Elicker 609-252-4611

Ryan Asay 609-252-5020

Ranya Dajani 609-252-5330



Price: \$64.85 (09/30/2014)
Price Target: \$72.00

OUTPERFORM (1)

Steve Scala, R.Ph., CFA
617.946.3923
steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA
617.946.3857
kathy.miner@cowen.com

Jean Perreault
617.946.3967
jean.perreault@cowen.com

Key Data	
Symbol	NYSE: LLY
52-Week Range:	\$67.14 - 47.53
Market Cap (MM):	\$72,457.5
Net Debt (MM):	\$184.4
Cash/Share:	\$4.83
Dil. Shares Out (MM):	1,117.3
Enterprise Value (MM):	\$72,653.4
ROIC:	NA
ROE (LTM):	NA
BV/Share:	\$16.10
Dividend:	\$1.96
Yield:	3.02%

FY (Dec)	2013A	2014E	2015E
Earnings Per Share			
Q1	\$1.14	\$0.70A	\$0.72
Q2	\$1.16	\$0.68A	\$0.84
Q3	\$1.11	\$0.77	\$0.91
Q4	\$0.74	\$0.65	\$0.88
Year	\$4.15	\$2.80	\$3.35
P/E	15.6x	23.2x	19.4x
Consensus EPS	\$4.14	\$2.78	\$3.16

Consensus source: Thomson Reuters

Revenue (MM)			
Year	\$23,113.0	\$19,690.0	\$20,975.0
EV/S	3.1x	3.7x	3.5x

Eli Lilly

Growth Recovery In '15; Pipeline Promising

The Cowen Insight

Strong EPS growth outlook starting in '15, improving pipeline visibility, and reasonable valuation support our enthusiasm for the stock.

The favorable Alimta U.S. District Court patent ruling added \$1B+ to our 2017-18 Alimta sales estimates and boosted EPS forecasts. The adverse U.K. Alimta decision was already factored into our thinking. Admittedly, pipeline results have been mixed so far but visibility has improved overall, LLY's margin targets are aggressive but achievable, 2014-20E EPS CAGR of 12% is among the best in pharma, and the dividend yield and P/E multiple are attractive.

After Down 2014, EPS Should Grow Strongly 2015-2017

We estimate EPS to decline 33% to \$2.80 in 2014, pressured by the Cymbalta exclusivity lapse and minor dilution from Lohmann Animal Health. EPS should rebound strongly in 2015-17, and then grow 4-5% 2018-20. The pending Novartis Animal Health acquisition (estimated closing Q1:15) could limit upside in year one before turning accretive, but we still expect 20% EPS growth in 2015. We assume Alimta generics in 2019, implying either a loss on appeal or litigation settlement. Forecast 2014-20 EPS CAGR of 12% is among the top in the pharma group.

Margin Expansion Story Could Surprise

Lilly believes it has targeted the correct range of R&D spend to support growth (will reduce R&D by \$0.8-1B in 2014) and drive margin expansion starting in 2015. We believe Lilly's guidance for SG&A as a percentage of sales of 28-30% and R&D as a percentage of sales of 18-20% could be achieved before consensus expectations of 2019. Our models assume these targets are achieved in 2018.

Late Stage Pipeline To Generate Much News Flow

2014 pipeline news includes: Cyramza filing for 2L NSCLC; Necitumumab filing for 1L squamous NSCLC (Fast Track); ixekizumab (psoriasis) top line H2:14; abemaciclib (CDK4/6) Phase III initiation in breast and lung cancer; baracitinib (RA) Phase III readout late 2014; tabalumab (lupus) Phase III top line H2:14; and potential regulatory approvals for dulaglutide and empagliflozin.

Metabolic

Peglispro Filing Expected Q1:2015 On Mixed Phase III Data

Peglispro (LY2605541), a new basal insulin, is a PEGylated insulin lispro designed to have a large hydrodynamic size (7.8nm in diameter, 4x larger than lispro) which delays insulin absorption and reduces clearance, resulting in prolonged duration of action. Lilly believes Peglispro could be differentiated from Lantus by 1) a better hypoglycemic profile, 2) greater weight loss, 3) better HbA1c profile, and 4) lower meal-time insulin dose. Data to date have shown a flat steady-state profile, a long half-life and duration of action, low within-patient variability and an acceptable safety profile.

In May 2014, Lilly announced top-line data from three of its Phase III trials in T2DM: IMAGINE-2 (insulin naïve), IMAGINE-4 (patients on basal and meal insulin), and IMAGINE-5 (patients on basal insulin only). In all trials, Peglispro demonstrated superiority to insulin glargine in HbA1c reduction. For the secondary endpoints, Peglispro demonstrated statistically significant lower rates of hypoglycemia and comparable to statistically significant less weight gain. Safety findings were consistent with Phase II trials. In all 3 trials, Peglispro patients demonstrated a small but statistically significant increase in triglycerides. In two trials (4 & 5), there was a small but statistically significant reduction in HDL vs. insulin glargine. In two trials (2 & 4), LDLs were similar to glargine, but in IMAGINE 5, LDL was significantly decreased at 52 weeks. Adverse CV events were similar among the two arms. In all 3 trials, more Peglispro patients demonstrated increased ALTs; no Hy's Law (liver injury) reported; In IMAGINE-2 (insulin naïve), liver fat was unchanged for Peglispro and decreased in glargine patients. In IMAGINE-5, liver fat increased from baseline and then stabilized at 26 weeks; no change in glargine patients.

Top-line data from Phase III trials in T1DM was announced in September 2014 and again, Peglispro demonstrated superiority to insulin glargin in lowering HbA1c. Nocturnal hypoglycemia and weight gain trends also favored Peglispro. However, elevated triglycerides and liver enzymes were also more prevalent, although no Hy's Law was reported. Full data for all T1DM and T2DM trials will be presented at medical meetings in 2015. Lilly expects to file in the U.S. and E.U. by the end of Q1:2015. We forecast Peglispro sales of \$30MM in 2015, \$75MM in 2016, \$150MM in 2018, and \$250MM in 2020.

Basal Insulin Peglispro (BIL) Vs. Insulin Glargine (Lantus) – Top-Line Efficacy Data

Trial	Indication	n	Duration	HbA1C Reduction - Non-Feriority*	HbA1C Reduction - Superiority	SS Decrease In Nocturnal Hypoglycemia**	SS Reduction In Weight Gain**
IMAGINE-2	T2DM - insulin naïve	BIL = 1,003 Glarg = 535	52 weeks; subset to 78 wks	Yes	Yes	Yes	Comparable to yes
IMAGINE-4	T2DM - on basal & mealtime insulin	BIL = 691 Glarg = 678	26 weeks	Yes	Yes	Yes	Comparable to yes
IMAGINE-5	T2DM - on basal insulin	BIL = 307 Glarg = 159	52 weeks	Yes	Yes	Yes	Comparable to yes
IMAGINE-1	T1DM - also on mealtime insulin	BIL = 295 Glarg = 160	78 weeks	Yes	Yes (at 26, 52, and 78 weeks); and SS more pts. <7% HbA1c	Yes	Yes; even weight loss
IMAGINE-3	T1DM - also on mealtime insulin	BIL = 664 Glarg = 450	52 weeks	Yes	Yes (at 52 weeks); and SS more pts. <7% HbA1c	Yes	Yes; even weight loss

* primary endpoint

** secondary endpoint

Source: Cowen and Company

Basal Insulin Peglispro (BIL) Vs. Insulin Glargine (Lantus) – Top-Line Safety Data

Trial	Indication	n	Duration	SS Increase In Triglycerides	SS Decrease In HDL	SS Changes In LDL	CV Event Rate	Increase In ALT To >3x ULN	Change In Liver Fat (fm baseline)**	Total Hypoglycemia	Other
IMAGINE-2	T2DM - insulin naïve	BIL = 1,003 Glarg = 535	52 weeks; subset to 78 wks	Yes (small)	No	No	Similar	Yes*	No (vs. decrease in glargine pts.)	NA	NA
IMAGINE-4	T2DM - on basal & mealtime insulin	BIL = 691 Glarg = 678	26 weeks	Yes (small)	Yes (small)	No	Similar	Yes*	Not measured	NA	NA
IMAGINE-5	T2DM - on basal insulin	BIL = 307 Glarg = 159	52 weeks	Yes (small)	Yes (small)	yes (decrease at 52 wks)	Similar	Yes*	Increase - stabilized at 26 wks. (vs. no chg. in glargine pts.)	NA	NA
IMAGINE-1	T1DM - also on mealtime insulin	BIL = 295 Glarg = 160	78 weeks	Yes (small)	No	No	No MACE	Yes*	Yes	Increase (due to increase in daytime rates); SS higher rate of severe hypoglycemia	No SS increase in blood pressure; greater injection site reactions
IMAGINE-3	T1DM - also on mealtime insulin	BIL = 664 Glarg = 450	52 weeks	Yes (small)	Yes (small)	Yes (increase - small)	MACE event rate lower	Yes*	Yes	Increase (due to increase in daytime rates); Numerically lower severe hypoglycemia, but not SS	Increase in blood pressure (<2mmHg mean chg at 52 wks); greater injection site reactions

*No Hy's Law reported

**Measured in a subset of patients

Source: Cowen and Company

Our physician experts remain cautious on the potential for Peglispro, at least pending a review of the full data. Specifically, they would like to see "substantially better" HbA1c lowering; they do not believe that nocturnal hypoglycemia is a major concern for most patients; the weight lowering is a neutral; and the increase in TGs is a concern.

Lilly does not believe a CV endpoint trial will be necessary for approval. In February 2013, FDA did not approve Novo's degludec citing CV risk. FDA is requiring Novo to conduct a randomized CV outcomes study to disprove excess CV risk prior to approving degludec. Given the TG elevation associated with Peglispro, it is possible that the FDA could require Lilly to conduct a similar CV outcomes study, which could delay submission.

Peglispro Effective, But Elevated Liver And Lipid Levels Seen In Phase II Trials

In type II diabetics, Peglispro was superior in reducing nocturnal hypoglycemia compared to glargine (48% reduction, p=0.021). When assessed by continuous glucose monitoring (CGM) for 3 consecutive hours at weeks 0, 6, and 12 study visits, LY patients spent less time with interstitial glucose below 70mg/dL than glargine treated patients. Significantly fewer LY treated patients experienced any episodes of hypoglycemia as assessed by GGM compared to those treated with glargine (50% for LY vs. 78.3% for glargine, p=0.036), including fewer episodes of nocturnal hypoglycemia (20.5% for LY vs. 47.8% for glargine, p=0.027). Endpoint triglycerides were significantly higher in LY treated patients than those treated with glargine (p<0.01); no changes in HDL or LDL were observed.

In patients with type I diabetes, LY demonstrated superior blood glucose lowering compared to glargine over the course of 8-weeks as measured by daily mean blood glucose (244 for LY vs. 152 for glargine, p<0.01) and HbA1c (-0.59% for LY vs. -0.43% for glargine, p<0.001). LY treatment was associated with statistically significant increases in ALT, AST, triglycerides, and LDL and a significant decrease in HDL (p<0.02 for all changes). Our physician consultants are particularly concerned with the increases in LFTs as these likely are related to PEG-toxicity. The overall impact of LDL-C elevations must be assessed through longer-term studies, which could be conducted in the post approval setting. Our physician consultants believe that novel basal insulins have yet to demonstrate a meaningful benefit over glargine and that absolute risk reductions have not been impressive.

Both type I and type II patients treated with LY experienced significant weight loss compared to patients treated with glargine. Type I patients on LY lost 1.2kg compared to glargine patients who gained 0.7kg (p<0.001). Type II patients on LY lost 0.84kg compared to glargine patients who gained 0.3kg (p<0.001). No correlation between weight loss, BMI, or hypoglycemia was observed. Should weight loss with LY be confirmed in larger Phase III trials, this could be viewed as a commercial advantage given that marketed insulins are associated with weight gain.

Our physician consultants do not believe that LY2605541 will replicate weight loss observed in Phase II trials and believe it is unlikely that any insulin produces weight loss.

A comparison of basal insulins in development is below:

Comparison Of Basal Insulins

Drug	HbA1c Reduction From Baseline	Severe Nocturnal Hypoglycemia (event rate per pt. yr.)	Weight (kg)
Lantus (SNY)	0.2-1.3	0.4-5.0	+0.1 to +3.9
Toujeo (SNY)	0.6-1.4	2.1-2.2	-0.6 to +1.0
Levemir (NVO)	0.6-2.0	5.0-8.0	+0.5 to +1.2
Degludec (NVO)	1.1	0.3-1.4	+3.6
Peglispro (LLY)	0.7	Lower than Lantus	-0.54

Source: Cowen and Company

LY2963016 Glargine Mimetic Receives Tentative FDA Approval But Litigation To Delay Launch

Basaglar (LY2963016/insulin glargine) received tentative FDA approval in August 2014 but is subject to the 30-month stay due to the patent infringement litigation with Sanofi. The FDA cannot grant final approval until the end of the 30-month period (mid-2016) unless the court rules in favor of Lilly prior to that time. Given the FDA's lack of guidance on biosimilars, Lilly does not anticipate that LY2963016 will be substitutable for glargine at the pharmacy. Nonetheless, Lilly believes it is well positioned to compete in this space given its knowledge of the diabetes market, manufacturing capabilities, and deep understanding of physician/patient needs. It remains unclear as to how intellectual property issues may impact this strategy.

The NDA for LY2963016 was submitted late December 2013 through the 505(b)(2) pathway. Sanofi filed a suit against Lilly at the end of January 2014 alleging infringement of three patents relating to pen injector devices and two patents relating to insulin glargine formulations, triggering a 30-month stay of litigation. In July 2014, Sanofi filed a second suit in the same court alleging infringement relating to the use of insulin glargine in a cartridge. LY2963016 was submitted in the E.U. earlier in 2013 (trade name Abasria in the E.U.) and in June 2014 received a positive CHMP opinion. LY2963016 was also filed in Japan in late 2013. Lilly anticipates launch in the E.U. in 2015 upon lapse of Lantus (SNY) intellectual property. Lilly plans to leverage its existing footprint in the marketing of its insulin glargine, as opposed to adding additional selling resources. Lilly has indicated that it is interested in higher concentration formulations of insulin glargine and can accomplish this without violating Sanofi's IP, although the Lantus U300 patent is still pending.

Our physician consultants would like to see 6-12 months of bioequivalence data demonstrating sufficient glycemic control and an acceptable hypoglycemia profile to prescribe a glargine biosimilar. Even should a generic glargine demonstrate bioequivalence to Lantus, our physician experts believe that patients have developed a level of comfort with Lantus that will make switching to another insulin very difficult. We forecast Basaglar/Abasria sales of \$100MM in 2016, \$300MM in 2018, and \$500MM in 2020.

By ensuring that its full range of insulins can be produced at every manufacturing facility, Lilly believes it will be able to produce 2x the current demand without adding additional facilities. This process is expected to begin in 2015, improve insulin gross

margins by several percentage points over time, and make Lilly competitive on costs. Lilly also anticipates margins to benefit from the approval of new, high-value products and intends to invest in the pipeline to bring these agents to market.

Trulicity (Dulaglutide) Approved In U.S., EU; Non-Inferiority Achieved In AWARD-6

Trulicity (dulaglutide/GLP-1) is dosed once-weekly, is highly soluble, and uses a small 29-gauge needle. The commercial success of dulaglutide looks likely post the head-to-head study against liraglutide/Victoza (AWARD-6). Dulaglutide met its primary endpoint of non-inferiority compared to once-daily liraglutide as measured by reduction in HbA1c from baseline to 26 weeks. Adverse effects were similar for both groups, with GI events the most common. Lilly also looked at the data to determine if superiority was reached, but dulaglutide was not shown to be superior to liraglutide (nor was it expected to be).

Lilly believes it will be able to differentiate dulaglutide by its efficacy (only GLP-1 shown non-inferior to Victoza in lowering HbA1c (AWARD-6), and ease-of-use (once weekly dosing in a ready-to-use device). Lilly also believes these attributes can help expand the GLP-1 market. Our consultants believe that Victoza and Dulaglutide as the top two GLP-1s but are not convinced of differentiation between them.

Dulaglutide is also being evaluated vs. glargine in CKD patients (AWARD-7) and as an add-on to SUs in AWARD-8. There is a CV study (REWIND) in progress, which is expected to report in 2018.

Trulicity was approved in the U.S. and EU in September 2014 for adults with T2DM as an adjunct to diet and exercise. The labeling is on par with other marketed GLP-1s. It will be supplied in a pre-filled single-dose pen. Both the 0.75mg and 1.5mg doses of Trulicity will be priced at a WAC of \$17.44/day, which is between Victoza's 1.8mg (WAC = \$19.62/day) and Victoza 1.2mg (WAC=\$13.08/day). We estimate Trulicity sales of \$50MM in 2014, \$200MM in 2015, \$300MM in 2016, \$500MM in 2018, and \$700MM in 2020.

Updated AWARD Data Presented At ADA 2014

Updated AWARD Phase III data was presented at ADA 2014; top-line data of these studies had been presented previously.

AWARD 2 (Dulaglutide+met+SU vs. insulin glargin) – dulaglutide superior in A1c reduction at 1.5mg dose and non-inferior at 0.75mg dose; both groups demonstrated weight loss and less hypoglycemia vs. glargin; dulaglutide had greater GI side effects than glargin; Adverse events similar to GLP-1 class.

AWARD-2 Efficacy Data Summary

	Dulaglutide 1.5mg	Dulaglutide 0.75mg	Glargine
A1C change at 52 weeks (%)	-1.08	-0.76	-0.63
Weight change at 78 weeks (kg)	-1.8	-1.3	+1.6
Rates of hypoglycemia at 52 weeks*			
Total	5.2	4.8	7.9
Documented symptomatic	2.0	2.0	3.3
Nocturnal	0.9	0.7	2.1

* events/pt/yr

Source: Eli Lilly, ADA 2014

AWARD-2 Safety Data Summary

	Dulaglutide 1.5mg N = 273	Dulaglutide 0.75mg N = 272	Glargine N = 262
Any adverse event, n (%)	201 (73.6)	188 (69.1)	192 (73.3)
Gastrointestinal adverse event, n (%)			
Nausea	42 (15.4)	21 (7.7)	4 (1.5)
Diarrhea	29 (10.6)	25 (9.2)	15 (5.7)
Vomiting	18 (6.6)	10 (3.7)	3 (1.1)
Severe hypoglycemia, n (%)	2 (0.7)	0 (0.0)	2 (0.8)
Injection site reactions, n (%)	2 (0.7)	2 (0.7)	0 (0.0)
Pancreatitis, n (%)	2 (0.7)	1 (0.4)	0 (0.0)
Pancreatic cancer, n	0	0	0

Source: Eli Lilly, ADA 2014

AWARD 4 (dulaglutide + insulin lispro +/- met vs. glargine) – dulaglutide superior in A1c reduction at 1.5mg and 0.75mg doses; this is first study of a GLP-1 with mealtime insulin; dulaglutide had statistically significant less weight gain than glargine; dulaglutide had higher rate of GI side effects, but characterized as mild and transient; hypoglycemia risk was lower at 1.5mg dose and similar at 0.75mg dose compared to glargine.

AWARD 4 Efficacy Data Summary

	Dulaglutide 1.5mg	Dulaglutide 0.75mg	Glargine
A1C change at 26 weeks (%)	-1.64	-1.59	-1.41
Weight change at 52 weeks (kg)	+0.3	+1.6	+3.7
Rates of hypoglycemia at 26 weeks *			
Total	43.8	52.3	63.2
Documented symptomatic	32.3	38.7	44.4
Nocturnal	3.7	4.7	9.2
Severe	0.1	0.1	0.1

* Events/pt/yr

Source: Eli Lilly, ADA 2014

AWARD 4 Safety Data Summary

	Dulaglutide 1.5mg N = 295	Dulaglutide 0.75mg N = 293	Glargine N = 296
Any adverse event, n (%)	217 (73.6)	230 (78.5)	206 (69.6)
Gastrointestinal adverse events, n (%)			
Nausea	76 (25.8)	52 (17.7)	10 (3.4)
Vomiting	49 (16.6)	46 (15.7)	18 (6.1)
Diarrhea	36 (12.2)	31 (10.6)	5 (1.7)
Injection site reactions, n (%)	1 (0.3)	4 (1.4)	0
Pancreatitis, n (%)	0	0	0
Pancreatic cancer, n	0	0	0

Source: Eli Lilly, ADA 2014

AWARD 6 (dulaglutide + met vs. liraglutide 1.8mg) – dulaglutide non-inferior on A1c although numerically better than lira (1.42% reduction vs 1.36% respectively) – this is first weekly GLP-1 to show non-inferiority to daily Victoza; both groups showed weight loss but liraglutide demonstrated a statistically greater reduction of 0.7kg (liraglutide reduction of 3.6kg from baseline to 26 weeks vs. 2.9kg for dulaglutide); dulaglutide and liraglutide had similar safety and tolerability profiles; GI effects most common side effects in both; nausea similar in both groups.

AWARD 6 Efficacy Data Summary

	Dulaglutide 1.5mg	Liraglutide 1.8mg
A1C change at 26 weeks (%)	-1.42	-1.36
Percent to goal at 26 weeks (%)		
A1C <7.0%	68.3	67.9
A1C ≤6.5%	54.6	50.9
Weight change at 26 weeks (kg)	-2.9	-3.6

Source: Eli Lilly, ADA 2014

AWARD 6 Safety Data Summary

	Dulaglutide 1.5mg N = 299	Liraglutide 1.8mg N = 300
Any adverse event, n (%)	185 (61.9)	189 (63.0)
Gastrointestinal adverse event, n (%)	107 (35.8)	107 (35.7)
Nausea	61 (20.4)	54 (18.0)
Vomiting	21 (7.0)	25 (8.3)
Diarrhea	36 (12.0)	36 (12.0)
Dyspepsia	24 (8.0)	18 (6.0)
Study Drug Discontinuations for GI AE	9 (3.0)	13 (4.3)
Injection site reactions, n (%)	1 (0.3)	2 (0.7)
Hypoglycemia ($\leq 70\text{mg/dL}$) \pm symptoms		
Total (events/pt./year)	0.34	0.52
Pancreatitis, n	0	0
Pancreatic cancer, n	0	0

Source: Eli Lilly, ADA 2014

Dulaglutide Effective In AWARD-3, But Not Clinically Differentiated As Monotherapy

At ADA 2013, Lilly presented Phase III data from dulaglutide's AWARD-III study comparing once-weekly dulaglutide (1.5mg and 0.75mg) to once-daily metformin (up to 2g). While dulaglutide delivered statistically superior HbA1c lowering at weeks-26 and -52, the ~0.2% improvement was not considered to be clinically meaningful. Given the modest improvement in HbA1c absent changes in fasting glucose and undifferentiated weight loss, clinical experts do not believe dulaglutide will supplant metformin as first-line standard of care in patients with newly diagnosed T2DM (AWARD-3 baseline HbA1c of 7.6). A summary of dulaglutide's efficacy in AWARD-3 is below:

AWARD-3 Efficacy Summary

	Dulaglutide 1.5mg	Dulaglutide 0.75mg	Metformin 2g
Week-26			
A1c Week	-0.78*	-0.71*	-0.56
% patients with A1c <7	61.50*	62.60*	53.60
Change fasting glucose (mg/dL)	29.00	26.00	24.00
Weight change (kg)	-2.29	-1.36#	-2.22
Week-52			
A1c Week	-0.70*	-0.55*	-0.51
% patients with A1c <7	60.00*	53.20	48.30
Weight change (kg)	-1.93	-1.09#	-2.20
*Statistical superiority	#Statistical inferiority		

Source: ADA 2013

13/269 patients on 1.5mg of dulaglutide discontinued the study due to adverse events compared to 6/270 patients on the 0.75mg dose, indicative of a dose-dependent tolerability profile. The incidence of GI adverse events and hypoglycemia were higher in for dulaglutide compared to metformin. There were no cases of pancreatitis or pancreatic cancer observed across all patients groups in AWARD-3.

Dulaglutide Superior To Placebo And Exenatide In AWARD-1

Also at ADA 2013, Lilly presented the results of dulaglutide's AWARD-1 comparing once-weekly dulaglutide (1.5mg and 0.75mg) to QD exenatide in patients with T2DM on metformin (1.5-3g) or pioglitazone (30-45mg). Mean baseline HbA1c across all patients groups was 8.1. Dulaglutide demonstrated statistically superior HbA1c lowering compared to placebo and exenatide at both 24- and 52-weeks. The incidence of GI effects on dulaglutide 1.5mg were similar to exenatide while delivering fewer hypoglycemic events (hypoglycemia 3.2% for dula 1.5mg, 4.3% for dula 0.75mg, 12.3% for exenatide, and 1.4% for placebo).

A summary of dulaglutide's efficacy in AWARD-1 is below:

AWARD-1 Efficacy Summary

	Dulaglutide 1.5mg	Dulaglutide 0.75mg	Exenatide	Placebo
Week-26				
A1c Week	-1.51*	-1.30*	-0.99	-0.46
% patients with A1c <7	78.20*	65.80*	52.30	42.9
Weight change (kg)	-1.30	-0.20#	-1.07	+1.24
Week-52				
A1c Week	-1.36*	-1.07*	-0.80	N.A.
% patients with A1c <7	70.80*	59.1*	49.20	N.A.
Weight change (kg)	-1.01	+0.54#	-0.71	N.A.

*Statistical superiority #Statistical inferiority

Source: ADA 2013

Dulaglutide Delivers Superiority To Januvia In AWARD-5

At ADA, 2013, Lilly presented Phase III data from dulaglutide's AWARD-5 study comparing dulaglutide (1.5mg and 0.75mg) to Januvia (100mg sitagliptin, MRK) in patients with T2DM on background metformin therapy. AWARD-5 utilized an adaptive trial design wherein tolerable Phase II doses moved directly into a Phase III trial. The 3.0mg dose of dulaglutide was not carried forward to Phase III development because of an adverse impact on HR and BP. Baseline HbA1c across all patients groups in AWARD-5 was 8.1. Dulaglutide delivered statistically superior HbA1c lowering and weight loss at 26- and 52-weeks compared to Januvia. A summary of dulaglutide's efficacy in AWARD-5 is below:

AWARD-5 Efficacy Summary

	Dulaglutide 1.5mg	Dulaglutide 0.75mg	Exenatide	Placebo
Week-26				
A1c Week	-1.51*	-1.30*	-0.99	-0.46
% patients with A1c <7	78.20*	65.80*	52.30	42.9
Weight change (kg)	-1.30	-0.20#	-1.07	+1.24
Week-52				
A1c Week	-1.36*	-1.07*	-0.80	N.A.
% patients with A1c <7	70.80*	59.1*	49.20	N.A.
Change in fasting glucose (mg/dL)	-43.00	-29.00	-16.00	N.A.
Weight change (kg)	-1.01	+0.54#	-0.71	N.A.

*Statistical superiority #Statistical inferiority

Source: ADA 2013

GI AEs were higher in dulaglutide patients compared to Januvia. A modest increase in pulse rate was also observed in the dulaglutide group, consistent with other drugs in this class. No cases of pancreatitis or pancreatic cancer were observed in dulaglutide treated patients. A summary of dulaglutide's safety in AWARD-5 is below:

AWARD-5 Safety Summary

	Dulaglutide 1.5mg	Dulaglutide 0.75mg	Sitagliptin
Week-52 (%)			
Nausea	17.4	13.9	5.1
Diarrhea	14.5	9.9	2.9
Vomiting	12.8	7.6	2.2
Severe hypoglycemia	1.6	2.6	1.1
Injection site reactions	1.0	1.0	1.0

Source: ADA 2013

Tradjenta (linagliptin) Differentiated Pharmacokinetics And Pricing Strategies Driving Uptake

Tradjenta is a 3rd to market DPP-4 inhibitor that competes directly with Onglyza (AZN), Januvia (MRK), and Nesina (Takeda). All are available in Metformin IR/XR co-formulations. Jentadueto, the combination of Tadjenta and metformin, is marketed in the U.S. and E.U. This is an important addition to the Lilly portfolio given that 50% of DPP-IV prescriptions in the E.U. and 33% of DPP-IV prescriptions in the U.S. are for fixed-dose combinations. We forecast sales of Tadjenta of \$380MM (+53%) in 2014, \$510MM in 2015, \$660MM in 2016, \$960MM in 2018, and \$1,260MM in 2020.

Linagliptin CV Trials Unique

Linagliptin is currently in two CV outcomes trials: CAROLINA trial, comparing linagliptin to a sulfonylurea (glimepiride), and CARMELINA, which is the FDA required CV study. Both trials are expected to report data in 2018 although data from the CARMELINA study could be available sooner as the study enrolls a higher risk patient. We believe conducting the additional study versus a sulfonylurea alone increases the odds that a CV benefit may be shown

Safety Profile Unlikely To Aid In Differentiation

Tradjenta is a selective DPP-4 inhibitor that is differentiated by its low renal excretion (5%), which allows for a uniform dosing strength across all patient populations. Data from EASD showed similar pharmacokinetic profiles in healthy diabetics and patients with diabetic nephropathy. At EASD 2011, data showed Tadjenta maintained a 0.8% decrease in HbA1c observed at 24 weeks through 102 weeks of therapy, suggesting that Tadjenta is sufficient to provide sustained long-term control when used either as monotherapy or in combination for up to two years. No clinically significant increases in hypoglycemia or weight gain were observed over the 102 week observation period.

At EASD 2013, data was presented from two post-hoc, pooled analyses of clinical trials which looked at safety data of Tadjenta. One pooled analysis looked at trials which included 7,400 adults with type II diabetes (4,810 on Tadjenta, 2,590 on placebo). The data showed hypoglycemia incidence at 11.5% for Tadjenta vs. 14% for placebo; and overall incidence of AE or SAE similar with Tadjenta compared to placebo: 56.5% vs. 61.2% for AEs and 4.8% vs. 6.3% for SAEs. Another analysis looked at trials of 1,293 adults with type II diabetes who were 65 and older. This data showed: eGFR was not significantly changed by Tadjenta at 24 weeks, renal and urinary AEs were 5.5% with Tadjenta vs. 4.3% for placebo, incidence of hypoglycemia (investigator-defined) was lower in Tadjenta patients at 21.3% vs. 24.7% for placebo, and acute renal failure occurred in 0.5% on Tadjenta vs. 0.2% on placebo.

Our physician experts view DPP-IVs as less efficacious than GLP-1 analogs given their inability to engage GLP-1 in a wide variety of tissues. Head-to-head studies vs. GLP-1s have shown DPP-IVs to produce inferior lowering of HbA1c. However, despite their limited efficacy, DPP-IV success has been driven by their ease of use and acceptable safety profile. Primary care physicians often prefer prescribing an oral DPP-IV over an injectable GLP-1.

Jardiance Launched In U.S. And EU

Jardiance (empagliflozin) lowers blood sugars by inhibiting SGLT-2 and preventing the re-absorption of glucose by the kidney. This provides a means of improving glycemic control independent from the actions of insulin. In a dose ranging Phase IIb study (1245.9) empagliflozin decreased HbA1c by 0.63% after 12 weeks in patients with T2D.

An NDA was filed in H1:13 and a filing submitted in Japan in Q3:13. In January 2013, Lilly announced that four pivotal studies from the empagliflozin program met their primary endpoint of significant reduction in HbA1c. On March 5, 2014, Lilly and partner Boehringer Ingelheim received a CRL for empagliflozin reflecting previously cited deficiencies at the BI manufacturing plant where empagliflozin is produced. Neither empagliflozin nor other Lilly products were specifically listed in the FDA concerns. In June 2014, the FDA closed out the warning letter, and approval was granted in August. Jardiance is third to the market behind JNJ's Invokana and AZN's Farxiga. IP is protected through late 2020s. In May 2014, Jardiance received E.U. approval. Jardiance has been launched in the U.S., U.K., and Germany. Jardiance was also approved in Australia. In Q2:14, Lilly filed in the E.U. for an empagliflozin + metformin FDC.

Empagliflozin's FDA-required CV outcomes study (n=12,000) is ongoing with data expected in H1:2015. If completed in 2015, empagliflozin would be the first SGLT-2 with outcomes data - a potentially very favorable market position. We forecast empagliflozin sales of \$50MM in 2014, \$100MM in 2015, \$150MM in 2016, \$250MM in 2018, and \$350MM in 2020.

Our physician consultants do not view empagliflozin as differentiated from other SGLT-2 inhibitors. SGLT-2 inhibitors demonstrate additive efficacy as adjunctive therapy, but are likely to be used infrequently as monotherapy. Our physician experts do anticipate using SGLT-2 inhibitors in the first-line setting, primarily in patients with uncontrolled hyperglycemia who are at risk for glucose toxicity. The modest weight loss associated with SGLT-2 inhibitors may aid adoption. Concerns about potential urinary infections with the class persist and could be an overhang. Use of specific SGLT-2s will be primarily dictated by cost and marketing.

SGLT2 Inhibitors

Candidate Name	Company	Phase/Development Status
Invokana (canagliflozin)	Johnson & Johnson	Marketed
Forxiga/Farxiga (dapagliflozin)	AstraZeneca	Marketed
Jardiance (empagliflozin)	Eli Lilly/Boehringer Ingelheim	Marketed
ertugliflozin	Merck/Pfizer	Phase III
Suglat (ipragliflozin)	Astellas Pharma	Approved 1/14 in Japan, co-mkt w/MRK; EU, U.S. development discontinued
LX4211	Lexicon Pharmaceuticals	Phase II for T1DM; Phase III planned for T2DM; dual SGLT1+2 inhibitor
Iuseogliflozin (TS-071)	Taisho Pharmaceuticals	Filed in Japan April 2013; 5 Phase III studies demonstrated efficacy and safety

Source: Company data, clinicaltrials.gov, Cowen and Company

Empagliflozin + Linagliptin Combo Filed In U.S.

In April 2014, Lilly filed for U.S. approval of a fixed dose combo of empagliflozin (Jardiance) and linagliptin (Tradjenta). If approved, it would become the first marketed SGLT-2 and DPP-4 combination. The company estimates that about 25% of SGLT-2 use is in addition to a DPP4 agent.

In September 2014, results from a Phase III study comparing the combo to its components demonstrated that the empagliflozin/linagliptin combo provided a sustained reduction in blood glucose at 52 weeks in T2DM patients. Overall, the combo was well-tolerated with a safety profile similar to the individual compounds.

In patients also on metformin, the combo demonstrated significant reductions in HbA1c at both doses studied. In treatment-naïve patients (and not on metformin), the 10mg/5mg empa/linna combo provided statistically significant reductions in HbA1c compared to empagliflozin 10mg and linagliptin 5mg. However, the 25mg/5mg empa/linna did not reach a statistically significant reduction versus empagliflozin 25mg.

Empagliflozin/Linagliptin Combo Phase III Results

	Empagliflozin/Linagliptin 25/5mg	Empagliflozin/Linagliptin 25/5mg	Empagliflozin 25mg	Empagliflozin 10mg	Empagliflozin 5mg
Add-On To Metformin					
% HbA1c reduction (52 weeks) vs. baseline	-1.21	-1.04	-0.69	-0.70	-0.45
Hypoglycemic events (% reported)	3.6	2.2	3.5	1.4	2.3
Genital infections (% reported)	2.2	5.9	8.5	7.9	2.3
Urinary tract infections (% reported)	10.2	9.6	13.5	11.4	15.2
Treatment-naïve patients					
% HbA1c reduction (52 weeks) vs. baseline	-1.18	-1.25	-1.02	-0.87	-0.51
Hypoglycemic events (patients reporting)	0	0	1	4	1
Genital infections (% reported)	5.9	2.9	4.4	5.2	3.0
Urinary tract infections (% reported)	12.5	15.4	10.4	16.3	10.4

Source: Boehringer Ingelheim

Empagliflozin Demonstrates Meaningful Efficacy In Combination With Basal Insulin

At ADA 2013, Lilly presented Phase III data comparing empagliflozin (SGLT-2 inhibitor) plus a basal insulin to a basal insulin alone in patients with T2DM for 78-weeks. The basal insulin dose was fixed for the first 18-weeks, after which dose adjustments were permitted at the discretion of the investigator. The addition of empagliflozin promoted significant decreases in HbA1C at both 18- and 78-weeks, reduced insulin requirements, promoted significant weight loss, and decreased BP. Similar rates of hypoglycemia were reported between treatment groups (36.1% on empagliflozin vs. 35.3% for basal insulin alone). Adverse events consistent with urinary tract infections were more commonly reported in empagliflozin patients (11.6% for empagliflozin 25mg, 14.8% for empagliflozin 10mg, and 8.8% for basal insulin alone). Genital infections also occurred more frequently in empagliflozin treated patients (5.2% for empagliflozin 25mg, 7.7% for empagliflozin 10mg, and 1.8% for basal insulin alone).

A summary of empagliflozin's efficacy in combination with basal insulin is below:

Empagliflozin Efficacy Summary As Add On To Basal Insulin

	PBO	Empa 10mg	Empa 25mg
HbA1c (%)			
Baseline (week-18)	8.1	8.26	8.34
Change from baseline (week-18)	-0.01	-0.57	-0.71
Difference from PBO		-0.56	*
Difference from PBO		-0.70	*
Baseline (week-78)	8.09	8.27	8.29
Change from baseline (week-78)	-0.02	-0.48	-0.64
Difference from PBO		-0.46	*
Difference from PBO		-0.62	*
Insulin Dose (IU)			
Baseline	47.84	45.13	48.43
Change from baseline (week-78)	5.45	-1.21	-0.47
Difference from PBO		-6.66	*
Difference from PBO		-5.92	*
Fasting glucose (mg/dL)			
Baseline	142.00	138.00	146.00
Change from baseline (week-78)	3.00	-10.00	*
Difference from PBO		-15.00	*
Body weight (kg)			
Baseline	90.50	91.60	94.70
Change from baseline (week-78)	0.70	-2.20	*
Difference from PBO		-2.00	*
Systolic BP (mmHg)			
Baseline	133.90	132.40	132.80
Change from baseline (week-78)	0.10	-4.10	*
Difference from PBO		-2.40	

*p<0.05

Source: ADA 2013

Empagliflozin A Reasonable Addition to Metformin

At ADA 2013, Lilly presented Phase III data comparing empagliflozin + metformin to metformin alone in patients with T2DM. Empagliflozin promoted improvements in HbA1c, fasting and postprandial blood glucose, and body weight compared to metformin alone. Hypoglycemia (1.4% for empa 25mg, 1.8% for empa 10mg, and 0.5% for metformin alone) and genital infections (4.7% for empa 25mg, 3.7% for empa 10mg, and 0% for metformin alone) were reported more frequently in patients on empagliflozin compared to metformin alone.

A summary of empagliflozin's efficacy as an add on to metformin is below:

Empagliflozin Efficacy Summary As Add On To Metformin

	PBO	Empa 10mg	Empa 25mg
HbA1c (%)			
Baseline	7.90	7.94	7.86
Change from baseline	-0.13	-0.70	-0.77
Difference from PBO		-0.57*	-0.64*
Patients with HbA1c <7 (%)	23	75	74
Odds ratio vs. PBO		4.72*	4.67*
Mean daily glucose (mg/dL)			
Baseline	169.53	168.03	167.87
Change from baseline	-1.99	-9.64	-14.36
Difference vs. PBO		-7.65*	-12.37*
Fasting glucose (mg/dL)			
Baseline	156.02	154.58	149.42
Change from baseline	6.38	-20.04*	-22.38*
2hr postprandial glucose (mg/dL)			
Baseline	264.44	254.62	252.09
Change from baseline	5.91	-46.00*	-44.56*
Body weight (kg)			
Baseline	79.73	81.59	82.21
Change from baseline	0.45	-2.08	-2.46
Difference vs. PBO		1.63*	-2.01*

*p<0.05

Source: ADA 2013

Empagliflozin Compares Favorably To Januvia As Monotherapy

At ADA 2013, Lilly presented Phase III data comparing empagliflozin to placebo or Januvia (sitagliptin 100mg) for 24-weeks. Empagliflozin and sitagliptin delivered statistically significant reductions in HbA1c, but only empagliflozin demonstrated significant improvements in blood pressure and body weight compared to placebo. Consistent with other trials, genital infections occurred more frequently in empagliflozin patients.

A summary of empagliflozin's efficacy as monotherapy is below:

Empagliflozin vs. Januvia As Monotherapy

	PBO	Empa 10mg	Empa 25mg	Sita 100mg
HbA1c (%)				
Baseline	7.91	7.87	7.86	7.85
Change from baseline	0.08	-0.66	-0.78	-0.66
Difference from PBO		-0.74*	-0.85*	-0.73*
Patients with HbA1c <7 (%)	25	72	88	75
Odds ratio vs. PBO		4.12*	6.15*	4.76*
Body weight (kg)				
Baseline	78.23	78.35	77.80	79.31
Change from baseline	-0.33	-2.26	-2.48	0.18
Difference vs. PBO		-1.93*	-2.15*	0.52
Systolic BP (mmHg)				
Baseline	130.40	133.00	129.90	132.50
Change from baseline	-0.30	-2.90	-3.70	0.50
Difference from PBO		-2.60*	-3.40*	0.80

*p<0.05

Source: ADA 2013

Evista Off Patent As Of March 2014

Evista (raloxifene), a selective estrogen receptor modulator (SERM), is indicated for the treatment and prevention of osteoporosis in post-menopausal women and for the reduction in risk of invasive breast cancer in post-menopausal women with osteoporosis and post-menopausal women at high risk for breast cancer. Evista has been unable to capitalize on its lack of progesterone properties and non-estrogen profile, possibly because women on Evista experience hot flashes while those on Premarin do not. Evista holds a strong position in the Japanese osteoporosis market because bisphosphonates are approved at half the U.S. dose. Evista once-weekly is marketed in Japan with Lilly's partner Chugai. Evista's patents expired in August 2013 (E.U.) and March 2014 (U.S.), and will expire July 2018 in Japan. Lilly has an agreement with Prasco for an authorized generic in the U.S. We estimate Evista sales of \$440MM (-58%) in 2014, \$270MM in 2015, \$260MM in 2016, \$140MM in 2018, and \$55MM in 2020.

Unique Profile, Increased Compliance Should Drive Moderate Forteo Growth

Forteo (teriparatide), parathyroid hormone (PTH) 1-34, is the only agent currently approved that builds bone primarily by increasing the activity of osteoblasts (cells that deposit bone). Our consultants note that Forteo is an important addition to the osteoporosis treatment armamentarium, but it is only appropriate for severe patients refractory to bisphosphonates or younger patients who tend to have more of an osteoblastic bone condition (vs. osteoclastic).

Forteo is administered by specialists after evaluating them for contraindications and then the patients are followed for side effects. Barriers to Forteo's use include its high cost (\$47.70/day), the need for daily injections (20 mcg), the rare but potential risk of osteosarcoma, and the limited therapeutic duration (24 months in U.S., 18 months in Europe). Patients can also develop hypercalcemia (symptoms include muscle and joint pain/change in mental status) but this is reversible upon discontinuation of treatment.

Our experts feel that the long discussion related to the black box warning over osteosarcoma as well as the daily subQ injection turns some patients off treatment. Despite these limitations, Forteo's differentiated mechanism of action has driven solid growth. Our consultants believe that Forteo will be used in 15% of osteoporotic patients. A low compliance rate among U.S. patients offers potential upside. Lilly is implementing plans to improve patient adherence and adoption. Forty percent of patients requiring Forteo utilize Medicare. Medicare Part D insurance access has improved and private insurance requires \$60 co-pay per treatment. A glucocorticoid-induced osteoporosis (GIOP) indication was approved by the EMEA in February 2008 and FDA in July 2009. Forteo pen was approved and launched in mid-2008. We forecast Forteo sales of \$1,335MM (+7%) in 2014, \$1,430MM in 2015, \$1,525MM in 2016, \$1,675MM in 2018, and \$1,825MM in 2020.

Recombinant Parathyroid Hormone Fracture Reduction Rates

	Vertebral*	Non-Vertebral*
20mcg	63%	54%
40mcg	69%	54%

*statistically significant

1,637 women with ≥ 1 prevalent vertebral fractures were randomly assigned to 1 of 3 equal study arms. All patients received daily calcium (1000 mg) and vitamin D (400-1200 U) supplements. The median follow-up was 21 months.

Source: Endocrine Society

Recombinant Parathyroid Hormone Side Effect Summary

	Placebo	PTH 20mcg	PTH 40mcg
Back pain	22.6%	16.8%	15.8%
Nausea	7.5	9.4	17.8
Headache	8.3	8.1	13

Source: Endocrine Society

A trial was conducted to measure bone mineral density and geometry at the femoral neck and shaft in postmenopausal women. Patients ($n=84$) were randomized to daily injections of Forteo 20 or 40 mcg, or placebo. Hip measurements of bone density and geometry were performed at baseline and at 20.1 months on average. The endpoints of this study included bone mineral density (BMD), cross-sectional area, section modulus (a measure of bending strength), and buckling ratio (an index of cortical instability). The results support Forteo's efficacy on bone.

Forteo Percent Difference From Placebo

	Femoral Neck		Femoral Shaft	
	Forteo 20mcg	Forteo 40mcg	Forteo 20mcg	Forteo 40mcg
BMD	6.4*	12.5*	8.9*	3.1
Cross sectional area	3.3	13.4*	7.9*	3.7
Section modulus	0	14.8*	6.9*	4.2
Average Cortex	6.8*	12.7*	10.0*	3.3
Buckling ratio	-9.1*	-10.3*	-10.2*	-2.6

* $p < 0.05$

Source: ASBMR

Forteo May Be More Effective Than Fosamax In Treating Glucocorticoid-Induced Osteoporosis

An 18-month randomized double-blind controlled study comparing Forteo to Fosamax in 428 patients with glucocorticoid-induced osteoporosis was published in the NEJM in November, 2007. The primary endpoint was change in LS BMD and secondary endpoints were total hip BMD, time to changes in BMD, bone markers, fractures, and safety. Within 6 months of therapy, patients administering Forteo had a greater increase in LS BMD than those taking Fosamax ($p<0.001$). Other findings after 12 months of therapy included: (1) new vertebral fractures were statistically significantly less in the Forteo arm than placebo arm ($p=0.004$); (2) patients taking Forteo had greater total hip BMD ($p=0.01$); and (3) there were similar rates of nonvertebral fractures between the two treatment arms. Compliance to treatment protocol was similar in both arms. Although further studies are warranted, results from this trial suggest that patients taking glucocorticoids for more than 3 months and have osteoporosis or are at high risk for a fracture should receive Forteo instead of Fosamax as a first-line treatment agent.

Baricitinib Moves To Phase III in RA

Eli Lilly and Incyte are developing an oral small molecule that inhibits JAK1/2 (baricitinib/LY3009104, formerly INCB28050) for the treatment of autoimmune diseases including RA. Baricitinib has shown good efficacy and safety in Phase IIb, and the companies plan to develop the drug as a once-a-day treatment given its long half-life. Lilly and Incyte reported proof of concept data from a 127-patient 6-month Phase II RA trial on '050 in 2010.

Final 6-month Phase IIb data for baricitinib was presented at ACR 2012. Selective inhibition of JAK1/2, but not JAK3, has been hypothesized to provide a differentiated efficacy/safety profile compared to pan-JAK inhibitors such as Pfizer's Xeljanz (tofacitinib, approved November 2012). Baricitinib delivers dose-dependent improvements (2mg, 4mg, and 8mg) in ACR20/50/70, but the efficacy of baricitinib appears undifferentiated from Xeljanz. Similar to Xeljanz, baricitinib resulted in dose-dependent changes in hemoglobin, lymphocyte and neutrophil count, LDL-C, and HDL-C. Baricitinib recently advanced to Phase III. Given little evidence of differentiation and significant lag in development relative to Xeljanz, we believe baricitinib's potential is capped. We estimate baricitinib sales of \$50MM in 2016, \$150MM in 2018, and \$250MM in 2020.

Baricitinib Efficacy and Safety Similar To Tofacitinib

When comparing Phase IIb data for both compounds, ACR20/50/70 for baricitinib 4mg is numerically higher than for tofacitinib 5mg, although the clinical relevance of this unknown. In addition to significant improvements in ACR scores, baricitinib and tofacitinib demonstrated similar improvements in HAQ-DI after 12-weeks in Phase II. A comparison of Phase II data for baricitinib and tofacitinib is presented below:

Comparison Of Baricitinib And Tofacitinib Phase IIb Efficacy

	Baricitinib*			Tofacitinib**				
	2mg	4mg	8mg	1mg	3mg	5mg	10mg	15mg
ACR 20	63%	78%	73%	24%	39%	57%	74%	68%
ACR 50	20%	48%	55%	7%	29%	37%	46%	54%
ACR 70	10%	28%	24%	6%	16%	22%	38%	33%

Source: *Company data, ACR 2012; **Company data, Phase IIb data from ACR 2009

While no deaths or opportunistic infections were observed in the Phase II study of baricitinib, the most common treatment-emergent adverse event class was infections (12% for placebo vs. 14% for baricitinib vs. 11-24% for tofacitinib in Phase II). Similarly, no opportunistic infections, malignancies, or lymphomas were observed in early Phase II studies with tofacitinib; however, these emerged as adverse events of serious concern during Phase III development. Like tofacitinib, dose-dependent changes in hemoglobin, lymphocyte and neutrophil counts, low-density lipoprotein, and high-density lipoprotein were observed on baricitinib with changes observed most frequently on the 8mg dose. In June 2013, Lilly reported that clinical improvements observed at weeks-12 and -24 were sustained through 52-weeks. Among patients who remained on the 4mg dose, treatment-emergent serious infections occurred in 4% of patients. Among patients who received the 8mg dose, serious infections occurred in 2% of patients (no opportunistic infections or TB were observed). There was one death in the 8mg group due to a suspected myocardial infarction.

Broad Phase III RA Program Under Way

A broad Phase III program in methotrexate naïve patients, DMARD failures, and inadequate responders to anti-TNFs is underway. Baricitinib's Phase III program is summarized below:

Baricitinib Phase III Program

Study	Patients	Comparator	Primary Endpoint	Estimated Completion
RA-BEGIN (JADZ)	Early RA w/ limited or no prior methotrexate, naïve to other DMARDs	4mg baricitinib vs. MTX vs. baricitinib + MTX	Non-inferiority to MTX on ACR20 at Week 24	1/15
RA-BEAM (JADV)	Patients w/ inadequate response to MTX and documented bone erosions	4mg baricitinib vs. adalimumab vs. placebo	Superiority ACR20 vs. placebo at Week 12	1/14
RA-BUILD (JADX)	Patients w/ active RA with inadequate response to DMARDs	2mg and 4mg baricitinib vs. placebo	Superiority ACR20 (4mg dose) vs. placebo at Week 12	12/14
RA-BEACON (JADW)	Patients w/ active RA who have had an inadequate response to an anti-TNF	2mg and 4mg baricitinib vs. placebo	Superiority ACR20 (4mg dose) vs. placebo at Week 12	6/14
RA-BEYOND (JADY)	Patients completing any of the Phase III studies are eligible for enrollment in LTE study	2mg and 4mg doses	Efficacy and safety	6/20

Source: Company data

Lilly will pursue additional indications for baricitinib in psoriasis and diabetic nephropathy (Phase II ongoing, estimated completion 2014). Lilly has developed a compassionate use program for non-IL1 dependent pediatric auto-inflammatory disorders.

Anti-Inflammatory

Ixekizumab Phase III Studies In Plaque Psoriasis Positive: Filing Expected H1:15

Ixekizumab (directly targets circulating IL-17A) treats moderate to severe psoriasis. In August 2014, Lilly reported top line results from three Phase III trials which demonstrated ixekizumab as statistically superior to etanercept (Enbrel) and placebo on skin clearance measures, with up to 41% able to achieve clear skin at week 12. Lilly believes this Phase III efficacy and safety data could distinguish ixekizumab as a potential best-in-class biologic for the treatment of moderate-to-severe plaque psoriasis. Ixekizumab is also being evaluated in ankylosing spondylitis and psoriatic arthritis. We estimate ixekizumab sales of \$100MM in 2015, \$200MM in 2016, \$400MM in 2018, and \$600MM in 2020.

Phase III Programs All Hit Endpoints

In all three Phase III UNCOVER studies, patients with moderate-to-sever plaque psoriasis received either ixekizumab (80mg every 2 or 4 weeks, after a 160mg starting dose) or placebo for 12 weeks. In the active comparator trials (UNCOVER-2 and 3), patients may have been assigned to Enbrel 50mg twice weekly for 12 weeks. In UNCOVER-1, responders were assigned to continue treatment with either placebo or ixekizumab (80mg every 4 or 12 weeks) for up to 60 weeks.

For patients treated with ixekizumab every 2 or 4 weeks, 78-90% achieved at least a PASI 75 at 12 weeks. And 31-41% of these achieved PASI 100 at week 12 (vs 5-7% of patients on Enbrel achieving PASI 100). Statistically significant improvement in skin clearance was seen as early as week 1. In UNCOVER-1, high levels of response were maintained through 60 weeks.

Adverse events were comparable in the 12 week portion across all three trials; rate and severity of AEs were comparable to Enbrel in the active comparator trials. The most frequent side effects (>5% across all 3 studies) were nasopharyngitis and injection site reaction.

Full data will be presented in 2015. Lilly plans to file in H1:15.

Phase II Data: Ixekizumab Very Effective In Moderate-To-Severe Psoriasis

Ixekizumab met the primary endpoint of reduction in PASI75 at 12 weeks at all doses (10-150mg) in its Phase II study of 142 patients with moderate-to-severe plaque psoriasis. The 25mg, 75mg, and 150mg doses of ixekizumab showed similar improvements in PASI75 with the 10mg dose appearing numerically inferior. Significant improvements in PASI75 were observed after 1-week with the 150mg dose and between 4-6weeks with all other doses.

PASI75 At Week 12

Treatment	Number of Patients	% of Patients at 12 weeks
Ixe 150mg	28	82
Ixe 75mg	29	83
Ixe 25mg	30	77
Ixe 10mg	28	29
Placebo	27	8

All ixe p values <0.001

Source: Company data

While PASI75 has traditionally been the standard by which currently marketed psoriasis drugs have been measured, many patients remain unsatisfied by only a 75% resolution of symptoms. PASI90 and PASI100 may therefore be better measures of drug efficacy and patient satisfaction. Ixekizumab 25-150mg increased the PASI90 response rate and the 75mg and 150mg doses increased the number of patients achieving PASI100 at 12 weeks. The 150mg dose achieved PASI90/100 between 4 and 6-weeks while the 25mg and 75mg doses demonstrated significant improvements in PASI90/100 between weeks 6 and 8. The 150mg dose of ixekizumab appears numerically superior to all other doses on the PASI90 endpoint and similar to the 75mg dose on the PASI100 endpoint.

PASI90 At Week 12

Treatment	Number of Patients	% of Patients at 12 weeks
Ixe 150mg	28	71
Ixe 75mg	29	59
Ixe 25mg	30	50
Ixe 10mg	28	18
Placebo	27	0

All ixe p values <0.001

Source: Company data

PASI100 At Week 12

Treatment	Number of Patients	% of Patients at 12 weeks
Ixe 150mg	28	39
Ixe 75mg	29	38
Ixe 25mg	30	17
Ixe 10mg	28	0
Placebo	27	0

All ixe p values <0.001

Source: Company data

Symptom Improvements Extended Across Difficult-To-Treat Forms Of Psoriasis

Patients whose psoriasis extends to the nails and scalp can be particularly difficult to treat. Ixekizumab improved the nail (NAPSI) and scalp (PSSI) severity scores. NAPSI was significantly reduced at 12 weeks by the 75-150mg doses while PSSI was significantly improved with the 25-150mg doses. Improvements were observed at the earliest time points (2-4 weeks) with the 75mg and 150mg doses.

NAPSI At Week 12

Treatment	Mean % Change From Baseline
Ixe 150mg	-49
Ixe 75mg	-57
Ixe 25mg	-24
Ixe 10mg	14
Placebo	7

All ixe p values 0.001-0.005

Source: Company data

PSSI At Week 12

Treatment	% of Patients at 12 weeks
Ixe 150mg	-85
Ixe 75mg	-95
Ixe 25mg	-87
Ixe 10mg	-43
Placebo	-30

All ixe p values 0.001-0.005

Source: Company data

Safety Profile Appears Clean In Phase II; Requires Verification In Larger, Extended Duration Phase III Program

Ixekizumab's toxicity profile appeared to be relatively benign in its Phase II trial. No serious adverse events were observed. The rate of adverse events was similar in all patients treated with ixekizumab compared to placebo (63% for both groups). The most commonly occurring side effects in ixekizumab treated patients were infections (33% in ixekizumab patients vs. 26% in placebo) and injection site reactions (0-10% in ixekizumab patients vs. 0% in placebo). No statistically significant differences were observed in grade 3-4 neutropenia between treatment groups.

Directly Targeting IL-17A Could Improve Side Effect Profile

Ixekizumab directly targets circulating IL-17A, while other competitive agents target the IL-17 receptor. Because the IL-17 receptor binds a number of cytokines, inhibition of the receptor may cause a less specific response compared to neutralization of only IL-17A. This additional specificity could improve the adverse event profile for ixekizumab compared to agents that target the IL-17 receptor and may differentiate ixekizumab from other agents targeting the IL-17 pathway. Whether or not ixekizumab's specificity will translate to improved tolerability remains to be determined in the larger ongoing Phase III trials.

A Need for Improved Biologics Exists

Lilly estimates that as many as 7.5MM patients in the U.S. have psoriasis, that 17% of these patients have moderate-to-severe disease, and that as many as 20% of all patients with moderate-to-severe disease are treated with a biologic agent. Lilly believes that physicians' level of comfort with biologics is increasing and that agents with an improved risk-benefit ratio could expand the biologics market in psoriasis. Because patients' disease continues to progress on currently marketed biologic therapies, the need exists for novel biologics that target new mechanisms. Ixekizumab's Phase III trial (currently enrolling) is designed to establish a clear risk-benefit profile through the addition of an extended maintenance therapy arm. Long-

term (265 week) data could increase physicians' willingness to adopt ixekizumab ahead of agents for which such data does not exist.

Tabalumab Fails in RA; Phase III Lupus Trials Ongoing

Lilly's anti-BAFF mAb, tabalumab (LY-2127399), binds to both membrane-bound and soluble BAFF whereas competitor agents only bind to soluble BAFF. In December 2012, Lilly discontinued a single study (FLEX-M) with tabalumab in RA as the result of a futility analysis that suggested the trial would not meet its primary endpoint in methotrexate failures. In February 2013, Lilly took an interim look at another study (FLEX-V) in TNF failures and determined that study also would not meet its primary endpoint and discontinued the entire development program for RA. However, Tabalumab continues in late-stage development for lupus, which is where our consultants believe the anti-BAFF mechanism should be explored. The Phase III program is fully enrolled and expected to complete in 2014. Steroid sparing and flare reduction endpoints are particularly important. We forecast tabalumab sales of \$10MM in 2016, \$30MM in 2018, and \$50MM in 2020.

Cardiovascular

Effient Adoption Slow; Opportunity Limited Post TRILOGY Failure

In July 2009, Lilly/Daiichi's Effient (prasugrel) received FDA approval with a competitive label in the ACS-PCI market despite the boxed warning and lack of superiority claim. Lilly and partner Daiichi launched Effient in August 2009 in the U.S. with a 13% premium to brand Plavix (\$5.45/day versus \$4.80/day). Lilly believes that a health-economic sub study of TRITON-TIMI 38 that demonstrated Effient reduced medical costs by \$221/patient over the 14.7 months supports the premium. Effient is currently on hospital formularies and stocked in cath-labs accounting for 89% of the PCI volume in the U.S. Effient is currently available without restriction in more than 92% of commercial managed care lives in either Tier 2 or Tier 3. Lilly believes that several factors negatively impacted Effient's launch including: (1) protracted FDA process prior to approval highlighted Effient's negative attributes and not its benefits; (2) REMS and medication guide also focused on the negatives; (3) marketing material that highlights benefits in MI and diabetes was approved only in February 2010; and (4) low initial outpatient access tempered willingness of interventional cardiologists to prescribe Effient at the time of PCI. Our cardiology consultants highlight Effient's bleeding risk as its biggest hurdle.

In Europe, despite the widespread availability of generic clopidogrel, Lilly believes Effient has achieved favorable pricing. Reimbursement covers 100% of the labeled population in most countries. In September 2009, NICE recommended Effient for use in the NHS in approximately 50% of the ACS-PCI patients. Effient is available in over 70 countries outside the U.S., including all five major E.U. countries. The availability of AstraZeneca's Brilinta is another headwind for Effient.

The U.S. compound patent expires April, 2017 and the company assumes generics will launch at that time. Lilly does have a method-of-use patent (with aspirin) that expires in 2022. In January 2014, Lilly filed a lawsuit in southern Indiana District Court against Par seeking a ruling that the method-of-use patent is valid and infringed. A similar lawsuit was filed against 13 other generic companies in March and April 2014, including Mylan who also alleges the compound patent is invalid. We estimate Effient sales of \$540MM (+6%) in 2014, \$585MM in 2015, \$630MM in 2016, \$320MM in 2018 (U.S. patent expires 4/2017), and \$170MM in 2020.

Effient and Brilinta each have advantages and disadvantages. Based on Brilinta's pivotal Phase III data, our physician consultants believe that, because Effient appears more potent and is taken only once a day, it should be used in patients requiring more potent therapy, are likely to be non-compliant, have history of severe asthma or COPD, or are at risk for brady arrhythmias. On the other hand, Brilinta should be used in patients who are more likely to go to surgery. In PLATO, Brilinta was given upstream compared to where Effient was given in TIMI 38. Therefore, more patients could be eligible for Brilinta. Our interventional cardiologist consultants conclude that superior effectiveness over Plavix—and not price—will determine the market shares in PCI, even in the face of Plavix generics.

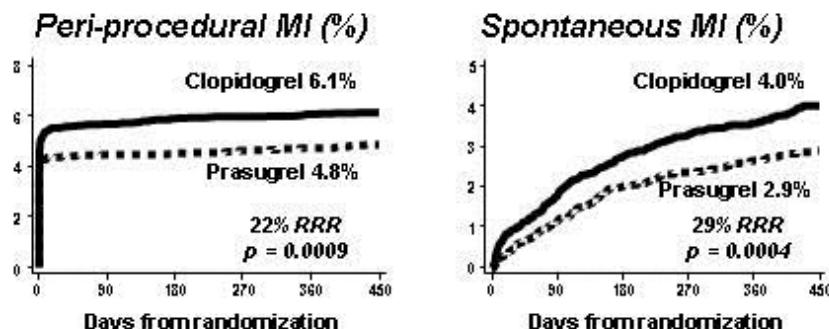
TRITON-TIMI 38 Conclusive: Benefit Outweighs the Risk

The results of TRITON-TIMI 38, presented at AHA in November 2007, demonstrated overwhelming superiority for Effient versus Plavix contrasted by significantly worse bleeding in certain sub-groups. The net clinical benefit, a prespecified but not FDA agreed upon endpoint of death, MI, stroke, and major bleeds (non-CABG), was 13.9% versus 12.2% (HR 0.87, p=0.004). Efficacy was predominantly driven by nonfatal MI prevention and there was a significant increase in life-threatening bleeding. There was evidence of harm or the lack of net clinical benefit in subjects with a history of TIA/stroke, or age ≥ 75 and weight $\leq 60\text{kg}$.

Superior Efficacy Throughout Study Driven By Prevention Of Nonfatal MIs

Effient was statistically superior to Plavix in both the primary and the 30 and 90 day secondary endpoints. However, in the individual components of the primary composite endpoint, only the reduction in nonfatal MIs was statistically different, with positive trends seen in the reduction of CV death and nonfatal stroke endpoints. A benefit in CV mortality would have supported a stronger risk-benefit profile given the increased risk of life-threatening and fatal bleeds. The MI benefit was detailed at ESC 2008. At 15 months, prasugrel significantly reduced the risk of new/recurrent MI compared with clopidogrel (7.4% vs. 9.7%, HR 0.76, p<0.0001). This benefit was observed with respect to both peri-procedural MI (4.8% vs. 6.1%, HR 0.78, p=0.0009) and spontaneous/secondary MI (2.9% vs. 4.0%, HR 0.71, p=0.0004). Considering spontaneous/secondary MI, prasugrel reduced the risk of both new ST-elevation MI (0.3% vs. 0.9%, HR 0.31, p<0.0001), as well as non-ST elevation MI (2.6% vs. 3.2%, HR 0.81, p=0.046). Moreover, when the late effects of prasugrel beyond 30 days were considered, patients treated with prasugrel had a significantly lower risk of any MI (2.9% vs. 3.7%, HR 0.77, p=0.01), including spontaneous MI (2.5% vs. 3.2%, HR 0.78, p = 0.024). Our consultants are encouraged that the nonfatal MI benefit was not just associated with peri-procedural events but extended to MIs throughout the 12-15 month study. The efficacy benefit was seen as early as three days (benefit of loading dose) and a Landmark analysis confirms the benefit through 15 months (benefit of maintenance dose).

Effient Vs. Plavix In Non-Fatal MI



Source: ESC 2008

Bleeding Significantly Worse But Subgroups Appear To Drive Difference

Bleeding rates were consistently and significantly higher for Effient across the safety endpoints. The Plavix bleeding rate of 1.8% was much lower than seen in CURE, potentially due to improved current patient management. The life threatening bleeds and especially fatal bleeds in TIMI 38 are a major concern. The data suggest that patients with a previous history of stroke or TIA, or those patients with increased Effient exposures (≥ 75 years and ≤ 60 Kg), were more susceptible to increased bleeding. The intracranial hemorrhages (ICH) (19 vs. 17) were driven by six bleeds in the Effient arm in patients with a history of TIA/stroke versus zero in the Plavix arm ($p=0.02$). Subtracting out the above-mentioned subgroups from the 26 fatal bleeds (21 vs. 5, Effient vs. Plavix; $p=0.002$), the difference is not statistically different (6 vs. 4). The increased bleeding in these subpopulations may have resulted in the absence of the significant CV mortality benefit, potentially confirming Angiomax's ACUITY data and demonstrating the relationship between bleeding and survival. However, these data will require further analyses. The imbalance in the CABG-related bleeding (13.4 vs. 3.2%; Effient vs. Plavix) rates will require additional analyses as this may further limit Effient's potential, but our physician consultants believe that this can be managed by delaying likely non-urgent CABG surgery. Lilly stated that the ≥ 75 years and ≤ 60 kg subgroups had Effient maintenance dose exposures similar to that seen with the 15mg dose in the Phase II studies.

Effient Fails To Meet Endpoint in TRILOGY

TRILOGY ACS (Targeted platelet Inhibition to clarify the Optimal strategy to medically manage Acute Coronary Syndromes), initiated in June 2008, was a 10,300 patient, multi-center, double-blind, randomized, controlled trial evaluating the safety and efficacy of Effient against Plavix in reducing the risk of cardiovascular death, heart attack or stroke in ACS patients who were medically managed without a planned artery-opening procedure. Patients randomized to Effient received a 30mg loading dose and then either a 10 mg or 5 mg maintenance dose depending on weight and age, or a Plavix 300mg loading dose followed by 75 mg maintenance dose. TRILOGY had a superiority design and was modified to include cancer screening as a result of TIMI 38.

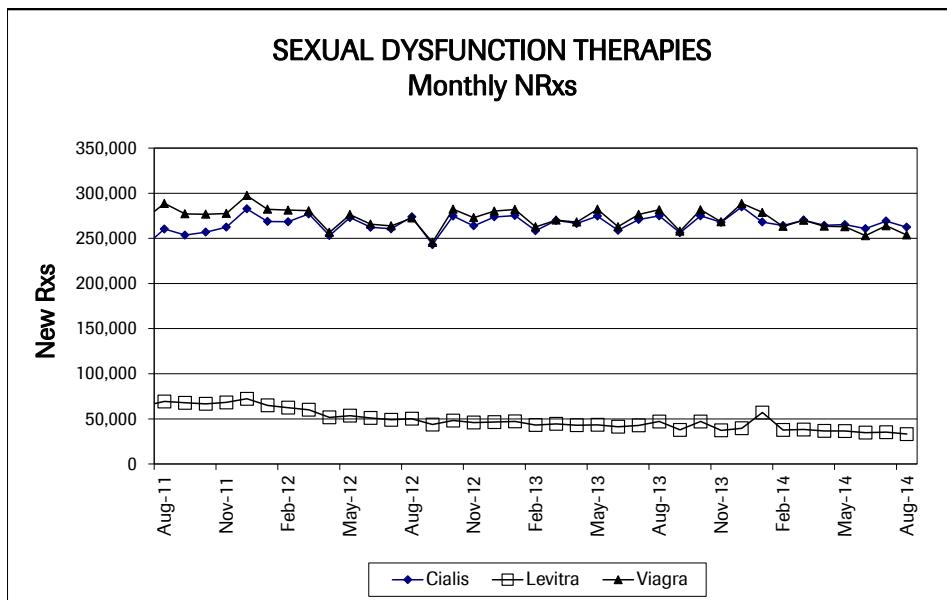
Lilly presented results from TRILOGY at ESC 2012. Effient did not meet its primary endpoint of demonstrating superior CV event reduction compared to Plavix. At 30 months, 13.9% of patients on Effient versus 16.0% of patients on Plavix had experienced the combined primary endpoint of MI, stroke, or CV death (HR=0.91, 95%

CI 0.79-1.05, p=0.21). The rate of serious bleeding was not statistically different between treatment groups (3.3% on Effient vs. 2.1% on Plavix, p=0.27). However, rates of TIMI major or minor bleeding were significantly higher in patients on Effient compared to those on Plavix (HR=1.54, 95% CI 1.06-2.23, p=0.02). Inability to penetrate the large medically managed ACS population significantly clips Effient's potential.

Dosing Flexibility Has Boosted Cialis to a Tie For Leadership In U.S. Market Share

Lilly has focused its marketing message on Cialis's dosing flexibility. As Cialis has efficacy up to 36 hours post dosing, and no interaction with high-fat meals, Lilly has portrayed Cialis as the option that allows the most spontaneity. This message has made Cialis a co-leader in the U.S. market

Sexual Dysfunction Therapies



Source: IMS America

In January 2008, the FDA approved chronic daily 2.5mg and 5mg doses of Cialis for the treatment of erectile dysfunction. Viagra and Levitra are unsuitable for daily-dosing. Cialis QD has been launched worldwide. The wholesale price for Cialis once daily is comparable to Cialis for use as needed. Lilly believes this dosing scheme is attractive to the 5-10% of men who are the most frequent users of on-demand Levitra and Viagra. As such patients typically generate significantly more revenue than the average patient, enticing them to switch to Cialis is a sustainable competitive advantage. In particular, Lilly believes that even on the cut-price daily version of Cialis, each patient would generate about 50% more revenue to Lilly than the average user. In March 2008, it was announced that Sanofi would help promote Cialis to U.S. urologists. We project Cialis sales of \$2,290MM (+6%) in 2014, \$2,400MM in 2015, \$2,510MM in 2016, \$1,075MM in 2018, and \$715MM in 2020, post the 11/17 patent expiration.

The following table depicts key attributes of Cialis, Levitra, and Viagra. Given that all of the drugs function via a common mechanism of action, pharmacokinetics and pharmacodynamics differentiate them. Cialis' rapid onset, high degree of selectivity,

and dosing convenience (long duration of action and lack of food interaction), carve out a unique position for it among the PDE5 inhibitors.

PDE5 Inhibitor MED Drugs

Attribute	Cialis	Levitra	Viagra	Comment
Time to onset of action	16 min.	NA	11 min.	Likely to be relatively similar for all drugs
t ½ (h)	16-20	4	4	Cialis' available as a daily regimen
Food Interaction	No	Yes	Yes	Impacts drug absorption
Duration of action	Yes	NA	NA	Longer half-life provides for larger window of effect (intercourse >1 in 24h period)
IC ₅₀ (nM) for PDE5*	1	0.7	6	Target enzyme in corpus cavernosum muscle of penis
IC ₅₀ (nM) for PDE6*	780	157	10	PDE isoform in retina
IC ₅₀ (nM) for PDE1*	>10,000	180	80	PDE isoform believed to mediate flushing
Most common side effects	Headache/dyspepsia	Headache/flushing	Headache/flushing	Differential selectivity causes different side effect profile
Nitrate interaction	Yes	NA	Yes	Inhibition of other PDEs potentiates effects of nitrates

Source: Cowen and Company, Company data. *Low numbers imply greater affinity for enzyme

Licensing Agreement With Sanofi For OTC Cialis

In May 2014, Lilly entered into an agreement with Sanofi to pursue regulatory approval for OTC Cialis (tadalafil). Sanofi acquired exclusive rights to apply for approval and market Cialis OTC in the U.S., E.U., Canada, and Australia. Sanofi would provide Cialis OTC after the patent expiration.

Cialis Approved For BPH

Lilly targets patients with both BPH and ED. In the U.S. 50% of men with ED also have BPH and Cialis may offer an alternative for men who do not receive a benefit from current BPH therapy. Cialis' BPH is also approved in Japan. FDA approved the 5mg dose of Cialis for the concurrent treatment of BPH and ED.

Adcirca Approved For PAH

In November 2008, Lilly licensed the U.S. rights for Adcirca (tadalafil) to United Therapeutics and took a \$150MM equity stake in the company. In May 2009, FDA approved Adcirca with a recommended dose of 40mg once-daily. Data presented at ESC 2008 and CHEST 2008 demonstrated that tadalafil 40mg, taken once daily, was well tolerated and improved exercise capacity, HRQoL, and delayed time to clinical worsening. Adcirca's extended half-life allows once-daily dosing compared to approximately 3x daily dosing with Pfizer's Revatio. Adcirca was launched with a WAC of \$15.20/pill (compared to branded Revatio's \$41.64/day), although competition from generic Revatio could narrow the pricing gap. Adcirca's pricing translates to about \$5,472 per patient per year. This is about 18% of the price of the endothelin antagonists.

Evacetrapib Could Be Successful On LDL Reduction Alone

Evacetrapib, a CETP inhibitor, lowers LDL by 18-40% and Lilly believes it can be successfully developed and approved on LDL reduction alone. An interim look upon achieving 75% of CV events may take place in Q1:2015 in the event-driven Phase III

ACCELERATE trial (n=12,000; enrollment complete). ACCELERATE, a study in patients at risk of a second CV event, is expected to finish in January 2016. Evacetrapib enjoys a short terminal half-life unlike MRK's anacetrapib, which takes weeks to clear, problematic should safety issues arise. While Lilly does include angina as an endpoint in ACCELARATE, the study could be successful even without the benefit of this component. Lilly believes it and Merck are about 6 months apart in the CETP inhibitor race. We estimate evacetrapib sales of \$50MM in 2016, \$150MM in 2018, and \$250MM in 2020.

CNS

Cymbalta In Decline Post Launch Of Generics In U.S.

Cymbalta (duloxetine; SNRI) is marketed for acute and maintenance treatment of MDD, diabetic peripheral neuropathic pain (DPNP), fibromyalgia (FMS) and generalized anxiety disorder (GAD) in the U.S. and for MDD and DPNP in the E.U. Cymbalta is co-marketed in Japan by Shionogi where it was approved for MDD in 2009. Cymbalta lost exclusivity in December 2013 (U.S.), and in the E.U. in August 2014 and loses exclusivity in Japan in January 2018. There is an authorized generic on the U.S. market. Lilly does not expect generics to enter the E.U. market until 2015. We estimate Cymbalta sales of \$1,520MM (-70%) in 2014, \$910MM in 2015, \$445MM in 2016, \$300MM in 2018, and \$250MM in 2020.

Cymbalta is differentiated from other SNRI's because of an approval in DPNP and FMS. Lilly estimates that 15-20% of prescriptions are for DPNP and that approximately 2-3MM diabetic patients in the U.S. currently experience painful symptoms of DPNP. DPNP is a smaller market than depression but growing more rapidly (+15-20%). Cymbalta's claim for fibromyalgia was supported by five clinical trials enrolling approximately 1,400 patients in total. There is a mood component in 80% and MDD in 30% of FMS patients.

Zyprexa Decline Continuing

We forecast Zyprexa sales of \$1,005MM (-16%) in 2014, \$815MM in 2015, \$685MM in 2016, \$480MM in 2018, and \$285MM in 2020. The U.S. patent expired in October 2011 and mid-2011 in major foreign markets. Generics have been launched in many markets. Exclusivity in Japan ends in 12/15.

In Q1:09, Lilly launched Zyphadera, Zyprexa's four-week depot formulation, in several European countries and in December 2009, FDA approved Zyprexa Relprevv. Relprevv can be initiated without oral supplementation, an advantage over JNJ's Consta. However, our physician consultants would rather deal with the extrapyramidal side effects of Risperdal Consta over the metabolic disturbances associated with Zyprexa, in long-acting formulations. Consta and paliperidone palmitate can be given as gluteal and deltoid injections which is an advantage over the gluteal-only route for LAI. Risperdal Consta has no hepatic clearance and can therefore be used in a broader patient population without concern.

Strattera Patent Victory To Maintain Franchise Through 2017

On August 12, 2010 the U.S. District Court for the District of New Jersey ruled that Strattera's '590 method-of-use patent was invalid. Actavis, Apotex, Aurobindo, Mylan, Sandoz, Sun, and Teva each submitted an ANDA seeking permission to market generic versions of Strattera prior to the expiration of the '590 patent (expiring 2017),

and alleged that this patent was invalid. In July 2011, the Court of Appeals for the Federal Circuit overturned this decision, upholding the patent. In October 2011, the Federal Circuit Court of Appeals denied the generic manufacturers' petition for a rehearing en banc. Straterra now looks positioned to maintain exclusivity through May 2017. We forecast worldwide Straterra sales of \$715MM (+1%) in 2014, \$710MM in 2015, \$720MM in 2016, \$245MM in 2018, and \$135MM in 2020 post the 05/17 patent expiration.

With the favorable court ruling, Straterra prescription shares are starting to improve (from 44.8% in May 2012 to 45.6% in August 2014). Lilly had focused upon more careful patient selection, specifically in teens and adults, and high-risk behavior in inattentive teens, which occurs outside of school, representing a potential advantage for Straterra's 24-hour control. ADHD patients that also suffer from anxiety may be an attractive market niche for Straterra, given that stimulant use is contraindicated for patients suffering from anxiety. Straterra marketing efforts targeting adults focused on patients with a prior history of abuse and/or impulsive behavior, where stimulants frequently are avoided. In May 2008, Straterra was approved for the maintenance treatment of ADHD in children and adolescents. Straterra has been launched in 66 countries including all major E.U. markets. Our E.U. physician experts view foreign markets as an opportunity, and they believe Straterra is viewed as best-in-class given a cultural aversion to stimulants in the E.U. However, market penetration has been slow as ADHD is under-diagnosed in the E.U. In Q2:13, Straterra received E.U. approval for use in adult ADHD, becoming the first drug approved in the E.U. for this indication.

EXPEDITION 3 Trial Of Solanezumab Under Way

Lilly announced that, based on discussions with regulators, it will not file solanezumab in the U.S. based on the EXPEDITION 1 and 2 trials and will conduct an additional Phase III trial. Lilly does not plan to submit for conditional marketing authorization in the E.U. based solely on existing analyses of the data from EXPEDITION 1 and 2. The decision is consistent with physician expert commentary that a minimum of a 3 point change in ADAS-Cog is necessary to be clinically meaningful and that solanezumab's ~2 point change in ADAS-Cog is of debatable clinical relevance. The EXPEDITION-3 trial will focus on mild patients and only those with amyloid pathology. The primary endpoints will be ADAS-Cog14 and ADCS-instrumental ADL, which the company believes is more appropriate for mild Alzheimer's patients. Given that Lilly required 3 years to enroll and execute the EXPEDITION trials (~2,000 patients), we believe an additional trial is unlikely to generate Phase III data before 2017. The study is currently 50% enrolled and Lilly targets trial completion by the end of 2016. We do not include sales for solanezumab in our Lilly model. Lilly believes that, should EXPEDITION 3 show the same results as EXPEDITION 1 and 2, then that should be sufficient for solanezumab (Alzheimer's) approval in the U.S.

Solanezumab Failed To Impress In Initial Phase III Trials

In October 2012, Lilly announced that solanezumab (Alzheimer's) failed to meet the primary cognitive and functional endpoint in either of its Phase III EXPEDITION trials. However, a prespecified secondary analysis of pooled mild-to-moderate data showed a statistically significant slowing of cognitive decline driven by patients with mild Alzheimer's disease (additional subanalysis where completed that showed improvement in mild patients, moderates showed no improvement). The ongoing extension study will continue as planned.

Solanezumab Yields Small Changes in Cognitive Function

Placebo treated patients experienced a decline in ADAS-Cog of approximately 4-5 points after 18-months and solanezumab demonstrated a 1-1.7 point improvement in ADAS-Cog relative to placebo, but these patients still experienced a decline. Our physician consultants believe a minimum of a 3 point difference in ADAS-Cog is required to be clinically meaningful. Absolute differences across various sub-analyses are presented below:

Efficacy Summary For Solanezumab's Phase III EXPEDITION Program

	EXPEDITION-1*		EXPEDITION-2**		EXPEDITION-1&2***	
	Mild	Mild+Moderate	Mild	Mild+Moderate	Mild	Mild+Moderate
Δ ADAS-Cog	NP	1	1.6	1.39	NP	1.41
ADAS-Cog p-value	0.007	0.12	0.08	0.06	0.0008	0.009
Δ ADCS-ADL	NP	0.19	NP	1.34	NP	NP
ADCS-ADL p-value	0.3	0.84	0.04	0.12	0.04	0.3
ADCS-iADL p-value	0.49	0.79	0.03	0.14	0.03	0.41

*primary ADAS-Cog endpoint for EXP1 was ADAS-Cog 11

**ADAS-Cog endpoint for EXP2 was ADAS-Cog14

***EXP1&2 depicts ADAS-Cog14; NP= not provided

Source: ANA 2012

Lack of Relationship Between Cognitive and Functional Improvement

Interestingly, functional changes were not observed in the mild cohort from EXPEDITION-1, which is the cohort that drove the improvement in ADAS-Cog. Similarly, functional changes were observed in mild patients from EXPEDITION-2 where cognitive improvement was not observed.

Solanezumab Appears Well Tolerated

There were no “MedDRA preferred term” events where the overall rate was ≥2% and the event rate in the combined solanezumab arms was at least 2x the rate of the placebo arm. A summary of adverse events from EXPEDITION-1&2 is presented below:

Safety Summary For Solanezumab's Phase III EXPEDITION Program

	Solanezumab (n=1,027)	Placebo (n=1,026)
ARIA E	9 (0.9%)	4 (0.4%)
ARIA H	50 (4.9%)	57 (5.6%)
Hemorrhagic stroke	8 (0.8%)	5 (0.5%)
Non-hemorrhagic stroke	10 (1%)	12 (1%)
Subarachnoid hemorrhage	3 (0.3%)	2 (0.2%)
Cardiac arrhythmias	51 (5%)	38 (3.7%)
Cardiac ischemia	18 (1.8%)	12 (1.2%)

Source: ANA 2012

Biomarker Data Mixed

Lilly presented biomarker data from solanezumab's Phase III EXPEDITION trials at CTAD 2012. Solanezumab-mediated increases in plasma Abeta 1-42/1-40 ratios were suggestive of target engagement; LLY and ADCS analyses are generally consistent on this measure. Placebo treated patients showed a numerical increase whereas solanezumab treated patients showed a numerical decrease in CSF Abeta as measured by Amyvid scans (12% of all patients received Amyvid scans). No differences in downstream markers, including CDR-SB (LLY analysis shows slight trend towards benefit with solanezumab in mild patients), p-Tau, or volumetric MRI, were observed by ADCS investigators. Amyvid-positive and mild patients treated with

solanezumab showed a trend toward decreased hippocampal volume as measured by MRI.

A β p3-x Antibody and Solanezumab May Be an Ideal Combination for the Prevention and Treatment of AD

Our physician experts believe an ideal drug for the prevention and treatment of Alzheimer's disease (AD) should target pre-existing plaques and prevent new plaques from forming. In December 2012, DeMattos, *et al.* (Lilly Neuroscience) published a paper in Neuron describing a novel A β p3-x plaque-specific antibody in a mouse model of AD. A β p3-x demonstrated superior efficacy in removing pre-existing plaques from neurons compared to bapineuzumab (PFE/JNJ/ELN), but did not prevent the deposition of new plaques. While antibodies such as solanezumab have shown only limited efficacy in removing existing neuronal plaques, solanezumab prevents soluble monomers from forming new plaques. A β p3-x and solanezumab appear to have a benign safety profile and have not been associated with vasogenic edema. Our physician consultants believe the combination of A β p3-x and solanezumab provides an ideal combination for the secondary prevention and treatment of Alzheimer's disease. Phase I trials for A β p3-x were expected to start at year end 2013. Our physician experts believe an 18-month trial may be sufficient given A β p3-x's promise in mild-to-moderate disease.

High Plaque Burden In Mild-To-Moderate AD A Challenge For Existing Antibodies, But...

DeMattos, *et al.* demonstrated that a majority of bapineuzumab (or CD6) is saturated by interstitial A β and is unable to bind to and remove existing plaques, limiting its efficacy in the presence of high plaque burdens such as in mild-to-moderate AD. CD6 was very effective in limiting the deposition of new plaques in a prevention model of AD; however, A β p3-x was ineffective in prevention mode. While the authors did repeat the same experiments with solanezumab, the results are unlikely to be dramatically different from bapineuzumab.

...A β p3-x Appears Very Effective In Targeting Pre-Existing Plaques

A plaque specific antibody such as anti A β p3-x target A β in existing plaque without microhemorrhage. Given that all patients with diagnosable AD, be it prodromal or mild-to moderate disease, have significant plaque burden at the time of diagnosis, an antibody such as A β p3-x (which removes plaques) is required to improve cognition and function.

Solanezumab and A β p3-x Likely an Effective Combination for the Prevention and Treatment of Alzheimer's Disease

Given that neither solanezumab nor A β p3-x is associated with vasogenic edema, our physician experts believe solanezumab and A β p3-x could be combined without significant toxicity. Our physician experts believe the ability of A β p3-x to remove existing plaques and solanezumab's efficacy in plaque prevention could produce the most effective treatment regimen to date.

Lilly To Collaborate With AstraZeneca On BACE Inhibitor

In September 2014, Lilly announced an agreement with AstraZeneca to co-develop and commercialize AZD3293, an oral BACE inhibitor for Alzheimers that has completed Phase I trials. The phase I studies demonstrated that AZD3293 reduces

beta-amyloid in the CSF of Alzheimers patients and healthy volunteers. Lilly will pay AZN \$50MM upfront and up to \$500MM in development and regulatory milestones. Lilly will lead clinical development and Astra will be responsible for manufacturing. The two companies will share costs equally for development and commercialization and net-revenues post-launch. The companies intend to quickly initiate Phase II/III trials in early Alzheimers.

CGRP Antibody Targets Migraine

In January 2014, Lilly acquired back all development rights for a calcitonin gene-related peptide (CGRP) antibody from Arteaus Therapeutics, based on positive Phase II study results. CGRP-antibody is being evaluated for the prevention of frequent, recurring migraine headaches. CGRP-antibody binds/inhibits the activity of CGRP which is a sensory neuropeptide with vascular and pro-inflammatory effects. Lilly had licensed the CGRP-antibody to Arteaus in 2011 to develop the molecule through proof-of-concept stage. Lilly incurred a Q4:13 pre-tax charge of \$57MM related to the acquisition. Lilly plans to do additional Phase II dosing and formulation studies before moving to Phase III in migraine. Studies will also be initiated in osteoarthritis.

Amyvid Is First Approved Diagnostic Agent For Detection Of Beta-Amyloid In AD But Reimbursement Limitations Dampen Outlook

Avid Radiopharmaceuticals was a molecular diagnostics company that developed molecular imaging compounds intended for the detection and monitoring of chronic diseases. Avid's lead program was Amyvid (florbetapir F-18, 18-F-AV-45) for the detection of amyloid plaques in the brain. In April 2012, the FDA approved Amyvid for use in patients being evaluated for Alzheimer's disease and other causes of cognitive decline. Through the acquisition of Avid, Lilly also acquired a diagnostics platform with novel compounds for the detection and monitoring of diabetes and Parkinson's disease. Lilly purchased all outstanding Avid shares with an upfront payment of \$300MM. Avid shareholders will be eligible for \$500MM in additional payments contingent upon certain commercial and regulatory milestones for Amyvid. In a Phase III study Amyvid -PET image scoring was the median rating of all readers and demonstrated a significant correlation with post-mortem AD diagnosis and regional plaque burdens. While grading the severity of disease with this method may be challenging and show variability between readers, a more simplified diagnosis of amyloid positive or negative appears robust.

In late September 2013, CMS (Centers for Medicare & Medicaid Services) finalized its decision on reimbursement for Amyvid and determined that evidence to date does not support routine use of Amyvid for diagnosing Alzheimer's or other memory disorders. CMS recommends payment (estimated at \$3,000 per test) only for use of Amyvid in scans that are part of clinical trials and are used to help demonstrate a measurable benefit in outcomes or an improved therapeutic approach. CMS states there are evidentiary gaps that must be reconciled prior to reevaluating its coverage decision.

Oncology

Alimta A Major Player In NSCLC; Favorable Patent Ruling Extends Exclusivity In U.S.

In September 2008, Alimta, in combination with cisplatin, received FDA approval for first-line treatment of locally advanced or metastatic NSCLC of non-squamous histology. Alimta is also approved for mesothelioma and second-line NSCLC. In Europe, Alimta was approved for first-line therapy of non-squamous histology.

In July 2009, Alimta was approved in the U.S. and E.U. as a maintenance therapy for locally advanced or metastatic NSCLC specifically with non-squamous histology. However, in September 2012 Lilly reported that Alimta's Phase III POINTBREAK study, evaluating the maintenance use of Alimta, did not meet its primary endpoint of overall survival vs. paclitaxel ($HR=1.0$, $p=0.949$) and significantly more drug-related grade 3-4 adverse drug events occurred in the Alimta arm. In June 2013, Lilly announced that the addition of Alimta to Avastin-containing regimens failed to demonstrate a PFS, OS, ORR, or DCR improvement compared to Avastin/carboplatin induction followed by Avastin maintenance in the Phase III PRONOUNCE study.

Avastin remains the global leader in 1st-line NSCLC (estimated 40% WW share) and sees opportunities to grow in the maintenance market. Lilly's vitamin dosage regimen patent, which expires in 2022, was upheld by an April 2014 U.S. District Court ruling, although Teva has appealed. In the U.K., the patent was denied. We now expect generics in 2019. We estimate Alimta sales of \$2.86B (+6%) in 2014, \$3.05B in 2015, \$2.85B in 2016, \$2.48B in 2018, and \$835MM in 2020.

Vitamin Dosage Patent 7,772,209 Upheld In U.S., Giving Alimta Exclusivity Through 2022

Alimta's 932 compound patent expires in July 2016 (2017 with pedi exclusivity). In July 2011, the district court entered judgment in Lilly's favor, upholding the compound patent's validity. In August 2012, the U.S. Court of Appeals for the Federal Circuit (CAFC) affirmed the district court's judgment. Teva and APP filed a petition for en banc review of the CAFC's decision, but this petition was denied.

A new use-patent covering associated vitamin dosage regimens— expiring in 2022 in the U.S. and 2020 in the E.U. — was issued (7,772,209). Teva, Barr, Pliva, Accord, and APP filed litigation challenging the 209 patent that covers the co-administration of an antifolate with a methylmalonic acid lowering agent to prevent premetrexed-associated toxicities. A claim regarding the “effective amount of folic acid and methylmalonic acid lowering agent” is disputed as being indefinite. Additionally, several claims within the patent preamble have been challenged. 209 was the subject of a trial in the U.S. District Court for the Southern District of Indiana in August 2013 (involving Teva, APP, Pliva and Barr). In April 2014, the court upheld Lilly's patent, giving Alimta exclusivity until 2022 (with pediatric extension). An appeal has been filed, but is not viewed as a near term risk. The Accord/Apotex cases were consolidated but their trial has been stayed pending resolution of appeal.

The current Alimta label states:

Prior to treatment with Alimta initiate supplementation with oral folic acid and intramuscular vitamin B₁₂ to reduce the severity of hematologic and gastrointestinal toxicity. Instruct patients to initiate folic acid 400 mcg to 1,000 mcg orally once daily beginning 7 days before the first dose. Continue folic acid during the full course of therapy and for 21 days after the last dose. Administer vitamin B₁₂ 1 mg intramuscularly 1 week prior to the first dose and every 3 cycles thereafter. Subsequent vitamin B₁₂ injections may be given the same day as treatment with Alimta. Do not substitute oral vitamin B₁₂ for intramuscular vitamin B₁₂. Administer dexamethasone 4 mg by mouth twice daily the day before, the day of, and the day after Alimta administration.

In Europe, the compound patent expires December 2015 and the vitamin regimen patent expires June 2021. Generic manufacturers filed an opposition to EPO's decision to grant the vitamin dosage patent. The Opposition Division upheld the patent, and

the generic manufacturers (Actavis and others) appealed. In May 2014, the English High Court ruled against Lilly on the vitamin dosage patent. The English court also granted similar non-infringement declaration in France, Italy, and Spain. Lilly has filed an appeal. A similar case against Actavis was heard in Germany in March 2014, and in April 2014, the German trial court ruled in Lilly's favor. The generics have appealed the decision.

Alimta Targeting NSCLC and Other Opportunities

Every year, about 100K patients in the U.S. receive first-line therapy for advanced NSCLC. Alimta is likely only to be used in non-squamous patients (55-75% of patients), leaving on average 67K patients as candidates. The addition of maintenance and second line therapies creates a combined opportunity of roughly the same size. Physicians might use the same drug in the first line and as maintenance treatment but they rarely use the same drug in both first and second line NSCLC. This brings Alimta's market potential to approximately 100K treatments per year at approximately \$20-25K per treatment, just in the U.S. A Phase II study to customize first-line chemotherapy with Alimta in head and neck cancer is underway.

Alimta Market Share In Non-Squamous NSCLC

	1st-Line	Maintenance	1st-Line Pts. Receiving Maintenance
E.U.*	45-62%	62-74%	21-57%
U.S.	39%	79%	60%
Japan	73%	77%	43%

*France, Germany, Italy, Spain, and U.K.

Source: Eli Lilly

Alimta 1st Line NSCLC

Efficacy of ALIMTA + Cisplatin vs. Gemcitabine + Cisplatin in First-Line Non-Small Cell Lung Cancer – ITT Population and Histology Subgroups.

ITT Population and Histology Subgroups	Median Overall Survival in Months (95% CI)			Adjusted Hazard Ratio (HR) (95% CI)	Superiority p-value
	ALIMTA + Cisplatin	Gemcitabine + Cisplatin	N		
ITT Population (N = 1725)	10.3 (9.8 – 11.2)	N=862	10.3 (9.6 – 10.9)	N=863	0.94a (0.84 – 1.05)
Adenocarcinoma (N=847)	12.6 (10.7 – 13.6)	N=436	10.9 (10.2 – 11.9)	N=411	0.84 (0.71–0.99)
Large Cell (N=153)	10.4 (8.6 – 14.1)	N=76	6.7 (5.5 – 9.0)	N=77	0.67 (0.48–0.96)
Other (N=252)	8.6 (6.8 – 10.2)	N=106	9.2 (8.1 – 10.6)	N=146	1.08 (0.81–1.45)
Squamous Cell (N=473)	9.4 (8.4 – 10.2)	N=244	10.8 (9.5 – 12.1)	N=229	1.23 (1.00–1.51)

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = total population size.

a Statistically significant for noninferiority, with the entire confidence interval for HR well below the 1.17645 noninferiority margin (p <0.001).

Source: EMEA Gemzar Label

Cyramza Approved In Second Line Gastric Cancer

In April 2014, Cyramza (ramucirumab), a VEGF r2 antagonist, was approved in the U.S. for use in 2nd-line gastric cancer. Cyramza has orphan drug status (estimated 22,000 patients will be diagnosed with gastric cancer in the U.S in 2014); it will be priced at an average cost of \$24,000/patient (4 doses). Ramucirumab was filed in the E.U. in Q4:13 and is expected to be filed in Japan later this year.

Ramucirumab is also under evaluation in other cancers. In June 2014, full Phase III data for second-line NSCLC (REVEL) was presented; ramu met its primary endpoint of OS, although the 1.4 month benefit and HR of 0.857 were not as strong as our physician experts had hoped. Cyramza met its primary OS endpoint in the Phase III, second line CRC trial RAISE. Full data will be presented in 2015 and regulatory submissions will be made in H1:15. In June 2014, Lilly announced that Cyramza did not meet its primary endpoint of OS in second-line HCC (REACH). We estimate Cyramza sales at \$60MM in 2014, \$200MM in 2015, \$500MM in 2016, \$1,000MM in 2018, and \$2B in 2020.

REVEL Data To Support H2:14 Filing In NSCLC

The REVEL trial of ramucirumab in combination with chemo in second-line non-small cell lung cancer (NSCLC), showed a statistically significant improvement in the primary endpoint of overall survival in the ramucirumab plus docetaxel arm compared to the control arm of placebo plus docetaxel (10.5 months vs. 9.1; HR 0.857, p=0.023). REVEL also showed a statistically significant improvement in median PFS in the ramucirumab arm of 4.5 months vs. 3.0 for docetaxel (HR 0.76). The study included 1,253 non-squamous and squamous patients. The most common adverse events were decreased white blood cell count (neutropenia/ leukopenia), febrile neutropenia, fatigue/asthenia and hypertension. Lilly plans to file on these data in 2014. There are about 30K refractory NSCLC patients in the U.S. each year. Assume a similar number in the E.U. and 50% penetration at \$50K per treatment course, Cyramza could generate \$1.5B in this tumor type alone, assuming the data is clinically convincing in addition to statistically significant.

Cyramza Development Program

Study	Primary Endpoint	Scheduled Completion Date
NSCLC: A Study of Chemotherapy and Ramucirumab vs. Chemotherapy Alone in Second Line Non-small Cell Lung Cancer Participants Who Received Prior First Line Platinum Based Chemotherapy (REVEL); n=1,253; Docetaxel +/- ramu 10mg/kg q3wks	Overall survival	January 2014 Met primary endpoint Will file based on this trial
Gastric: A Study of Paclitaxel With or Without Ramucirumab in Metastatic Gastric Adenocarcinoma (RAINBOW); n=665	Overall survival	October 2013 Met primary endpoint
HCC: A Study of Ramucirumab (IMC-1121B) Drug Product (DP) and Best Supportive Care (BSC) Versus Placebo and BSC as 2nd-Line Treatment in Patients With Hepatocellular Carcinoma After 1st-Line Therapy With Sorafenib (REACH); n=544; BSC +/- ramu 8mg/kg q2wks	Overall survival	August 2013 Did not meet primary endpoint
CRC: A Study in Second Line Metastatic Colorectal Cancer (RAISE); FOLFOX/bevacizumab resistant; n=1,050; FOLFOX +/- ramu 8mg/kg q2wks	Overall survival	September 2014 Met primary endpoint
Gastric: Study of IMC-1121B (Ramucirumab) With Best Supportive Care in Patients With Gastric Cancer and Adenocarcinoma (REGARD)	Overall survival	July 2012 Met primary endpoint
Breast Cancer: Phase III Study of Docetaxel + Ramucirumab or Placebo in Breast Cancer (ROSE)	Progression free survival	February 2013 Did not meet primary endpoint

Source: clinicaltrials.gov, Company data

Cyramza Met Endpoint In Combo 2nd-Line RAINBOW Gastric Study

Ramucirumab + paclitaxel succeeded in the Phase III RAINBOW trial for advanced gastric cancer on the primary endpoint of OS. Ramucirumab had already succeeded for advanced gastric cancer in 2012 in the separate REGARD study. REGARD compared ramucirumab vs. best supportive care, arguably a weak comparator, and met its OS endpoint only narrowly (p = 0.047). Data presented in January 2014 for RAINBOW, showed that ramucirumab + paclitaxel improved OS by 2.2 months (from 7.4 to 9.6, p = 0.0169). Full data, shown below, was released in September 2014. With approximately 10,000 deaths from gastric cancer annually in the U.S. alone, ramucirumab appears to have at least multi-hundred million dollar potential in this indication.

Summary Of Ramucirumab Efficacy Data in RAINBOW

	Ramucirumab + Paclitaxel	Placebo	p-value
OS	9.6 months	7.4 months	0.0169
PFS	4.4 months	2.9 months	<0.0001
ORR	28%	16%	0.0001

Source: Company data

Summary Of Ramucirumab Safety Data in RAINBOW

	Ramucirumab + Paclitaxel	Placebo
Neutropenia	41%	19%
Leukopenia	17%	7%
Hypertension	15%	3%
Fatigue/asthenia	12%	5%

Source: Company data

Cyramza Benefit In Gastric Cancer Small In REGARD Study

Data from ramucirumab's Phase III gastric cancer trial (REGARD) narrowly met its primary endpoint of improved OS versus best supportive care ($p=0.0473$), but its modest 1.4 month OS benefit is of debatable clinical meaningfulness. Ramucirumab also demonstrated a very modest improvement in PFS compared to placebo (2.1 months for ramucirumab vs. 1.3 months for placebo). Grade ≥ 3 adverse events occurring more frequently on ramucirumab included hypertension, abdominal pain, hyponatremia, and fatigue. We believe a comparison to chemotherapy represents a much higher bar and may be required for approval in gastric cancer. Lilly has completed the U.S. and E.U. submissions based on REGARD for ramu as a single agent treatment for gastric cancer.

Summary Of Ramucirumab Efficacy Data in REGARD

	Ramucirumab	Placebo	p-value
OS	5.2 months	3.8 months	0.0473
PFS	2.1 months	1.3 months	<0.0001
12-week PFS	40%	16%	NA
Disease Control Rate	49%	23%	<0.0001
ORR	3.4%	2.6%	NA

Source: ASCO-GI Abstracts, Company data

Summary Of Ramucirumab Safety Data in REGARD

	Ramucirumab	Placebo	p-value
Hypertension	7.2%	2.6%	NA
Abdominal pain	5.1%	2.6%	NA
Hyponatremia	3.4%	0.9%	NA
Fatigue	4.2%	3.5%	NA
Ascites	4.2%	4.3%	NA
Decreased appetite	3.4%	3.5%	NA
Anemia	6.4%	7.8%	NA

Source: ASCO-GI Abstracts, Company data

CYRAMZA Phase III Second-Line Colorectal Cancer Trial Met Primary OS Endpoint

In September, LLY announced that the RAISE trial met its primary OS endpoint. RAISE studied ramucirumab in combination with chemotherapy in patients with second-line metastatic colorectal cancer. Ramucirumab plus FOLFIRI was compared to placebo plus FOLFIRI after bevacizumab, oxaliplatin and a fluoropyrimidine as first-line. The

study also showed a statistically significant improvement in PFS in the ramucirumab-plus-FOLFIRI arm compared to the placebo-plus-FOLFIRI arm. The most common (>5% incidence) grade >/=3 adverse events occurring more frequently in the ramucirumab arm included neutropenia, fatigue, hypertension, and diarrhea. LLY will present RAISE in 2015 with filings in H1:15.

Cyramza Misses Endpoint In HCC

In June 2014, Lilly reported that Cyramza demonstrated favorable, but not statistically significant, OS in patients with hepatocellular cancer. The company also reported improvements in secondary endpoints of PFS and ORR. Safety data was consistent with other trials. Lilly indicated that certain subpopulations responded more favorably. The company plans to share this data with the FDA.

Cyramza Not Successful In Breast Cancer

The Phase III ROSE trial of ramucirumab in breast cancer missed its primary endpoint of PFS. ROSE compared ramucirumab plus docetaxel vs. docetaxel alone in first-line, HER-2(-) metastatic breast cancer. PFS reported favored the ramucirumab arm, though not statistically significantly; the interim OS analysis showed no benefit. We view the failure of the breast cancer trial as a minor disappointment. Anti-angiogenic agents such as Roche's Avastin and AMGN/ONXX/Bayer's Nexavar have produced mixed to poor results in breast cancer in the past, suggesting it was unlikely that ramucirumab would succeed.

Necitumumab Phase III Meets OS Endpoint in Stage IV, Squamous NSCLC

A Phase III trial (SQUIRE) for necitumumab (EGFR inhibitor) in combo with gemcitabine and cisplatin (vs. chemo alone) in stage IV, metastatic, squamous NSCLC met its primary endpoint of increased OS. Reported OS was 11.5 months for the necitumumab arm versus 9.9 months for the control arm (HR of 0.84, p=0.012). However, both the 1.6 month benefit and the HR were below the targets anticipated by our physician experts, of 2 months and <0.80, respectively. The most common AEs were rash and hypomagnesemia; thromboembolism was also reported but less frequently. Thromboembolism was the reason for the halt in enrollment in two prior Phase II trials. Lilly plans to file for approval by the end of 2014. We forecast necitumumab sales of \$50MM in 2015, \$200MM in 2016, \$400MM in 2018, and \$600MM in 2020.

There are approximately 173K new cases of lung cancer each year in the U.S., of which approximately 85% is NSCLC. Approximately 30% of NSCLC patients have the squamous form, suggesting that there are 45K first-line squamous NSCLC patients in the U.S. each year. Assuming a \$65K/course price, necitumumab could represent a \$2B opportunity in the U.S. alone. Of course, penetration into that population will be dependent upon necitumumab's efficacy and side effects.

The randomized SQUIRE Phase III study enrolled 1093 patients with Stage IV squamous NSCLC who were treatment naïve for metastatic disease. Patients were randomized to either arm with necitumumab plus gemcitabine/cisplatin or to gemcitabine/cisplatin alone. Radiographic assessment of disease was done every six weeks until documentation of progressive disease (PD). Chemo continued for a maximum of six cycles in each arm (unless PD or toxicity occurred). The necitumumab arm produced a statistically significant improvement in overall survival compared to the control arm.

Enrollment in two Phase II studies in squamous cell NSCLC (INSPIRE and SQUIRE) was stopped following a DSMB review because of safety concerns related to an increase in thromboembolism in patients on necitumumab. The risk of thromboembolism was significantly less in patients who had already received at least two doses; these patients were permitted to complete the study. Investigators continued to assess patients after 2 cycles to determine if there is a benefit from therapy. Both studies have overall survival as a primary endpoint. Trials will remain ongoing in non-squamous cell lung cancers and solid tumors.

Erbitux To Decline Through 2017; Recover Thereafter

Lilly acquired Erbitux as part of its November 2008 acquisition of ImClone. Erbitux, a chimeric monoclonal antibody directed against the extracellular domain of the epidermal growth factor receptor (EGFR), inhibits EGF-mediated cell growth by blocking the receptor from binding EGF. Erbitux was first approved in 2004 for the treatment of irinotecan-refractory metastatic colorectal cancer (mCRC) patients, either in combination with irinotecan or as a monotherapy for those who are intolerant to chemotherapy. In June 2006, Erbitux was approved for the treatment of locally or regionally advanced SCCHN in platinum-resistant patients. In November 2011, the label was expanded to include first-line treatment of recurrent locoregional or metastatic SCCHN in combination with platinum-based therapy with 5-FU. In May 2012, FDA issued a complete response letter for Erbitux's application to expand its label to include first-line NSCLC. The CRL requested an additional trial showing an improvement in OS as well as a validated diagnostic biomarker to predict patient response to Erbitux. Lilly and Bristol do not plan to resubmit the application. In July 2012, the FDA approved Erbitux to be used with FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin) as a first line treatment for those with metastatic colorectal cancer with EGFR-expressing, and KRAS wild type tumors.

Lilly's agreement with U.S. partner BMY and E.U. partner Merck KgA both cease in 2018; LLY gains full economics in the U.S. (versus 35% royalty) but loses the royalty in the E.U. LLY indicated that this has positive implications for Erbitux profitability to LLY. We forecast WW Erbitux royalties to Lilly of \$330MM (+5%) in 2014, \$315MM in 2015, \$295MM in 2016, \$400MM in 2018, and \$760MM in 2020.

CALGB Study Showed No Difference Between Avastin and Erbitux in mCRC

A Phase III randomized study (CALGB/SWOG 80405) comparing Avastin to Erbitux, when used with combination chemo in mCRC KRAS wild-type was presented at ASCO 2014. The study showed no significant difference between the two arms. Median OS for the Avastin arm was 29.0 months vs. 29.9 months for Erbitux ($HR=0.925$, $p=0.34$). Median PFS was 10.8 months for Avastin vs. 10.4 months for Erbitux ($HR = 1.04$, $p=0.55$). No new adverse events were seen with either agent.

Olaratumab Moving Into Phase II

Olaratumab (IMC-3G3) is a monoclonal antibody targeting platelet-derived growth factor receptor alpha (PDGF R alpha). PDGF is found in tumor stroma and blood vessels. A Phase II study in ovarian and NSCLC cancer is under way. A Phase II study in glioblastoma is also under way. We estimate olaratumab sales of \$25MM in 2017, \$50MM in 2018, and \$100MM in 2020.

Other Oncology Priority Assets

CDK 4/6 Inhibitor (abemaciclib/LY2835219) – Under evaluation as single agent in breast, NSCLC, glioblastoma, melanoma, and colorectal cancers.. Lilly believes its CDK 4/6 inhibitor is distinguished by its ability to be dosed continuously whereas competitive products are dosed intermittently for toxicity reasons. If the toxicity is mechanism-based, the ability to dose continuously might signal lower efficacy. However, abemaciclib's different chemical structure (compared to Pfizer's palbociclib and Novartis' LEE011) may be the basis for the different toxicity/efficacy characteristics. We estimate abemaciclib sales of \$25MM in 2017, \$50MM in 2018, and \$100MM in 2020.

At ASCO 2014, Phase I data for abemaciclib in advanced NSCLC (n=57) was presented which demonstrated an overall 49% disease control rate. The DCR for patients with KRAS mutant-type was 55% versus 38% for KRAS wild-type. Lilly plans to initiate a Phase II biomarker study in NSCLC with abemaciclib + SOC vs erlotinib + SOC. A Phase I safety study in HR+ metastatic breast cancer of abemaciclib +fulvestrant was also presented. No major AEs were seen; grade 3 neutropenia and leukopenia were the most common side effects. By year end, Lilly will initiate a Phase II monotherapy trial (MONARCH-1) in previously treated HR+/HER2- breast cancer, and Phase II studies of abemaciclib + fulvestrant (MONARCH-2) and abemaciclib +letrazole or anastazole (MONARCH-3).

At AACR 2014, Phase I data for abemaciclib was presented. While based on small numbers, the data look quite good relative to palbociclib, and the discussant post the palbo presentation called some of the responses to the LLY drug striking. The LLY Phase I trial studied LY2835219 monotherapy in five different tumors types, including 47 patients with metastatic breast cancer who had received about seven prior therapies. All patients received the drug orally BID for 28 days until progression or significant side effects. Of the 47 patients with metastatic breast cancer, 36 were HR-positive. Nine (19%) had a partial response, and 24 (51%) had stable disease. Disease progressed despite treatment in 11 patients. All nine patients who had a partial response, and 20 of the 24 patients who had stable disease had HR-positive BC: partial response and stable disease rates were 25% and 55%. The disease control rate was 81% for HR-positive disease, and progression free-survival was 9.1 months.

c-Met Antibody – A bi-valent antibody which inhibits tumor growth by blocking HGF and degrading MET receptor. Phase I studies are ongoing in NSCLC, prostate cancer, RCC, uveal melanoma, and HCC cohorts. There are two Phase II trials ongoing in NSCLC, specifically targeting EGFR mutant populations. A companion diagnostic is in development with Dako. We estimate c-Met Mab sales of \$25MM in 2017, \$50MM in 2018, and \$100MM in 2020.

TGF-betaR1 – A potential first-in-class molecule that blocks TGF-beta signaling and modulates the immune system. A Phase I study has completed. Phase II studies initiated in hepatocellular carcinoma, 2nd-line glioblastoma multiforme and 1st-line pancreatic cancer in combo with gemcitabine. We estimate TGF-betaR1 sales of \$25MM in 2017, \$50MM in 2018, and \$100MM in 2020.

Immunocore Collaboration – In July 2014, Lilly entered into a collaboration with Immunocore to develop novel T cell-based cancer therapies using their Mobilising Monoclonal T-Cell Receptor Against Cancer (ImmTAC) technology. Immunocore received \$15MM upfront per program and potential royalty and milestone payments for developed products.

EPS To Decline In 2014, Strong Growth Expected 2015-17

Cymbalta Patent Expiration Challenges 2014

Cymbalta sales could be slashed by 70% to \$1.52B in 2014, post the June 2013 patent expiration and 6-month pediatric extension (LOE began in December 2013). In 2014, LLY revenues are forecast to decline 15% to \$19.69B. Gross margin is forecast to contract 5.7pp to 73.1%, SG&A to decline 12% to \$6.305B, and R&D to be down 18% to \$4.55B. Non-operating income is expected to increase to \$165MM reflecting gains from the sale of equity investments acquired as part of past business development transactions. The tax rate is estimated to remain stable at 19.1%, and shares outstanding decline by 14MM. With the acquisition of Lohmann Animal Health (closed April 2014), the company revised its 2014 guidance to reflect this transaction: revenue forecast raised \$200MM to \$19.4-20.0B and minimum net income lowered by \$100MM to \$2.9B for initial dilution. EPS guidance of \$2.72-2.80 remains unchanged.

LLY 2014 Guidance Vs. Cowen Estimates

	LLY Guidance	Cowen Estimates
Revenue	\$19.4-20.0B	\$19.69B
Gross P.M.	Approximately 73%	73.1%
SG&A	\$6.3-6.6B	\$6.305B
R&D	\$4.4-4.7B	\$4.55B
Other Income/(Expense)	\$100-200MM	\$165MM
Tax Rate *	Approximately 19%	19.1%
Minimum Net Income	\$2.9B	\$2.996B
EPS	\$2.72-2.80	\$2.80

* Assumes full year R&D tax credit; 2 points higher if not passed

Bold indicates update

Source: Cowen and Company

EPS Growth Of 20% Forecast For 2015, Although Novartis Animal Health May Limit Upside

We forecast a strong recovery in sales and EPS in 2015, driven by new products, acquisitions (including Novartis Animal Health; expected to close by end of Q1:15) and expense leverage. We estimate 2015 sales at \$20.975MM (+7%) which includes \$825MM from Novartis. The Novartis Animal Health acquisition (for \$5.4B cash) looks to be a good strategic fit, providing an expanded geographic footprint and a complementary product line (vaccines, aquaculture). We estimate LLY 2015 EPS at \$3.35 (+20%) with GPM expanding 3pp to 76.1% and operating margin rising 3.4pp to 21.4%. The Novartis Animal Health franchise operating margin of 18% is well below Elanco's 26% level, in part reflecting manufacturing plant issues. Lilly believes it can boost these margins up to Elanco's level, but this is unlikely to occur in year one, thus there could be some pressure on, or limited upside to, 2015 EPS. The Novartis transaction is expected to be accretive to LLY on a cash basis in 2016.

Strong Growth Continues In 2016-17, With Mid-Single Digit Gains In 2018-2020

We forecast 5% sales growth and 15-26% EPS growth in 2016-17, as new product top-line gains are enhanced by continuing expense leverage. All told, EPS are forecast to

grow 26% in 2016 and 15% in 2017 on 5% revenue expansion. We forecast 5% growth in EPS on a 2% revenue decline in 2018 (due to Cialis generics). Revenue growth of 3-6% is forecast for 2019-20 with 4% EPS growth. Lilly's forecast EPS growth rates in 2014-20 are above the industry average. Lilly's P&L framework for "years YZ," is a floor but generally below our expectations. Lilly guidance for the post-2014 period is summarized below. Consensus expectations are for Lilly achieving their SG&A and R&D spending targets in 2019. Our model assumes these levels can be attained in 2018.

Lilly "Years YZ" Guidance Versus Our Expectations

	LLY YZ Guidance	Cowen Last Published 2014 Estimates
Sales	~20B	\$19.69B
Gross P.M.	Mid 70%	73.1%
SG&A as a % of Revenue		32.0%
R&D as a % of Revenue	~25%	23.1%
Operating Expenses as a % of Revenue	Mid 50%	55.2%
Tax Rate	~25%	19.1%
Net Income	+\$3B	\$2.996B
Operating Cash Flow	+\$4B	\$5.5B
Capex	~\$900MM	\$1B
Dividend	+\$2B	\$2.1B

Source: Cowen and Company

Operating Margin Targets Post 2014

- SG&A — "Within a few years post 2014, move in line with industry average of 28-30% of revenue. Would be achieved by 2019"
 - Our models show 29.4-32.1% in 2015-20
- R&D — "Post 2014, return to levels more consistent with historical average of 18-20% of revenue. Would be achieved by 2019"
 - Our models show 18.7-22.6% in 2015-20

Source: Company data

Speculation On 2014-20P EPS Outcomes

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	'2013-16 CGR	'2013-20 CGR	'2014-20 CGR Comments
New Drugs	\$2.25	\$2.53	\$2.95	\$3.41	\$3.98	\$4.01	\$4.29	\$4.76	15%	11%	11% - Trajenta, Cyramza, Dulaglutide, Effient, novel insulins
Zyprexa	0.37	0.32	0.27	0.23	0.20	0.17	0.13	0.10	-15%	-17%	-17% - Drag on sales and EPS growth
In-Line Drugs	<u>1.18</u>	<u>(0.42)</u>	<u>(0.43)</u>	<u>(0.09)</u>	<u>(0.03)</u>	<u>0.19</u>	<u>0.11</u>	<u>(0.16)</u>	NM	NM	NM - \$6.6B 2020 vs. \$12.5B 2013
Total Drugs	3.80	2.42	2.78	3.55	4.15	4.37	4.53	4.70	-2%	3%	12%
Animal Health	<u>0.35</u>	<u>0.38</u>	<u>0.56</u>	<u>0.65</u>	<u>0.69</u>	<u>0.74</u>	<u>0.77</u>	<u>0.80</u>	23%	13%	13% - 18% of sales and 15% of EPS in 2020
LLY EPS -Diluted	\$4.15	\$2.80	\$3.35	\$4.20	\$4.85	\$5.10	\$5.30	\$5.50	0%	4%	12% - Versus +4%, +6% and +8% industry averages
% Change	+22%	-33%	+20%	+26%	+15%	+5%	+4%	+4%			

Source: Company reports, Cowen and Company

Eli Lilly 2013-20 Quarterly P&L Buildup (\$MM)

	Sales	% Chg	Gross P.M.	SG&A		R&D		Op. P.M.	Non-Op	Pretax P.M.	Tax Rate	Net Income	EPS (Dil.)	% Chg	Shares (MM)
	\$	%	%	\$MM	% SIs	\$MM	% SIs	%		%	%	\$	\$	%	\$MM
Q1	\$5,602	0%	79.3%	\$1,652	29.5%	\$1,348	24.1%	25.8%	\$34	26.4%	15.5%	\$1,248	\$1.14	24%	1092
Q2	5,930	6%	80.3%	1,868	31.5%	1,330	22.4%	26.4%	12	26.6%	20.5%	1255	1.16	40%	1084
Q3	5,773	6%	79.2%	1,652	28.6%	1,377	23.9%	26.8%	-31	26.2%	20.5%	1203	1.11	40%	1084
Q4	5,809	-2%	76.1%	1,954	33.6%	1,475	25.4%	17.1%	10	17.3%	20.5%	798	0.74	-13%	1085
2013	\$23,113	2%	78.8%	\$7,126	30.8%	\$5,531	23.9%	24.0%	\$24	24.1%	19.2%	\$4,504	\$4.15	22%	1086
Q1	\$4,683	-16%	73.9%	\$1,485	31.7%	\$1,109	23.7%	18.5%	\$56	19.7%	18.7%	\$749	\$0.70	-39%	1076
Q2	4,936	-17%	75.9%	1,664	33.7%	1,195	24.2%	18.0%	54	19.1%	22.0%	734	0.68	-41%	1076
Q3E	4,845	-16%	73.0%	1,400	28.9%	1,110	22.9%	21.2%	25	21.7%	22.0%	820	0.77	-31%	1070
Q4E	5,212	-10%	70.0%	1,756	33.7%	1,135	21.8%	14.5%	30	15.1%	12.0%	693	0.65	-12%	1065
2014E	\$19,690	-15%	73.1%	\$6,305	32.0%	\$4,550	23.1%	18.0%	\$165	18.8%	19.1%	\$2,996	\$2.80	-33%	1072
Q1E	\$4,745	1%	76.5%	\$1,530	32.2%	\$1,155	24.3%	19.9%	\$20	20.3%	21.0%	\$762	\$0.72	3%	1060
Q2E	5,370	9%	76.0%	1,755	32.7%	1,195	22.3%	21.1%	-15	20.8%	21.0%	882	0.84	23%	1055
Q3E	5,255	8%	76.0%	1,580	30.1%	1,195	22.7%	23.2%	-15	22.9%	21.0%	951	0.91	18%	1050
Q4E	5,605	8%	76.0%	1,875	33.5%	1,200	21.4%	21.1%	-15	20.9%	21.0%	924	0.88	36%	1045
2015E	\$20,975	7%	76.1%	\$6,740	32.1%	\$4,745	22.6%	21.4%	(\$25)	21.2%	21.0%	\$3,519	\$3.35	20%	1053
2016P	\$22,025	5%	76.5%	\$6,820	31.0%	\$4,500	20.4%	25.1%	(\$50)	24.9%	21.0%	\$4,329	\$4.20	26%	1030
2017P	\$23,120	5%	76.0%	\$6,950	30.1%	\$4,400	19.0%	26.9%	(\$20)	26.8%	21.0%	\$4,899	\$4.85	15%	1010
2018P	\$22,760	-2%	76.3%	\$6,685	29.4%	\$4,250	18.7%	28.2%	\$10	28.2%	21.0%	\$5,079	\$5.10	5%	995
2019P	\$23,480	3%	76.5%	\$6,930	29.5%	\$4,400	18.7%	28.2%	\$40	28.4%	21.0%	\$5,271	\$5.30	4%	995
2020P	\$24,805	6%	76.8%	\$7,400	29.8%	\$4,780	19.3%	27.6%	\$70	27.9%	21.0%	\$5,473	\$5.50	4%	995

Source: Company data, Cowen and Company.

Eli Lilly Quarterly Sales Dynamics (\$MM)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
New Drugs																
Alimta - U.S.	\$1,122	\$262	\$305	\$310	\$332	\$1,209	\$246	\$321	\$330	\$350	\$1,245	\$275	\$345	\$350	\$370	\$1,340
Alimta - ACE (lc, ex fx)									250	260		260	260	275	280	
Alimta - ACE	811	211	212	228	236	887	243	251	255	260	1,010	255	255	275	280	1,065
Alimta - Japan	386	74	79	77	88	318	77	66	80	90	315	85	70	85	95	335
Alimta - Emerging ROW	274	69	74	76	70	289	66	74	80	75	295	70	75	85	80	310
Alimta - Worldwide	\$2,594	617	669	691	726	\$2,703	\$632	\$712	\$745	\$775	\$2,865	\$685	\$745	\$795	\$825	\$3,050
Trajenta - U.S.	\$56	\$24	\$24	\$29	\$41	\$119	\$31	\$37	\$40	\$45	\$150	\$40	\$45	\$45	\$50	\$180
Trajenta - ACE (lc, ex fx)									20	25		25	25	30	30	
Trajenta - ACE	12	7	10	11	14	41	15	18	20	25	80	25	25	30	30	110
Tragenta - Japan	5	3	10	14	18	46	16	18	20	20	75	25	25	30	30	110
Trajenta - Emerging ROW	16	8	11	11	14	44	15	18	20	20	75	25	25	30	30	110
Trajenta - Worldwide	\$89	43	55	65	87	\$249	\$77	\$90	\$100	\$110	\$380	\$115	\$120	\$135	\$140	\$510
Forsteo - U.S.	\$488	\$112	\$116	\$128	\$156	\$511	\$101	\$128	\$140	\$170	\$540	\$110	\$140	\$150	\$180	\$580
Forsteo - ACE (lc, ex fx)									65	75		70	75	75	75	
Forsteo - ACE	249	65	70	64	71	270	68	67	65	75	275	70	75	75	75	295
Forsteo - Japan	312	78	85	87	104	354	105	80	95	110	390	95	95	100	115	405
Forsteo - Emerging ROW	101	28	26	27	29	110	27	34	35	35	130	30	40	40	40	150
Forsteo - Worldwide	\$1,151	282	297	307	360	\$1,245	\$301	\$309	\$335	\$390	\$1,335	\$305	\$350	\$365	\$410	\$1,430
Effient - U.S.	\$339	\$84	\$104	\$93	\$97	\$377	\$88	\$100	\$100	\$105	\$395	\$95	\$105	\$105	\$110	\$415
Effient - ACE (lc, ex fx)									35	35		35	35	40	40	
Effient - ACE	109	30	30	30	32	121	29	31	35	35	130	35	35	40	40	150
Effient - Japan	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Effient - Emerging ROW	9	2	4	3	2	11	2	3	5	5	15	5	5	5	5	20
Effient - Worldwide	\$457	116	137	125	131	\$509	\$119	\$134	\$140	\$145	\$540	\$135	\$145	\$150	\$155	\$585
Cyramza									14	15	30	60	50	50	50	200
Trulicity									25	25	50	50	50	50	50	200
Ikekizumab												25	25	25	25	100
Necitumumab														25	25	50
LY2963016																
Jardiance																100
LY2605541															10	20
Baricitinib																30
Evacetrapib																
Erbitux revenue - U.S.	76	25	13	6	15	59	13	12	15	15	55	15	15	15	20	65

Source: Company data, Cowen and Company estimates

Eli Lilly Quarterly Sales Dynamics (\$MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
New Drugs - continued																
Hedgehog antagonist																
Bemaciclib																
Olaratumab																
Biosozumab																
TGF-alpha/Epireg Mab																
Chk-1 inhibitor																
c-Met inhibitor																
c-Met Mab																
p38 MAPK inhibitor																
PCSK9 Mab																
CXCR4 peptide inhibitor																
Gluc-R antagonist																
Florbenazine																
TGF-B R1 inhibitor																
Oxyntomodulin																
Myostatin Mab																
FGFR inhibitor																
Ferroportin Mab																
Tau imaging agent																
NOC-1																
CGRP Mab																
Tabalumab																
Livalo	50	0	0	0	0	0	0	5	0	5	10	0	5	5	5	15
Cialis - U.S.	\$782	\$214	\$215	\$234	\$280	\$943	\$205	\$267	\$275	\$285	\$1,030	\$220	\$280	\$290	\$300	\$1,090
Cialis - ACE (lc, ex fx)									200	210		205	200	215	220	
Cialis - ACE	732	194	196	191	198	778	195	190	205	210	800	205	195	215	220	835
Cialis - Japan	26	2	7	6	7	21	5	6	5	5	20	5	5	5	0	15
Cialis - Emerging ROW	387	105	112	96	104	417	127	105	100	110	440	130	110	105	115	460
Cialis - Worldwide	\$1,927	515	529	527	588	\$2,159	\$533	\$568	\$585	\$610	\$2,290	\$560	\$590	\$615	\$635	\$2,400
Erbitux Royalty - U.S.	\$222	\$51	\$54	\$57	\$60	\$221	\$52	\$56	\$55	\$55	\$220	\$50	\$50	\$55	\$55	\$210
Erbitux Royalty - ACE (lc, ex fx)									25	25		20	20	20	25	
Erbitux Royalty - ACE	0	0	0	0	0	0	20	19	25	25	90	20	20	20	25	85
Erbitux Royalty - Japan	0	0	0	0	0	0	6	6	5	5	20	5	5	5	5	20
Erbitux Royalty - Emerging ROW	99	19	25	24	26	94	0	0	0	0	0	0	0	0	0	0
Erbitux Royalty - Worldwide	\$321	70	79	81	85	\$315	\$78	\$81	\$85	\$85	\$330	\$75	\$75	\$80	\$85	\$315
Byetta U.S.	20	0	5	0	0	5										
Byetta Foreign	159	3	3	3	3	10										
Byetta Worldwide Sales Recorded By Lilly	179	3	8	3	3	15										
Total New Drugs	\$6,843	\$1,670	\$1,788	\$1,804	\$1,995	\$7,254	\$1,752	\$1,924	\$2,070	\$2,215	\$7,965	\$2,040	\$2,195	\$2,345	\$2,470	\$9,050
% Change	-12%	2%	5%	7%	9%	6%	5%	8%	15%	11%	10%	16%	14%	13%	12%	14%

Source: Company data, Cowen and Company estimates

Eli Lilly Quarterly Sales Dynamics (\$MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Established Drugs																
Humatrop - U.S.	\$166	\$24	\$35	\$45	\$35	\$139	\$10	\$42	\$40	\$30	\$120	\$15	\$30	\$35	\$30	\$110
Humatrop - ACE (lc, ex fx)									30	30		30	30	25	25	
Humatrop - ACE	109	30	30	28	30	118	29	30	30	30	120	30	30	25	25	110
Humatrop - Japan	101	21	22	20	22	84	18	19	15	15	65	15	15	15	15	60
Humatrop - Emerging ROW	16	5	4	4	4	17	4	5	5	5	20	5	5	5	5	20
Humatrop - Worldwide	\$392	79	91	97	91	\$358	\$61	\$95	\$90	\$80	\$325	\$65	\$80	\$80	\$75	\$300
Evista - U.S.	\$699	\$172	\$199	\$192	\$209	\$772	\$98	\$55	\$25	\$25	\$205	\$10	\$10	\$10	\$10	\$40
Evista - ACE (lc, ex fx)									5	5		5	5	5	5	
Evista - ACE	98	22	22	9	5	58	4	5	5	5	20	5	5	5	5	20
Evista - Japan	152	34	44	43	47	167	36	38	45	50	170	40	45	45	50	180
Evista - Emerging ROW	60	13	14	12	15	53	12	11	10	10	45	5	5	10	10	30
Evista - Worldwide	\$1,010	241	279	255	276	\$1,050	\$150	\$108	\$85	\$90	\$440	\$60	\$65	\$70	\$75	\$270
Cymbalta - U.S.	\$3,918	\$1,057	\$1,217	\$1,109	\$577	\$3,961	\$176	\$112	\$25	\$25	\$340	\$15	\$15	\$15	\$15	\$60
Cymbalta - ACE (lc, ex fx)									200	220		215	220	75	75	
Cymbalta - ACE	725	188	192	193	213	786	207	211	205	220	845	210	215	75	75	525
Cymbalta - Japan	199	40	46	38	51	174	49	39	35	45	170	45	35	30	40	150
Cymbalta - Emerging ROW	152	44	42	36	42	164	46	39	40	40	165	45	40	45	45	125
Cymbalta - Worldwide	\$4,994	1,328	1,497	1,376	883	\$5,085	\$478	\$401	\$305	\$330	\$1,520	\$315	\$305	\$165	\$125	\$910
Zyprexa - U.S.	\$361	\$32	\$20	\$33	\$39	\$124	\$27	\$40	\$25	\$20	\$110	\$20	\$10	\$10	\$10	\$50
Zyprexa - ACE (lc, ex fx)									55	55		55	55	50	50	
Zyprexa - ACE	455	76	75	71	71	292	60	58	55	55	230	55	55	50	50	210
Zyprexa - Japan	586	115	128	122	143	508	143	84	100	125	450	90	90	90	105	375
Zyprexa - Emerging ROW	300	62	61	53	96	271	53	62	50	50	215	45	45	45	45	180
Zyprexa - Worldwide	\$1,701	285	283	279	348	\$1,195	\$283	\$244	\$230	\$250	\$1,005	\$210	\$200	\$195	\$210	\$815
Strattera - U.S.	\$384	\$106	\$103	\$111	\$127	\$446	\$83	\$130	\$110	\$125	\$450	\$85	\$130	\$110	\$135	\$460
Strattera - ACE (lc, ex fx)									25	25		25	25	25	25	
Strattera - ACE	121	31	31	29	34	125	31	33	25	25	115	25	25	25	25	100
Strattera - Japan	69	18	21	21	28	88	28	23	25	30	105	25	25	25	35	110
Strattera - Emerging ROW	48	12	14	12	13	50	13	12	10	10	45	10	10	10	10	40
Strattera - Worldwide	\$621	167	168	173	201	\$709	\$154	\$197	\$170	\$190	\$715	\$145	\$190	\$170	\$205	\$710
Prozac - U.S.	\$77	\$19	\$21	\$20	\$17	\$76	\$16	\$17	\$20	\$15	\$70	\$20	\$15	\$15	\$15	\$65
Prozac - ACE (lc, ex fx)									10	10		5	5	10	10	
Prozac - ACE	42	9	10	9	11	39	8	8	10	10	35	5	5	10	10	30
Prozac - Japan	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Prozac - Emerging ROW	61	15	16	15	14	61	16	17	15	15	65	15	15	15	10	55
Prozac - Worldwide	\$180	43	46	44	42	\$176	\$40	\$42	\$45	\$40	\$170	\$40	\$35	\$40	\$35	\$150
Gemzar - U.S.	\$18	\$1	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Gemzar - ACE (lc, ex fx)									0	5		0	5	0	5	
Gemzar - ACE	16	2	2	2	2	7	3	1	0	5	10	0	5	0	5	10
Gemzar - Japan	125	19	18	16	18	70	11	11	10	10	40	10	10	5	5	35
Gemzar - Emerging ROW	131	31	28	27	29	115	28	28	25	20	100	20	20	20	20	80
Gemzar - Worldwide	\$290	53	48	44	49	\$193	\$42	\$40	\$35	\$35	\$150	\$30	\$35	\$30	\$30	\$125

Source: Company data, Cowen and Company estimates

Eli Lilly Quarterly Sales Dynamics (\$MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Established Drugs - continued																
Reopro - U.S.	\$45	\$11	\$12	\$11	\$9	\$44	\$7	\$9	\$5	\$5	\$25	\$5	\$5	\$5	\$5	\$20
Reopro - ACE (lc, ex fx)									15	15		15	15	10	10	
Reopro - ACE	82	19	19	17	17	71	17	17	15	15	65	15	15	10	10	50
Reopro - Japan	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Reopro - Emerging ROW	16	3	2	4	3	12	5	3	5	5	15	5	5	5	0	15
Reopro - Worldwide	\$143	34	33	32	29	\$127	\$28	\$29	\$25	\$25	\$105	\$25	\$25	\$20	\$15	\$85
Yentreve	20	5	5	5	5	20	5	5	5	5	20	5	5	5	5	20
Cynt	10	2	3	2	5	12	0	0	5	5	10	0	0	5	5	10
Actos - ACE (lc, ex fx)									10	10		5	5	5	5	10
Actos - ACE	65	10	9	11	11	41	8	6	10	10	35	5	5	5	10	25
Actos - Japan	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Actos - Emerging ROW	25	5	4	3	4	16	3	3	5	5	15	0	0	0	5	5
Actos - Worldwide	\$90	15	14	14	14	\$57	11	9	15	15	\$50	5	5	5	15	\$30
Axid	5	0	0	0	5	5	0	0	0	5	5	0	0	0	5	5
Oral Antibiotics																
Cedolor	\$55	\$15	\$15	\$10	\$10	\$50	\$15	\$10	\$10	\$10	\$45	\$10	\$10	\$10	\$10	\$40
Keflex	5	0	0	5	5	5	0	0	0	5	5	0	0	0	5	5
Lorabid	5	0	0	0	5	5	0	0	0	5	5	0	0	0	5	5
Other	5	0	0	0	5	5	0	0	0	5	5	0	0	0	5	5
Oral Antibiotic Total	\$70	15	15	10	25	\$65	15	10	10	25	\$60	10	10	10	25	\$55
Injectable Antibiotics																
Vancocin	\$66	\$18	\$18	\$19	\$20	\$75	\$28	\$26	\$20	\$20	\$95	\$30	\$35	\$25	\$25	\$115
Other Injectable Antibiotics	10	0	5	0	5	10	0	5	0	5	10	0	5	0	5	10
Injectable Antibiotic Total	\$76	\$18	\$23	\$19	\$25	\$85	\$28	\$31	\$20	\$25	\$105	\$30	\$40	\$25	\$30	\$125
Insulin																
Humalog - U.S.	\$1,371	\$378	\$352	\$358	\$434	\$1,521	\$375	\$413	\$380	\$455	\$1,625	\$400	\$440	\$405	\$480	\$1,725
Humalog - ACE (lc, ex fx)									155	165		160	170	165	170	
Humalog - ACE	586	146	151	149	164	609	158	161	160	165	645	160	170	165	170	665
Humalog - Japan	153	30	32	31	34	128	30	27	35	35	125	30	30	35	40	135
Humalog - Emerging ROW	285	78	94	79	103	353	82	100	85	105	375	90	105	90	110	395
Humalog - Worldwide	\$2,395	633	629	616	734	\$2,611	\$650	\$700	\$660	\$760	\$2,770	\$680	\$745	\$695	\$800	\$2,920
Humulin - U.S.	\$592	\$163	\$158	\$161	\$194	\$677	\$155	\$182	\$170	\$205	\$710	\$160	\$185	\$175	\$210	\$730
Humulin - ACE (lc, ex fx)									65	70		65	65	70	75	
Humulin - ACE	251	62	67	61	65	255	60	62	65	70	255	65	65	70	75	275
Humulin - Japan	29	6	6	5	6	23	5	5	5	5	20	5	5	5	5	20
Humulin - Emerging ROW	366	81	97	79	104	361	92	104	80	90	370	90	100	75	85	350
Humulin - Worldwide	\$1,239	312	327	307	370	\$1,316	\$316	\$352	\$320	\$370	\$1,355	\$320	\$355	\$325	\$375	\$1,375
Other insulins	25	5	5	5	10	25	5	5	5	10	25	5	5	5	10	25
Insulin Total	3,659	950	961	928	1,113	3,952	971	1,057	985	1,140	4,150	1,005	1,105	1,025	1,185	4,320
Dobutrex	5	0	0	0	5	5	0	0	0	5	5	0	0	0	5	5
Other	388	200	133	161	120	613	136	142	160	120	560	150	150	150	150	600
Established Drugs Total	\$13,655	\$3,433	\$3,598	\$3,439	\$3,237	\$13,706	\$2,403	\$2,411	\$2,185	\$2,385	\$9,395	\$2,095	\$2,250	\$1,995	\$2,195	\$8,535
Total Drugs	\$20,498	\$5,103	\$5,386	\$5,242	\$5,231	\$20,960	\$4,155	\$4,335	\$4,255	\$4,600	\$17,360	\$4,135	\$4,445	\$4,340	\$4,665	\$17,585
% Change	-14%	0%	6%	6%	-3%	2%	-19%	-20%	-19%	-12%	-17%	0%	3%	2%	1%	1%

Source: Company data, Cowen and Company estimates

Animal Health Quarterly Product Sales (\$MM)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
ANIMAL HEALTH																
Monensin-U.S.	\$360	\$95	\$95	\$95	\$95	\$380	\$100	\$100	\$100	\$100	\$400	\$105	\$105	\$105	\$105	\$420
Fgn	120	30	30	30	35	125	30	30	35	35	130	30	35	35	35	135
WW	480	125	125	125	130	505	130	130	135	135	530	135	140	140	140	555
Tylan-U.S.	85	20	20	20	25	85	20	20	20	25	85	20	20	20	20	85
Fgn	89	20	20	20	25	85	20	20	20	25	85	20	20	20	25	85
WW	174	40	40	40	50	170	40	40	40	50	170	40	40	40	50	170
Other	121	35	35	35	35	140	40	40	40	40	160	45	45	45	45	180
Total	\$775	\$200	\$200	\$200	\$215	\$815	\$210	\$210	\$215	\$225	\$860	\$220	\$225	\$225	\$235	\$905
Tilmicosin	\$435	\$110	\$110	\$115	\$120	\$455	\$115	\$120	\$120	\$120	\$475	\$120	\$125	\$125	\$125	\$495
Ractopamine	150	40	40	40	40	160	40	40	45	45	170	45	45	45	45	180
Avilamycin	110	25	30	30	30	115	30	30	30	30	120	30	30	30	30	125
Comfortus	40	10	10	10	20	50	15	15	15	15	60	15	15	20	20	70
Reconcile	40	10	10	10	20	50	15	15	15	15	60	15	15	20	20	70
Narasin	45	10	10	10	15	45	10	10	10	15	45	10	10	10	15	45
Novartis Animal Health															275	275
Other	441	94	134	115	118	461	92	161	140	147	540	155	185	165	170	675
Total Animal	\$2,036	\$499	\$544	\$530	\$578	\$2,151	\$527	\$601	\$590	\$612	\$2,330	\$610	\$925	\$915	\$940	\$3,390
Y/Y % Chg	+21%	2%	6%	11%	4%	6%	6%	10%	11%	6%	8%	16%	NM	NM	NM	NM

Source: Company data, Cowen and Company estimates

Lilly Quarterly Collaboration And Other Revenue Analysis (\$MM)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Collaboration/Other Revenue																
Byetta																
U.S. Byetta + Bydureon Sales	\$620															
Foreign Sales	159	\$40	\$0	\$0	\$0	\$40										
Worldwide Sales	779	40	0	0	0	40										
Contribution to Lilly:																
U.S.	70															
Byetta Contribution to Lilly	70															
Total Collaboration/Other Revenue	\$70	\$0														
Lilly Revenue	\$22,603	\$5,602	\$5,930	\$5,772	\$5,809	\$23,111	\$4,683	\$4,936	\$4,845	\$5,212	\$19,690	\$4,745	\$5,370	\$5,255	\$5,605	\$20,975
Y/Y % Chg	-13%	0%	6%	6%	-2%	2%	-16%	-17%	-16%	-10%	-15%	1%	9%	8%	8%	7%

Source: Company data, Cowen and Company

Eli Lilly Annual Sales Dynamics (\$MM)

	2012	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2019-20 CGR	Comments
New Drugs												
Alimta - U.S.	\$1,122	\$1,209	\$1,245	\$1,340	\$1,425	\$1,475	\$1,525	\$500	\$250			- Patent exp 1/17 (with pedi extension); vitamin supplementation patent 2022 U.S.; LLY prevailed in lower court; appeals underway
Alimta - ACE (lc, ex fx)												
Alimta - ACE	811	887	1,010	1,065	800	600	400	200	100			- Patent exp 12/15; vitamin supplementation patent 2020 in EU but defeated in U.K. Court
Alimta - Japan	386	318	315	335	300	250	200	150	100			- Patent exp 12/15; method-of-use patent 2022 EU
Alimta - Emerging ROW	274	289	295	310	325	340	355	370	385			
Alimta - Worldwide	\$2,594	\$2,703	\$2,865	\$3,050	\$2,850	\$2,665	\$2,480	\$1,220	\$835	-19%	-15%	- Thymidylate synthetase inhib.; mesothelioma, NSCL
Trajenta - U.S.	\$56	\$119	\$150	\$180	\$210	\$240	\$270	\$300	\$330			- 1% market share; patent expires 2023
Trajenta - ACE (lc, ex fx)												- Australia, Canada, Europe
Trajenta - ACE	12	41	80	110	150	190	230	270	310			- Approved; patent expires 2023
Tragenta - Japan	5	46	75	110	150	190	230	270	310			- Approved; patent expires 2023
Tragenta - Emerging ROW	16	44	75	110	150	190	230	220	310			
Tragenta - Worldwide	\$89	\$249	\$380	\$510	\$660	\$810	\$960	\$1,110	\$1,260			- Linagliptin; DPP4 inhibitor; CV safety trial initiated 11/10; 50/50 share of gross profit with BI
Forteo - U.S.	\$488	\$511	\$540	\$580	\$620	\$640	\$660	\$680	\$700			- Patent expiration 2018, 2019
Forteo - ACE (lc, ex fx)												- Australia, Canada, Europe
Forteo - ACE	249	270	275	295	315	335	355	375	395			- Patent expiration 6/13, 2018, 2019
Forteo - Japan	312	354	390	405	420	435	450	465	480			- Patent expiration 7/18
Forteo - Emerging ROW	101	110	130	150	170	190	210	230	250			
Forteo - Worldwide	\$1,151	\$1,245	\$1,335	\$1,430	\$1,525	\$1,600	\$1,675	\$1,750	\$1,825	5%	6%	- Parathyroid hormone; osteoporosis; two year duration of treatment
Effient - U.S.	\$339	\$377	\$395	\$415	\$435	\$300	\$75	\$50	\$25			- 5.1% market share; patent expiration 11/17
Effient - ACE (lc, ex fx)												- Australia, Canada, Europe
Effient - ACE	109	121	130	150	170	190	210	150	100			- Patent expiration 2/19
Effient - Japan	0	0	0	0	0	0	0	0	0			
Effient - Emerging ROW	9	11	15	20	25	30	35	40	45			
Effient - Worldwide	\$457	\$509	\$540	\$585	\$630	\$520	\$320	\$240	\$170	-18%	-14%	- Prasugrel; TRILOGY (medically mgd patients) missed endpoint; ACCOAST (pre-tx), TRIGGER (drug eluting stents) ongoing
Cyramza			60	200	500	750	1,000	1,500	2,000	79%	NM	- Anti-KDR/VEGFR2; ramu; 2 nd line gastric-US approved, filed in EU; 2nd line lung met endpoint, filing in 2014; Ph III CRC; Ph II for RCC, mel
Trulicity			50	200	300	400	500	600	700	NM	NM	- Dulaglutide; GLP-1Fc; type 2 diabetes; submitted US and EU Q3:13; currently-underway CV study may not be required
Izekizumab				100	200	300	400	500	600	NM	NM	- IL-17; Psoriasis/PsA Phase III; Psoriasis data due Q4:14; RA completed Phase II but no imminent plans to move to Phase III
Necitumumab				50	200	300	400	500	600	NM	NM	- IMC-11F8; human anti-EGFR; squamous NSCLC trial hit endpoint (filing in 2014), colon, solid tumors
LY2963016					100	200	300	400	500	NM	NM	- New insulin glargine; diabetes; Phase III; NDA filed in EU Q2:13, U.S. Q4:13; SNY suit prompted 30 month stay
Jardiance			50	100	150	200	250	300	350	38%	NM	- Empagliflozin; SGLT2 inhibitor; NDA filed H1:13; submitted in Japan Q3:13; approved EU 5/14
LY2605541				30	75	100	150	200	250	NM	NM	- Basal peglispro insulin; diabetes; NDA filing by Q1:15; mixed data in Type 2, awaiting data in Type 1
Baricitinib					50	100	150	200	250	NM	NM	- Rheumatoid arthritis; JAK-1/JAK-2 inhibitor; Phase III; with Incyte
Evacetrapib					50	100	150	200	250	NM	NM	- CETP inhibitor; atherosclerosis; ACCELERATE trial fully enrolled; Phase III data in 2015
Eributix revenue - U.S.	76	59	55	65	70	75	80	85	90	9%	6%	

Source: Company data, Cowen and Company estimates.

Eli Lilly Annual Sales Dynamics (\$MM) (continued)

	2012	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR Comments
New Drugs - continued											
Hedgehog antagonist					25	50	75	100	NM	NM - Cancer; Phase II	
Bemaciclib					25	50	75	100	NM	NM - CDK4/6 inhib.; cancer; Phase III initiation possible; may allow for continuous dosing but behind PFE and NVS; early data promising	
Olaratumab					25	50	75	100	NM	NM - PDGFR alpha MAb; Phase II for cancer	
Biosozumab					25	50	75	100	NM	NM - Sclerostin Mab; osteoporosis; Phase II; Phase III start delayed until 2015 given injection site reaction with current formulation	
TGF-alpha/Epireg Mab					25	50	75	100	NM	NM - Chronic kidney disease; Phase II	
Chk-1 inhibitor					25	50	75	100	NM	NM - Cancer; Phase II	
c-Met inhibitor					25	50	75	100	NM	NM - Cancer; Phase II	
c-Met Mab					25	50	75	100	NM	NM - Cancer; Phase II	
p38 MAPK inhibitor					25	50	75	100	NM	NM - Cancer; Phase II	
PCSK9 Mab					25	50	75	100	NM	NM - Cardiovascular disease; Phase II	
CXCR4 peptide inhibitor					25	50	75	100	NM	NM - Cancer; Phase II	
Gluc-R antagonist					25	50	75	100	NM	NM - Diabetes; Phase II	
Florbenazine					25	50	75	100	NM	NM - Parkinson's Disease imaging; Phase II	
TGF-B R1 inhibitor					25	50	75	100	NM	NM - Cancer; Phase II	
Oxynormodulin					25	50	75	100	NM	NM - Diabetes; Phase II	
Myostatin Mab					25	50	75	100	NM	NM - Disuse atrophy; Phase II	
FGFR inhibitor					25	50	75	100	NM	NM - Cancer; Phase II	
Ferroportin Mab					25	50	75	100	NM	NM - Anemia; Phase II	
Tau imaging agent					25	50	75	100	NM	NM - Alzheimer's diagnostic; Phase II	
NOC-1					25	50	75	100	NM	NM - Depression; Phase II	
CGRP Mab					25	50	75	100	NM	NM - Migraine prevention; Phase II	
Tabalumab					10	20	30	40	50	NM	NM - BAFF antibody; lupus in Phase III; RA studies stopped for lack of effectiveness
Livalo	50	0	10	15	20	25	30	35	40	26%	NM - Statin for hyperlipidemia; from Kowa; Latin American rights retained, U.S. rights relinquished
Cialis - U.S.	\$782	\$943	\$1,030	\$1,090	\$1,150	\$1,200	\$250	\$150	\$50		- Patent expiration 11/17
Cialis - ACE (lc, ex fx)											- Australia, Canada, Europe
Cialis - ACE	732	778	800	835	870	900	300	200	100		- Patent expiration 11/17
Cialis - Japan	26	21	20	15	10	5	5	5	5		- Patent expiration 3/16
Cialis - Emerging ROW	387	417	440	460	480	500	520	540	560		
Cialis - Worldwide	\$1,927	\$2,159	\$2,290	\$2,400	\$2,510	\$2,605	\$1,075	\$895	\$715	-18%	-15% - MED; BPH rollout underway
Erbitux Royalty - U.S.	\$222	\$221	\$220	\$210	\$200	\$200	\$400	\$750	\$760		- Growth keyed to new indications, particularly first line NSCLC; LLY will gain sole rights to asset in 8/18
Erbitux Royalty - ACE (lc, ex fx)											- Australia, Canada, Europe
Erbitux Royalty - ACE	0	0	90	85	80	75	0	0	0		- Change in reporting of OUS revenue keyed to greater transparency on where drug is sold
Erbitux Royalty - Japan	0	0	20	20	15	10	0	0	0		- Merck KgA will own asset in 2018 due to fully paid up license
Erbitux Royalty - Emerging ROW	99	94	0	0	0	0					
Erbitux Royalty - Worldwide	\$321	\$315	\$330	\$315	\$295	\$285	\$400	\$750	\$760		
Byetta U.S.	20	5								NM	NM - Pen sales to Amylin
Byetta Foreign	159	10								NM	NM - Agreement terminate with BMY's purchase of royalty obligation (potentially 10/1/12) + 6 months for transfers
Byetta Worldwide Sales Recorded By Lilly	179	15								NM	NM
Total New Drugs	\$6,843	\$7,254	\$7,965	\$9,050	\$10,195	\$11,580	\$11,400	\$12,100	\$13,345	9%	9% - 31% of drug sales in 2013; 54% in 2020
% Change	-12%	6%	10%	14%	13%	14%	-2%	6%	10%		

Source: Company data, Cowen and Company estimates

Eli Lilly Annual Sales Dynamics (\$MM) (continued)

	2012	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR Comments
Established Drugs											
Humatrop - U.S.	\$166	\$139	\$120	\$110	\$100	\$90	\$80	\$70	\$60		
Humatrop - ACE (lc, ex fx)											- Australia, Canada, Europe
Humatrop - ACE	109	118	120	110	100	90	80	70	60		
Humatrop - Japan	101	84	65	60	50	40	30	20	10		
Humatrop - Emerging ROW	16	17	20	20	20	20	20	20	20		
Humatrop - Worldwide	\$392	\$358	\$325	\$300	\$270	\$240	\$210	\$180	\$150	-12%	-12% - Adult replacement indication could boost
Evista - U.S.	\$699	\$772	\$205	\$40	\$30	\$20	\$10	\$5	\$5		
Evista - ACE (lc, ex fx)											- Patent expired 3/14; authorized generic on the market; returns reserve in excess of \$60MM
Evista - ACE	98	58	20	20	20	20	20	20	20		- Australia, Canada, Europe
Evista - Japan	152	167	170	180	190	200	100	50	25		- Patent expiration 8/13
Evista - Emerging ROW	60	53	45	30	20	20	10	5	5		- Patent expiration 7/18
Evista - Worldwide	\$1,010	\$1,050	\$440	\$270	\$260	\$260	\$140	\$80	\$55	-29%	-34% - Osteoporosis, breast cancer prevention
Cymbalta - U.S.	\$3,918	\$3,961	\$340	\$60	\$50	\$40	\$30	\$20	\$10		
Cymbalta - ACE (lc, ex fx)											- Patent expired 12/11/13; authorized generic on the market; significant returns reserve
Cymbalta - ACE	725	786	845	525	80	60	40	20	10		- Australia, Canada, Europe
Cymbalta - Japan	199	174	170	150	130	110	25	15	5		- Data exclusivity expiration 8/14
Cymbalta - Emerging ROW	152	164	165	175	185	195	205	215	225		- Patent expiration 1/18
Cymbalta - Worldwide	\$4,994	\$5,085	\$1,520	\$910	\$445	\$405	\$300	\$270	\$250	-26%	-35% - Depression, pain, GAD, fibromyalgia, chronic pain
Zyprexa - U.S.	\$361	\$124	\$110	\$50	\$25	\$15	\$10	\$5	\$5		
Zyprexa - ACE (lc, ex fx)											- Patent expired 10/11; authorized generic sales booked here
Zyprexa - ACE	455	292	230	210	175	150	125	100	75		- Australia, Canada, Europe
Zyprexa - Japan	586	508	450	375	325	275	225	175	125		- Patent expired 9/11
Zyprexa - Emerging ROW	300	271	215	180	160	140	120	100	80		- Patent expires 12/15
Zyprexa - Worldwide	\$1,701	\$1,195	\$1,005	\$815	\$685	\$580	\$480	\$380	\$285	-19%	-19%
Strattera - U.S.	\$384	\$446	\$450	\$460	\$470	\$150	\$75	\$50	\$25		
Strattera - ACE (lc, ex fx)											- 44.3% market share; adverse U.S. patent decision overturned; patent expires 5/17
Strattera - ACE	121	125	115	100	90	80	70	60	50		- Australia, Canada, Europe
Strattera - Japan	69	88	105	110	120	80	60	40	20		- Patent expiration 4/17
Strattera - Emerging ROW	48	50	45	40	40	40	40	40	40		
Strattera - Worldwide	\$621	\$709	\$715	\$710	\$720	\$350	\$245	\$190	\$135	-24%	-21% - Attention deficit hyperactivity
Prozac - U.S.	\$77	\$76	\$70	\$65	\$55	\$45	\$35	\$25	\$15		
Prozac - ACE (lc, ex fx)											- Australia, Canada, Europe
Prozac - ACE	42	39	35	30	25	20	15	10	5		
Prozac - Japan	0	0	0	0	0	0	0	0	0		- Generic competition
Prozac - Emerging ROW	61	61	65	55	50	45	40	35	30		- Patents expired
Prozac - Worldwide	\$180	\$176	\$170	\$150	\$130	\$110	\$90	\$70	\$50	-18%	-16% - SSRI
Gemzar - U.S.	\$18	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0		
Gemzar - ACE (lc, ex fx)											- Australia, Canada, Europe
Gemzar - ACE	16	7	10	10	5	5	5	5	5		
Gemzar - Japan	125	70	40	35	25	15	10	5	5		
Gemzar - Emerging ROW	131	115	100	80	60	40	20	10	5		
Gemzar - Worldwide	\$290	\$193	\$150	\$125	\$90	\$60	\$35	\$20	\$15	-32%	-31% - Pancreatic, NSCLC, bladder, breast, ovarian; generics in U.S. and E.U.

Source: Company data, Cowen and Company estimates

Eli Lilly Annual Sales Dynamics (\$MM) (continued)

	2012	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR Comments
Established Drugs - continued											
Reopro - U.S.	\$45	\$44	\$25	\$20	\$15	\$10	\$5	\$5	\$5	-	- Australia, Canada, Europe
Reopro - ACE (lc, ex fx)											
Reopro - ACE	82	71	65	50	40	30	20	10	5	-	
Reopro - Japan	0	0	0	0	10	5	5	0	0	-	
Reopro - Emerging ROW	16	12	15	15	10	5	5	5	5	-28%	-26% - Supported by mixed view of competitive products
Reopro - Worldwide	\$143	\$127	\$105	\$85	\$75	\$50	\$35	\$20	\$15	-28%	-26% - Supported by mixed view of competitive products
Yentreve	20	20	20	20	20	20	20	20	20	0%	0% - Duloxetine for SUI; marketed in EU; not pursuing in U.S.
Cynt	10	12	10	10	10	10	10	10	10	0%	-3% - Hypertension, CHF; marketed in a few foreign markets
Actos - ACE (lc, ex fx)											- Australia, Canada, Europe
Actos - ACE	65	41	35	25	15	10	5	5	5	-	
Actos - Japan	0	0	0	0	0	0	0	0	0	-	
Actos - Emerging ROW	25	16	15	5	5	5	5	5	5	-24%	-22% - Certain foreign markets; LLY pays royalty to Takeda
Actos - Worldwide	\$90	\$57	\$50	\$30	\$20	\$15	\$10	\$10	\$10	-24%	-22% - Certain foreign markets; LLY pays royalty to Takeda
Axid	5	5	5	5	5	5	5	5	5	0%	0% - Fees from Reliant Pharmaceuticals and sales to PFE for OTC
Oral Antibiotics											
Ceclor	\$55	\$50	\$45	\$40	\$35	\$30	\$25	\$20	\$15	-17%	-16% - Ceclor CD outlicensed to Dura Pharmaceuticals
Keflex	5	5	5	5	5	5	5	5	5	0%	0%
Lorabid	5	5	5	5	5	5	5	5	5	0%	0%
Other	5	5	5	5	5	5	5	5	5	0%	0%
Oral Antibiotic Total	\$70	\$65	\$60	\$55	\$50	\$45	\$40	\$35	\$30	-11%	-10% - Declining focus
Injectable Antibiotics											
Vancocin	\$66	\$75	\$95	\$115	\$135	\$155	\$175	\$195	\$215	15%	16% - 3 year licensing deal for \$116MM or \$30MM/year ended in 2005
Other Injectable Antibiotics	10	10	10	10	10	10	10	10	10	0%	0%
Injectable Antibiotic Total	\$76	\$85	\$105	\$125	\$145	\$165	\$185	\$205	\$225	14%	15%
Insulin											
Humalog - U.S.	\$1,371	\$1,521	\$1,625	\$1,725	\$1,800	\$1,875	\$1,950	\$2,025	\$2,100	- 8.1% market share	-
Humalog - ACE (lc, ex fx)											- Australia, Canada, Europe
Humalog - ACE	586	609	645	665	685	705	725	745	765	-	
Humalog - Japan	153	128	125	135	145	155	165	175	185	-	
Humalog - Emerging ROW	285	353	375	395	415	435	455	475	495	-	
Humalog - Worldwide	\$2,395	\$2,611	\$2,770	\$2,920	\$3,045	\$3,170	\$3,295	\$3,420	\$3,545	4%	4% - Rapidly acting insulin; patent expired 5/13
Humulin - U.S.	\$592	\$677	\$710	\$730	\$750	\$770	\$790	\$810	\$820	-	- Australia, Canada, Europe
Humulin - ACE (lc, ex fx)											-
Humulin - ACE	251	255	255	275	295	315	335	355	375	-	
Humulin - Japan	29	23	20	20	20	20	20	20	20	-	
Humulin - Emerging ROW	366	361	370	350	330	310	290	270	250	-	
Humulin - Worldwide	\$1,239	\$1,316	\$1,355	\$1,375	\$1,395	\$1,415	\$1,435	\$1,455	\$1,465	1%	2% - No patent protection
Other insulins	25	25	25	25	25	25	25	25	25	0%	0% - Misc. products
Insulin Total	3,659	3,952	4,150	4,320	4,465	4,610	4,755	4,900	5,035	3%	4% - 5% patient growth; treatment intensifies
Dobutrex	5	5	5	5	5	5	5	5	5	0%	0% - U.S. patent expired 10/93; international supports
Other	388	613	560	600	600	600	600	600	600	1%	0% - Older products and Beirsdorf (German drug manuf.)
Established Drugs Total	\$13,655	\$13,706	\$9,395	\$8,535	\$7,995	\$7,530	\$7,165	\$7,000	\$6,895	-5%	-9% - 59% of drug sales in 2013; 28% in 2020
Total Drugs	\$20,498	\$20,960	\$17,360	\$17,585	\$18,190	\$19,110	\$18,565	\$19,100	\$20,240	3%	0% - Keyed to new products
% Change	-14%	2%	-17%	1%	3%	5%	-3%	3%	6%	-	

Source: Company data, Cowen and Company estimates

Animal Health Annual Product Sales (\$MM)

	2012	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR Comments
ANIMAL HEALTH											
Monensin-U.S.	\$360	\$380	\$400	\$420	\$440	\$460	\$480	\$500	\$520	4%	5%
Fgn	120	125	130	135	140	145	150	155	160	4%	4%
WW	480	505	530	555	580	605	630	655	680	4%	4% - Anti-infective/growth promoter for beef and poultry
Tylan-U.S.	85	85	85	85	85	85	85	85	85	0%	0% - Erythromycin for infections in swine, cattle, poultry
Fgn	89	85	85	85	85	85	85	85	85	0%	0%
WW	174	170	170	170	170	170	170	170	170	0%	0% - Mature, holds own despite off-patent
Other	121	140	160	180	200	220	240	260	280	10%	
Total	\$775	\$815	\$860	\$905	\$950	\$995	\$1,040	\$1,085	\$1,130	5%	5% - Mature established products
Tilmicosin	\$435	\$455	\$475	\$495	\$515	\$535	\$555	\$575	\$595	4%	4% - Respiratory antibiotic for cows, swine
Ractopamine	150	160	170	180	190	200	210	220	230	5%	5% - Paylean swine; growth promoter; alternative to Zilmax
Avilamycin	110	115	120	125	130	135	140	145	150	4%	4% - Produces leaner chickens; foreign markets only
Comfortus	40	50	60	70	80	90	100	110	120	12%	13% - Flea treatment for dogs
Reconcile	40	50	60	70	80	90	100	110	120	12%	13% - Pet separation anxiety for dogs
Narasin	45	45	45	45	45	45	45	45	45	0%	0% - Monteban; MFA for poultry
Novartis Animal Health					825	1,160	1,225	1,300	1,375	NM	NM - Purchased for \$5.4B, \$2B in debt, \$3.4B in OUS cash; expected to close by end Q1:15
Other	441	461	540	675	685	695	705	715	725	5%	7% - Reflects addition of Jansen (\$200MM in sales/yr), Lohmann (\$150MM in sales/yr), Novartis (\$1.1B in sales/yr)
Total Animal	\$2,036	\$2,151	\$2,330	\$3,390	\$3,835	\$4,010	\$4,195	\$4,380	\$4,565	12%	11% - New products drive growth
Y/Y % Chg	+21%	6%	8%	NM	13%	5%	5%	4%	4%		

Source: Company data, Cowen and Company estimates

Lilly Annual Collaboration And Other Revenue Analysis (\$MM)

	2012	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR Comments
Collaboration/Other Revenue											
Byetta											
U.S. Byetta + Bydureon Sales	\$620									NM	NM - Agreement with Amylin terminated 11/30/11
Foreign Sales	159	\$40								NM	NM - Agreement terminate with BMY's purchase of royalty obligation (potentially 10/1/12) + 6 months for transfers
Worldwide Sales	779	40								NM	NM - Type II diabetes; synthetic exendin-4; includes LAR; with Amylin
Contribution to Lilly:											
U.S.	70									NM	NM - LLY records 50% of gross profit (est. at 90%) thru 11/30/11, then 15% of net sales thru Q3:12, when BMY assumed to purchase
Byetta Contribution to Lilly	70									NM	NM - royalty obligation
Total Collaboration/Other Revenue	\$70	\$0	NM	NM							
Lilly Revenue	\$22,603	\$23,111	\$19,690	\$20,975	\$22,025	\$23,120	\$22,760	\$23,480	\$24,805	4%	1% - Industry average
Y/Y % Chg	-13%	2%	-15%	7%	5%	5%	-2%	3%	6%		

Source: Company data, Cowen and Company estimates

Eli Lilly Estimated 2013-20 Summary Balance Sheet (\$MM)

	2013A	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Assets:								
Cash & Equivalents	\$3,830	\$3,886	\$701	\$1,978	\$3,466	\$5,776	\$8,228	\$10,841
Short-Term Investments	1,567	1,500	1,500	1,500	1,500	1,500	1,500	1,500
Receivables	3,434	3,050	3,300	3,400	3,550	3,500	3,550	3,750
Inventories	2,929	3,100	2,950	3,050	3,250	3,200	3,250	3,400
Other Current Assets	1,344	1,400	1,450	1,550	1,600	1,600	1,650	1,750
Total Current Assets	13,105	12,936	9,901	11,478	13,366	15,576	18,178	21,241
Property, Plant & Equipment	7,976	8,000	8,390	8,810	9,015	8,875	8,920	9,425
Intangibles	4,331	4,700	4,800	4,800	4,700	4,700	4,600	4,600
Other Long-Term Assets	9,837	9,000	9,000	9,000	8,800	8,600	8,500	8,500
Total Long-Term Assets	22,144	21,700	22,190	22,610	22,515	22,175	22,020	22,525
Total Assets	\$35,249	\$34,636	\$32,091	\$34,088	\$35,881	\$37,751	\$40,198	\$43,766
Liabilities:								
Short-Term Debt	\$1,013	\$500	\$500	\$500	\$500	\$500	\$500	\$500
Accounts Payable	1,119	1,200	1,150	1,200	1,300	1,250	1,250	1,350
Other Current Liabilities	6,785	6,350	6,000	6,200	6,650	6,500	6,600	6,900
Total Current Liabilities	8,917	8,050	7,650	7,900	8,450	8,250	8,350	8,750
Long-Term Debt	4,200	5,000	4,000	4,000	4,000	4,000	4,000	4,000
Other Long-Term Liabilities	4,491	4,300	4,700	4,700	4,700	4,700	4,700	4,700
Total Liabilities	\$17,608	\$17,350	\$16,350	\$16,600	\$17,150	\$16,950	\$17,050	\$17,450
Net Equity	\$17,641	\$17,286	\$15,741	\$17,488	\$18,731	\$20,801	\$23,148	\$26,316

Source: Company data, Cowen and Company

Eli Lilly Estimated 2013-20 Working Capital Analysis (\$MM)

	2013A	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Inventories	\$2,929	\$3,100	\$2,950	\$3,050	\$3,250	\$3,200	\$3,250	\$3,400
COGS	\$4,908	\$5,284	\$5,010	\$5,176	\$5,549	\$5,406	\$5,518	\$5,767
Inventory Turns	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
Months	7.2	7.1	7.1	7.1	7.1	7.1	7.1	7.1
Accounts Receivable	\$3,434	\$3,050	3,300	3,400	3,550	3,500	3,550	3,750
Sales	\$23,113	\$19,690	\$20,975	\$22,025	\$23,120	\$22,760	\$23,480	\$24,805
Receivables Days	54.2	57.0	57.0	56.0	56.0	56.0	55.0	55.0
Other Current Assets	\$1,344	\$1,400	\$1,450	\$1,550	\$1,600	\$1,600	\$1,650	\$1,750
% of Sales	5.8%	7.0%	7.0%	7.0%	7.0%	7.0%	7.0%	7.0%
Accounts Payable	\$1,119	\$1,200	\$1,150	\$1,200	\$1,300	\$1,250	\$1,250	\$1,350
COGS	\$4,908	\$5,284	\$5,010	\$5,176	\$5,549	\$5,406	\$5,518	\$5,767
Payables Days	83.2	84.0	84.0	84.0	84.0	84.0	84.0	84.0
Other Current Liabilities	\$6,785	\$6,350	\$6,000	\$6,200	\$6,650	\$6,500	\$6,600	\$6,900
% of COGS	138.2%	120.0%	120.0%	120.0%	120.0%	120.0%	120.0%	120.0%
Net Working Capital (Ex. Cash, Debt)	(\$197)	\$0	\$550	\$600	\$450	\$550	\$600	\$650

Source: Company data, Cowen and Company

Eli Lilly Estimated 2013-20 Cash Flow Analysis (\$MM)

	2013A	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Operating Activities								
Net Income (Operations)	\$4,504	\$2,996	\$3,519	\$4,329	\$4,899	\$5,079	\$5,271	\$5,473
Depreciation & Amort.	1,446	1,400	1,600	1,600	1,600	1,500	1,500	1,500
Change in Working Capital	(827)	(197)	(550)	(50)	150	(100)	(50)	(50)
Other, net	<u>612</u>	<u>0</u>						
Net Cash Provided By Operations	\$5,735	\$4,200	\$4,569	\$5,879	\$6,649	\$6,479	\$6,721	\$6,923
Investing Activities								
Capital Expenditures	(\$1,012)	(\$1,000)	(\$1,000)	(\$1,000)	(\$1,100)	(\$1,100)	(\$1,200)	(\$1,200)
Asset Sales (net)	11,235	0	0	0	0	0	0	0
Acquisitions	(14,167)	(500)	(5,400)	0	0	0	0	0
Other, net	<u>1,871</u>	<u>0</u>						
Net Cash Provided By Investing	(\$2,073)	(\$1,500)	(\$6,400)	(\$1,000)	(\$1,100)	(\$1,100)	(\$1,200)	(\$1,200)
Financing Activities								
Debt Financings	\$0	\$1,000	\$2,000	\$0	\$0	\$0	\$0	\$0
Equity Financings	0	0	0	0	0	0	0	0
Net Debt Payments	(11)	(1,000)	(250)	(500)	(1,000)	(1,000)	(1,000)	(1,000)
Dividend Payments	(2,121)	(2,144)	(2,105)	(2,101)	(2,060)	(2,070)	(2,070)	(2,109)
Share Repurchase	(1,698)	(500)	(1,000)	(1,000)	(1,000)	0	0	0
Other, net (Incl. Currency)	<u>(22)</u>	<u>0</u>						
Net Cash Provided By Financing	(\$3,851)	(\$2,644)	(\$1,355)	(\$3,601)	(\$4,060)	(\$3,070)	(\$3,070)	(\$3,109)
Net Change in Cash & Equivalents	(\$189)	\$56	(\$3,186)	\$1,277	\$1,489	\$2,310	\$2,451	\$2,614
Ending Cash & Equivalents	\$3,830	\$3,886	\$701	\$1,978	\$3,466	\$5,776	\$8,228	\$10,841

Source: Company data, Cowen and Company

LLY DCF Analysis

9/26/2014 Assumptions			
Share Price	\$65	Output	
		Equity Value	\$76,655
		Estimated Share Price	\$72
Discount Rate	8.0%	Net Cash	\$184
Shares Outstanding (000)	1,070	Enterprise Value	\$76,471

LLY DCF

	2013A	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2021P	2022P	2023P	2024P	2025P	Terminal
Total Revenues	\$23,113	\$19,690	\$20,975	\$22,025	\$23,120	\$22,760	\$23,480	\$24,805	\$26,300	\$27,900	\$29,550	\$31,300	\$32,850	
% Change	+2%	-15%	+7%	+5%	+5%	-2%	+3%	+6%	+6%	+6%	+6%	+6%	+5%	
Cost of Goods	\$4,908	\$5,284	\$5,010	\$5,176	\$5,549	\$5,406	\$5,518	\$5,767	\$6,102	\$6,473	\$6,856	\$7,262	\$7,621	
Gross Profit	\$18,205	\$14,406	\$15,965	\$16,849	\$17,571	\$17,355	\$17,962	\$19,038	\$20,198	\$21,427	\$22,694	\$24,038	\$25,229	
Gross Margin - Total	78.8%	73.2%	76.1%	76.5%	76.0%	76.3%	76.5%	76.8%	76.8%	76.8%	76.8%	76.8%	76.8%	
SG&A	\$7,126	\$6,305	\$6,740	\$6,820	\$6,950	\$6,685	\$6,930	\$7,400	\$7,759	\$8,231	\$8,658	\$9,171	\$9,527	
% of Revs	30.8%	32.0%	32.1%	31.0%	30.1%	29.4%	29.5%	29.8%	29.5%	29.5%	29.3%	29.3%	29.0%	
R&D	\$5,531	\$4,550	\$4,745	\$4,500	\$4,400	\$4,250	\$4,400	\$4,780	\$5,076	\$5,301	\$5,615	\$5,947	\$6,143	
% of Revs	23.9%	23.1%	22.6%	20.4%	19.0%	18.7%	18.7%	19.3%	19.3%	19.0%	19.0%	19.0%	18.7%	
Operating Expenses	\$12,657	\$10,855	\$11,485	\$11,320	\$11,350	\$10,935	\$11,330	\$12,180	\$12,834	\$13,532	\$14,273	\$15,118	\$15,669	
% of Revenues	54.8%	55.1%	54.8%	51.4%	49.1%	48.0%	48.3%	49.1%	48.8%	48.5%	48.3%	48.3%	47.7%	
Operating Income	\$5,548	\$3,552	\$4,480	\$5,529	\$6,221	\$6,420	\$6,632	\$6,858	\$7,364	\$7,896	\$8,422	\$8,921	\$9,559	
% Operating Margin	24.0%	18.0%	21.4%	25.1%	26.9%	28.2%	28.2%	27.6%	28.0%	28.3%	28.5%	28.5%	29.1%	
Non-operating income	64	165	65	50	50	50	50	50	50	50	50	50	50	
EBIT	\$5,612	\$3,717	\$4,545	\$5,579	\$6,271	\$6,470	\$6,682	\$6,908	\$7,414	\$7,946	\$8,472	\$8,971	\$9,609	
% of Revs	24.3%	18.9%	21.7%	25.3%	27.1%	28.4%	28.5%	27.8%	28.2%	28.5%	28.7%	28.7%	29.3%	
D&A	\$1,446	\$1,400	\$1,600	\$1,600	\$1,600	\$1,500	\$1,500	\$1,500	\$1,550	\$1,550	\$1,550	\$1,600	\$1,600	
EBITDA	\$7,058	\$5,117	\$6,145	\$7,179	\$7,871	\$7,970	\$8,182	\$8,408	\$8,914	\$9,496	\$10,022	\$10,571	\$11,209	
% of Revs	30.5%	26.0%	29.3%	32.6%	34.0%	35.0%	34.8%	33.9%	33.9%	34.0%	33.9%	33.8%	34.1%	
Net Interest Income (Expense)	(\$40)	(\$0)	(\$90)	(\$100)	(\$70)	(\$40)	(\$10)	\$20	\$25	\$35	\$45	\$50	\$50	
Pre-Tax Income	\$5,572	\$3,717	\$4,455	\$5,479	\$6,201	\$6,430	\$6,672	\$6,928	\$7,439	\$7,981	\$8,517	\$9,021	\$9,659	
Taxes	\$1,069	\$705	\$935	\$1,172	\$1,317	\$1,359	\$1,403	\$1,451	\$1,557	\$1,669	\$1,779	\$1,884	\$2,018	
Income Tax Rate	19.2%	19.1%	21.0%	21.0%	21.0%	21.0%	21.0%	21.0%	21.0%	21.0%	21.0%	21.0%	21.0%	
Net Income	\$4,503	\$3,012	\$3,519	\$4,308	\$4,884	\$5,071	\$5,269	\$5,477	\$5,882	\$6,312	\$6,738	\$7,137	\$7,641	
% of Revs	19.5%	15.3%	16.8%	19.6%	21.1%	22.3%	22.4%	22.1%	22.4%	22.6%	22.8%	22.8%	23.3%	
NOPAT	\$4,543	\$3,012	\$3,609	\$4,408	\$4,954	\$5,111	\$5,279	\$5,457	\$5,857	\$6,277	\$6,693	\$7,087	\$7,591	
Adjustments:														
Capex	(\$1,012)	(\$1,000)	(\$1,000)	(\$1,000)	(\$1,100)	(\$1,100)	(\$1,200)	(\$1,200)	(\$1,250)	(\$1,300)	(\$1,350)	(\$1,350)	(\$1,350)	
Depreciation & Amortization	\$1,446	\$1,400	\$1,600	\$1,600	\$1,600	\$1,500	\$1,500	\$1,500	\$1,550	\$1,550	\$1,550	\$1,600	\$1,600	
Change In Working Capital	(\$827)	(\$197)	(\$550)	(\$50)	\$150	(\$100)	(\$50)	(\$50)	(\$50)	(\$50)	(\$50)	(\$50)	(\$50)	
Operating Free Cash Flow	\$4,110	\$3,215	\$3,569	\$4,858	\$5,534	\$5,371	\$5,519	\$5,727	\$6,082	\$6,512	\$6,888	\$7,337	\$7,841	\$98,017

Source: Cowen and Company.

Lilly Key Upcoming Events

Time Frame	Event Type	Product	Event
2014	Clinical	Abemaciclib	CDK 4/6; Phase III initiation in breast/lung cancer
		Baracitinib	Completion of first Phase III trial in RA - internal read out, late 2014/early 2015
		Peglispro	Phase III data in T1DM in Q3:14
		Tabalumab	Lupus Phase III data - internal read out, top-line H2:14
	Regulatory	Cyramza	Filing for 2L NSCLC
		Dulaglutide	Final E.U. approval for Type 2 diabetes and Cyramza in advanced gastric cancer by yearend (both have CHMP positive opinion)
		Insulin glargine	Possible litigation update
		Necitumumab	Filing for 1st-line squamous NSCLC late 2014 (will have Fast Track status)
	Corporate	Cymbalta	E.U. data package exclusivity expires H2:14 (generics cannot file until then)

Source: Cowen and Company

ELI LILLY R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Analgesia/Anesthesia							
Tanezumab				.			Pain
mGlu2/3 agonist		.					Chronic pain
Arthritis/Inflammation							
Baricitinib (INCB 28050)			.				Rheumatoid arthritis; JAK-1/JAK-2 inhibitor; DMARD
Ixekizumab			.				LY-2439821; IL-17 Mab; PIII psoriasis, psoriatic arthritis
Cancer/Oncology/Hematology							
Alimta			.		.		Thymidylate synthetase inhibitor; multi-targeted antifolate; intravenous; similar to 5-FU and UFT; locally advanced NSCLC
Necitumumab			.				Human anti-EGFR; PIII for squamous NSCLC; metastatic colorectal cancer; EU
Cyramza			Ramucirumab; human anti-KDR/VEGFR2; PIII in lung, gastric and liver cancers; PII for RCC, malignant melanoma; approved 4/2014 for gastric 2nd line monotherapy
Erbitux		.	.				Various PII/III indications
Abemaciclib		.					LY2835219; CDK 4/6 inhibitor; metastatic breast cancer
Chk1 inhibitor		.					Cancer
c-Met inhibitor		.					Cancer
c-Met MAb		.					Cancer
CXCR4 peptase inhibitor		.					Cancer
Ferroportin MAb		.					Anemia
FGFR inhibitor		.					Cancer
Galunisertib		.					Cancer
Hedgehog antagonist		.					Cancer
Olaratumab (LY-3012207)		.					IMC-3G3; PDGFR1 Mab; cancer
p38 MAPK inhibitor		.					Cancer
TGF Beta R1 Inhibitor Program		.					Solid tumors
CSF1R Mab		.					Cancer
Hepcidin Mab		.					Anemia
Notch inhibitor		.					Cancer
P13/mTOR inhibitor		.					Cancer
P70S6/AKT inhibitor		.					Cancer
Pan-Raf inhibitor		.					Cancer
TGFbR2 Mab		.					Cancer
VEGFR3 MAb		.					Cancer
Cardiovascular							
Evacetrapib		.					CETP; atherosclerosis; 11,000 patient outcomes study; data in 2015
PCSK9 Mab		.					Cardiovascular disease
Undisclosed		.					Cardiovascular disease
Undisclosed		.					Hypertension
Central Nervous System							
Cymbalta		.					PIII for other pain indications
Solanezumab		.	.				A-beta antibody; Alzheimer's disease; primary endpoints not met in EXPEDITION trials; another Phase III started Q3:13
CGRP Mab		.					Migraine prevention
Edivoxetine		.					CNS disorder
NOC-1		.					Depression
mGlu2 agonist		.					Bipolar disorder
N3pG-AB Mab		.					Alzheimer's disease

ELI LILLY R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Pomaglumetad		.					CNS disorder
Diabetes							
LY-2963016					2013		Diabetes; insulin glargine; approved in EU; tentative approval by FDA August, 2014; with BI
LY-2605541				.	2014		Diabetes; basal insulin pglispro; types 1 and 2 diabetes mellitus
Glucagon-R antagonist			.				Diabetes
Oxyntomodulin		⇒	.				Diabetes
Undisclosed		(3)					Diabetes
Endocrine/Metabolic/Hormones							
Blosozumab			.				Sclerostrin Mab; osteoporosis
Forteo			.				PII for treatment of low bone mass in anorexia nervosa
Myostatin Mab			.				Muscle disuse atrophy
Undisclosed		.					Muscle atrophy
Gastrointestinal							
Undisclosed		.					Ulcerative colitis
Immunological							
Tabalumab			.				LY-2127399; BAFF Mab; lupus
Undisclosed		.					Crohn's disease
Undisclosed		.					Lupus
Urology							
TGF α /Epireg Mab			.				Chronic kidney disease
Undisclosed		.					Anemia in CKD
Undisclosed		.					Chronic kidney disease
Total Drugs In Development	0	23	22	12	1		58

Progress since last update in bold; movement marked by arrow

Investor Relations Contacts: Phil Johnson 317-655-6874
Ilissa Rassner 317-276-1233

GlaxoSmithKline plc (ADR)

Visibility Needed

Price: \$45.97 (09/30/2014)
Price Target: \$49.00 (Prior \$59.00)

MARKET PERFORM (2)

Steve Scala, R.Ph., CFA

617.946.3923
steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA

617.946.3857
kathy.miner@cowen.com

Jean Perreault

617.946.3967
jean.perreault@cowen.com

Key Data

Symbol NYSE: GSK

52-Week Range: \$56.73 - 45.97

Market Cap (MM): \$111,469.0

Net Debt (MM): \$12,645.0

Cash/Share: NA

Dil. Shares Out (MM): 2,424.8

Enterprise Value (MM): NA

ROIC: NA

ROE (LTM): NA

BV/Share: NA

Dividend: \$2.59

Yield: 5.63%

FY (Dec)	2013A	2014E	2015E
Earnings Per Share			
Q1	p26.10	p21.00A	p20.00
Prior Q1	-	-	-
Q2	p25.30	p19.10A	p19.40
Prior Q2	-	-	-
Q3	p28.00	p25.00	p28.90
Prior Q3	-	p25.90	-
Q4	p29.00	p27.90	p27.70
Prior Q4	-	p27.00	-
Year	p108.40	p93.00	p96.00
Core EPS			
Revenue (MM)			
Year	£25,602.0	£23,450.0	£24,865.0

The Cowen Insight

A trend of downward earnings revisions, mixed results on recent new product rollouts, generic pressures, and pipeline uncertainties keep us on the sidelines.

We believe GSK's performance is tied to the company's ability to deliver accelerating earnings growth in tandem with rollouts of new drugs. The rollouts have been mixed, with new COPD agents Breo and Anoro off to modest starts. Success of these products is key to minimizing future generic pressure on Advair. Several other new products are in early stage rollouts or soon to launch. We are not particularly positive on Glaxo's recent business swaps, as oncology is a key therapeutic area for the industry overall, and we believe there is risk to the success of Bexsero (meningitis B vaccine). We rate GSK Market Perform pending greater visibility on new product success and EPS acceleration.

EPS Forecast to Be Down 14% In 2014; Modest Recovery In 2015-16, But 8-10% Gains Not Expected Until 2018-20

We forecast EPS of 93p in 2014 on an 8% decline in turnover. EPS in 2015-16 could grow 3-4% on 6% turnover gains. After flat EPS in 2017 (on +3% turnover), we estimate that EPS growth could be +8-10% and turnover growth +6-7% in 2018-20. However, our conviction in out year estimates is low. EPS estimates generally have been edging down in recent years, and this trend needs to cease for the stock to be a consistent performer.

Asset Swaps With Novartis Not Overly Compelling

In April, Glaxo announced plans to sell its oncology business to Novartis, acquire Novartis' vaccine portfolio (excluding influenza), and establish a joint venture with Novartis Consumer products. We view these transactions as an attractive financial maneuver, but strategically less compelling, given the appeal of oncology (unmet need, pricing, long duration assets), and risk in vaccines (uncertainty about endorsement of Bexsero for national immunization).

Many New Product Rollouts, But Breo And Anoro Off To Modest Starts

Glaxo is rolling out several new drugs; Tivicay for HIV, Breo for COPD (U.S.), asthma and COPD (E.U.), and asthma (Japan), and Anoro for COPD (U.S., E.U., Japan). The Breo and Anoro rollouts have been tepid reflecting contract timing limitations and modest differentiation.

Generic LABA/ICS Remain A Concern For Advair

Advair remains a big target and thus a risk, and FDA's issuance of surprisingly mild generic bioequivalence guidelines adds concern. Novartis' rollout of a non-substitutable generic Advair in European countries raises concerns about further approvals, and other generics are following NVS. However, should Breo's SUMMIT outcomes trial be successful (data in 2015), Advair concerns would likely diminish substantially.

GSK's Business Swaps With Novartis Graded C+

We view the sale of oncology products and acquisition of Novartis' Vaccines and Consumer businesses as largely a financial maneuver, and attractive from this standpoint but strategically questionable. The share base will potentially be lowered by 5% via the proceeds of the asset swap. Glaxo management has also announced aggressive margin targets. But oncology is the industry's most powerful therapeutic area, and Glaxo is all but exiting. Glaxo is retaining most of its oncology pipeline except for one drug but, should they develop any agents successfully, they will no longer have a footprint for their commercialization. And the fact that NVS took only one pipeline asset may speak to their promise. NVS vaccines business has struggled (2015 sales estimated at \$1.65B, 17% operating margin). Meningitis B is key and, while it likely will be approved, our vaccines experts question whether the ACIP will recommend it for routine vaccination in the U.S. GSK is already a leader in Consumer, and supplementing its portfolio with the Novartis products makes sense. But Novartis' products are now only coming back post manufacturing issues, so their future is not certain. The transaction is on track to close during H1:15.

Portfolio To Be Further Streamlined With Sale Of Mature Products

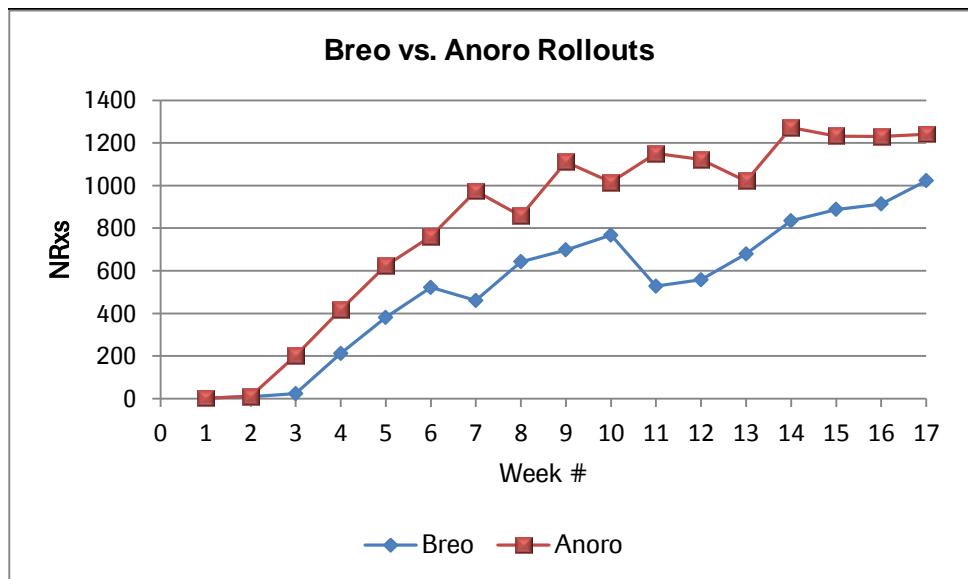
In July 2014, Glaxo indicated they seek to sell a portion of their Mature Products (in U.S. and E.U.) with estimated annual sales of £1B. The company hopes to have an agreement in place by year end.

Respiratory

Breo Rollout Tepid To Date; SUMMIT Key

In May 2013, FDA approved Breo (vitanterol/fluticasone furoate) for the treatment of COPD and prevention of COPD-related exacerbations. Breo's rollout began in November 2013, priced on par with Advair, and supported by a promotional shift away from Advair and a 25% increase in Glaxo's U.S. respiratory salesforce. The Breo device is very patient friendly and includes some upgrades including a bigger dose counter, one less step to administer, and a design that prevents double dose inhalations. Breo/Relvar is expected to supplement Advair revenues as part of a respiratory portfolio and decrease concern regarding Advair generics. However, Breo's rollout has been sluggish reflecting sampling and contract timing limitations. Breo now has 70% Medicare Part D access.

Breo and Anoro U.S. Rx Rollout Trends



Source: Cowen and Company

Breo has been approved for asthma and COPD in the E.U., and asthma in Japan. In June 2014, Glaxo/Theravance submitted a sNDA to the FDA for use of Breo in asthma at a once-daily dose of either 100/25mcg or 200/25mcg. We estimate Breo sales of £90MM in 2014, £310MM in 2015, £570MM in 2016, £1,000MM in 2018, and £1,440MM in 2020.

Strong Label In-Line With Our Expectations

Breo's label contains a black-box warning noting the increased risk of asthma-related death for LABA-containing medications. This warning has become standard for the LABA class and does not necessarily reflect Breo-specific data. As expected, the label notes an increase in the incidence of oropharyngeal candidiasis, pneumonia, and pneumonia-related hospitalizations and fatalities on Breo. Data from head-to-head studies versus Advair were not included in the label as these studies produced inconsistent results.

SUMMIT Results Pivotal

Should the SUMMIT study (to report late 2015 or early 2016) show a mortality benefit for Breo, 60% of doctors surveyed would prescribe mostly Breo to their patients. Only 8% would view this as a class effect. Advair narrowly missed demonstrating a mortality benefit in its outcomes trial (TORCH), but our pulmonology experts believe Breo is likely to be successful in SUMMIT. This is due to the fact that it will not incur a statistical penalty related to an interim look, is enriched for patients at high CV risk, and is evaluating molecules with inherently superior activity to those in Advair. In March, Glaxo announced that SUMMIT completed its planned enrollment of approximately 16,000 patients. As the study is event-driven, the exact trial duration is uncertain.

Salford Lung Study Is Another Key Datapoint

The Salford Lung Study (SLS) is a randomized “real-world” effectiveness trial (in the U.K.) evaluating the use of Breo/Relvar vs. standards of care in COPD and asthma patients. Data from this study is expected to be a factor in reimbursement discussions, especially in the E.U. It is a 12 month trial; data is expected in 2016. Patients are currently being recruited for the COPD arm; the asthma part will be after. Clinical results as well as the cost impact of once-daily dosing will be among the key pieces of data expected to emerge from this study.

Phase III Breo/Relvar COPD Data Solid

The goal of the first 24-week 1,224 patient Phase III study was to compare the efficacy and safety of two mid-to-high doses of FF/VI with its constituent components, FF and VI, and placebo in patients with moderate-to-severe COPD. The co-primary endpoints for this study were weighted mean 0-4h (day 168) and change in baseline trough (day 169) in FEV1. Weighted mean and trough FEV1 significantly improved with 25ug VI and FF/VI 200/25ug compared to placebo. Weighted mean FEV1 significantly improved for FF/VI 200/25ug versus FF200ug and trough FEV1 was significantly different for FF/VI 200/25ug versus VI 25ug. Chronic Respiratory Questionnaire Self-Administered Standardized (CRQ-SAS) dyspnea domain scores improved numerically for all comparisons except FF versus placebo. Peak FEV1 (0-4h) on Day 1 was numerically improved for all comparisons except FF/VI 200/25 vs. VI 25.

Breo/Relvar demonstrated numerical improvement in FEV1 compared to vilanterol alone, but not all increases were statistically significant; a 4-week study showed all doses of Breo/Relvar significantly increased weighted FEV1 compared to placebo. Theravance stated that significance was achieved at most time points. An improvement in FEV1 over vilanterol was subsequently observed across 4 studies.

In two 12-week COPD trials, Breo/Relvar (100/25ug, QD) demonstrated improvement over Advair in 0-24 hour weighted mean FEV1; one study demonstrated statistical superiority and the other a numerical improvement. Breo/Relvar (100/25ug QD) demonstrated statistical superiority in 0-24 hour weighted FEV1 over Advair (250/50 BID) in a 12-week COPD study ($p < 0.001$, $n=500$). Breo/Relvar demonstrated a numerical, but not statistically significant, improvement in FEV1 in a replicate study ($p=0.267$). Given the tough compare Advair represents in these head-to-head studies, we view these data as positive.

Across all COPD studies, the most common adverse events in the Breo/Relvar arms were nasopharyngitis, upper respiratory tract infection, oral candidiasis, headache, COPD, back pain, pneumonia, bronchitis and sinusitis. Glaxo also conducted a 52-week safety analysis to define the safety profile of Breo/Relvar across two Phase III studies (H2C871 and H2C970). On-treatment withdraw rates (FF/VI 50/25, FF/VI 100/25, FF/VI 200/25, VI 25ug) were 25%, 25%, 25%, and 29%, respectively. The incidence of withdraw due to adverse events was 7-8% in the FF/VI groups and 6% in the VI group. The most common on-treatment AEs were nasopharyngitis (14-19%), candidiasis (7-13%), and upper respiratory tract infections (9-11%). More patients receiving FF/VI (17-21%) than VI (14%) experienced AEs that were deemed treatment related. The incidence of local steroid effects and bone disorders (including fractures) was higher in patients receiving FF/VI than in patients receiving VI alone. No fatal AEs were considered by the investigator to be treatment related. A summary of adverse events is provided below:

Breo Adverse Events

n (%)	FF/VI 50/25 (n=820)	FF/VI 100/25 (n=806)	FF/VI 200/25 (n=811)	VI 25ug (n=818)
On-treatment AEs	620 (76)	621 (77)	622 (77)	575 (70)
On-treatment SAEs	136 (17)	123 (15)	124 (15)	126 (15)
Any fatal AE	16 (2)	10 (<1)	14 (2)	13 (2)
On treatment	14 (2)	8 (<1)	13 (2)	8 (<1)
Post-treatment	3 (<1)	3 (<1)	2 (<1)	5 (<1)
On-treatment AEs in >5% of patients				
Nasopharyngitis	112 (14)	128 (16)	158 (19)	112 (14)
Candidiasis	110 (13)	87 (1)	88 (11)	55 (7)
URI	84 (10)	90 (11)	75 (9)	78 (10)
Headache	61 (7)	57 (7)	67 (8)	60 (7)
COPD	53 (6)	56 (7)	53 (7)	53 (6)
Back pain	40 (5)	54 (7)	37 (5)	53 (6)
Pneumonia	46 (6)	49 (6)	45 (6)	23 (3)
Bronchitis	41 (5)	39 (5)	47 (6)	42 (5)
Sinusitis	47 (6)	42 (5)	40 (5)	36 (4)
Oropharyngeal pain	30 (4)	31 (4)	39 (5)	31 (4)

Source: Company data, ERS 2012

Several safety events were of special interest, including pneumonia deaths that occurred on drug. Seven presumed pneumonia deaths occurred on FF/VI, 6 on the 200/25ug and 1 on the 100/25ug dose (with concurrent COPD exacerbation). The 6 pneumonia deaths on 200/25ug occurred in the HZC871 study at a single study site in the Philippines. Our physician consultant suggested that patients who died at this study center may have had very low baseline FEV1s (<25% of predicted). Only 2 of the 6 patients who died of pneumonia received chest x-rays. Our physician consultant believes that the pneumonia deaths were likely a center-specific phenomenon, and are not drug related. A summary of the adverse events of special interest is shown below:

Breo Special Interest Adverse Events

n (%)	FF/VI 50/25 (n=820)	FF/VI 100/25 (n=806)	FF/VI 200/25 (n=811)	VI 25ug (n=818)
Local steroid effects	142 (17)	121 (15)	140 (17)	96 (12)
Lower respiratory tract infections	57 (7)	60 (7)	63 (8)	64 (8)
Pneumonia, all recorded	38 (6)	51 (6)	55 (7)	27 (3)
Hazard ratio (95% CI) for time to first pneumonia vs. VI	0.58 (0.35, 0.93)	0.54 (0.34, 0.85)	0.50 (0.31, 0.79)	--
Fatal pneumonia	0	1 (<1)	6 (<1)	0
Hypersensitivity	38 (5)	37 (5)	29 (4)	26 (3)
Bone disorders	24 (3)	27 (3)	21 (3)	9 (1)
Effects on glucose	18 (2)	15 (2)	15 (2)	14 (2)

Source: Company data, ERS 2012

No clinically relevant changes in clinical chemistry or hematology values, or in ECG-measured HR or QTc interval were observed.

Breo/Relvar Data In Asthma Viewed As Very Impressive

In December 2013, Glaxo reported positive results from a pivotal Phase III safety/efficacy study of Breo in asthma. The study was a 12-week, double-blind, trial evaluating Breo 200/25mcg, Breo 100/25mcg and fluticasone furoate (FF) 100mcg alone in 990 patients with moderate-to-severe asthma. The primary endpoint was weighted mean serial FEV₁ at the end of 12 weeks. Breo 100/25 demonstrated a statistically significant improvement in FEV₁ compared to FF (108ml, 95% CI (45,171, p<0.001). This was primary comparison in the study. Breo 200/25 also demonstrated

improvement of an additional 24ml over Breo 100/25. The most common AEs were headache, nasopharyngitis, URIs, and flu. The incidences were similar across all treatment arms.

In an earlier 76-week, 2,000-patient asthma exacerbations study, Breo/Relvar (100/25ug) significantly increased the time to the first severe exacerbation ($p=0.036$) and decreased the annual rate of severe exacerbations ($p=0.014$) compared to fluticasone furoate alone. The addition of vilanterol to fluticasone furoate also resulted in a statistically significant increase in trough FEV1 at all pre-defined time points ($p<0.001$). The most frequent adverse events across this study were headache, nasopharyngitis, upper respiratory tract infection, bronchitis, cough, oropharyngeal pain and influenza. There were no differences in the number of asthma-related hospitalizations between the treatment arms and no asthma-related deaths.

Our physician experts were very impressed by these data and suggested that these data may be the most exciting of all Breo/Relvar data to date. While all currently marketed ICS/LABA asthma products have a black box warning for increased risk of death and hospitalization as the result of exacerbations, these data are the only data suggesting that the addition of the LABA may actually prevent exacerbations. Our consultants view this as a significant differentiating factor for Breo/Relvar in asthma, but note that a second confirmatory trial may be necessary.

A 12-week, 600-patient study in mild-to-moderate asthmatics was not able to demonstrate an improvement in either trough or weighted mean FEV1 for Breo/Relvar (200/25ug) when compared to FF (200ug) alone (trough FEV1, $p=0.405$; weighted mean FEV1, $p=0.06$). In another 12-week study in 340 patients on inhaled corticosteroids, neither once daily vilanterol (25ug) nor twice-daily salmeterol (50ug) showed a benefit in 24-hour weighted mean FEV1 compared to placebo. Our consultants were not surprised by these data, noting that showing a statistical improvement over an ICS in mild patients presents a high hurdle.

Breo vs. FF In Asthma

	FF/VI	FF
Trough FEV1, mL difference from PBO (95% CI)	172 (87, 258)	136 (51, 222)
wmSerial FEV1 0-24h, mL difference from PBO (95% CI)	302 (178, 426)	186 (62, 310)
p-value vs. placebo Trough	<0.001	0.002
p-value vs. placebo wmSerial FEV1 0-24h	<0.001	0.003
p-value vs. FF trough FEV1	0.405	NA
p-value vs. FF mwSerial FEV1 0-24h	0.06	NA

Source: Company data, ERS 2012

One on-treatment SAE was reported (pancreatitis) by a single patient on FF; this SAE was not considered treatment related. More patients had on-treatment severe asthma exacerbations on placebo (9.4%) than on FF/VI (<1%) or FF (4.2%). Adjusted ratios relative to placebo for change from baseline in 24h urinary cortisol excretion at week-12 were 0.82 for FF/VI and 0.86 for FF.

At 24-weeks, Breo/Relvar (200/25ug) demonstrated superiority over FF (200ug) alone for both trough FEV1 ($p<0.001$) and weighted mean FEV1 ($p=0.048$) in moderate-to-severe asthma patients. FF (200ug) dosed once-daily was non-inferior to fluticasone propionate (500ug) dosed twice daily on improving lung function. The non-inferiority margin between FF and FP was 125mL. Secondary endpoints were change from baseline in percent rescue-free and percent symptom-free 24h periods and Asthma

Quality of Life Questionnaire (AQLQ) score. Our physician experts view these data as evidence that the addition of vilanterol to an ICS provides an incremental benefit in more severe asthma patients. Our consultants therefore view Breo/Relvar as approvable in moderate-to-severe asthma patients (the population where current ICS/LABA combinations are indicated).

FF/VI improved trough FEV1 over FF by 193mL and over FP by 210mL ($p<0.001$ for both measurements) and weighted serial FEV1 by 136mL over FF and 206mL over FP ($p=0.048$ and 0.003). The addition of VI to FF significantly increased the number of rescue-free (+11.7, $p<0.001$) and symptom-free days (+8.4, $p=0.001$). However, no differences in AQLQ scores were observed between treatment groups.

The incidence of AEs was similar amongst treatment groups. No significant differences in 24h urinary cortisol excretion (0.84 for FP, 0.91 for FF, 0.98 for FF/VI), vital signs, or ECG were noted after 24-weeks of treatment.

Adverse Effects By Treatment Group

	FF/VI (200ug/25ug), (n=197)	FF (200ug), (n=194)	FF (500ug BID), (n=195)
On-treatment AE	92 (47)	90 (46)	97 (50)
Treatment-related AE	17 (9)	8 (4)	16 (8)
AE leading to d/c	7 (4)	3 (2)	2 (1)
Most Frequent AEs			
Nasopharyngitis	15 (13)	27 (14)	39 (20)
Headache	11 (6)	13 (7)	15 (8)
Cough	3 (2)	6 (3)	13 (7)

Source: Company data, ERS 2012

In a second 24-week study comparing Breo/Relvar to Advair, Breo/Relvar did not meet the pre-specified criteria for superiority on 0-24 hour weighted mean FEV1 ($p=0.162$), although these data were not expected to achieve this hurdle by our physician experts. The twelve hour peak afforded by BID Advair dosing was viewed as a difficult compare for any ICS/LABA combination. Our consultants view non-inferiority to Advair in asthma as a positive for Breo/Relvar.

FF/VI and FP/SAL demonstrated significant improvements from baseline in 0-24h weighted FEV1 (341mL for FF/VI vs. 377mL for FP/SAL); these values were not statistically different from each other ($p=0.162$). No statistically significant differences were reported between FF/VI and FP/SAL for serial weighted mean FEV1 0-4h and clinic visit trough FEV1 (secondary endpoints). A greater number of patients receiving FF/VI vs. FP/SAL had an improvement of >0.5 points (minimally important difference) from baseline in their Total Asthma Quality of Life Questionnaire (+12) score (other endpoint; post hoc analysis) at week-24 (46% vs. 38%). No differences in reported exacerbations between treatment groups were observed. No SAEs were considered to be treatment related and no deaths were reported during the study. No clinically relevant differences between FF/VI and FP/SAL were reported for 24h urinary cortisol excretion or vital signs.

Breo vs. Advair Adverse Events

AEs	FF/VI (100ug/25ug), (n=403)	FP/SAL (250ug/50ug BID), (n=403)
On-treatment AEs	213 (53)	198 (49)
Nasopharyngitis	46 (11)	46 (11)
Headache	34 (8)	41 (10)
URI	26 (6)	16 (4)
Treatment-related AEs	19 (5)	15 (4)
SAEs	4 (<1)	5 (1)

Source: Company data, ERS 2012

Glaxo reported additional data for the fluticasone furoate (FF) component of Breo/Relvar in a 330 patient study of adults and adolescents with persistent asthma. In this study, FF met the primary endpoint of statistically significant change from baseline to 24-weeks in trough evening FEV1 compared to placebo ($p=0.009$). Fluticasone propionate also met this endpoint when compared to placebo ($p=0.011$). These data confirm the efficacy of the once daily steroid component of Breo/Relvar (FF) in the treatment of asthma. In this study, the most common adverse events in the FF arm were bronchitis, headache, nasopharyngitis, upper respiratory tract infection, pharyngitis, and sinusitis.

Anoro's Rollout Tepid Despite First-To-Market Position In U.S.

LAMA/LABA Anoro (umeclidinium/vilanterol) was FDA approved on its December, 2013 PDUFA date with a solid label. Rollout began at the end of April. Anoro is the first-to-market LABA/LAMA combination in the U.S. with a 12+ month advantage over Novartis' Ultibro/QVA149 (filing delayed until Q4:14 because of FDA concerns surrounding not having adequately defined a minimally effective dose of LAMA NVA237). Through July, Anoro had 27% Medicare coverage. Anoro was approved in the E.U. in May 2014, in Canada January 2014, and in Australia and Japan in July 2014. We estimate Anoro sales of £65MM in 2014, £340MM in 2015, £650MM in 2016, £1,250MM in 2018, and £1,750MM in 2020.

Despite a modest slowing of FEV1 decline in Advair's TORCH trial, the weight of evidence from randomized controlled trials suggests adding a corticosteroid to a bronchodilator does not dramatically improve FEV1 decline in patients with COPD. Our physician experts believe that LAMA/LABA combinations offer superior improvements in lung function and dyspnea and see LAMA/LABA combinations supplanting LABA/ICS combinations as first-line therapy in COPD.

Anoro Compares Favorably to Advair

In March 2014, Glaxo announced results from three Phase III studies comparing Anoro to Advair in COPD. In all three studies, Anoro demonstrated a statistically significant improvement in lung function with FEV improvement over Advair of 80ml, 74ml, and 101ml respectively.

Study DB2113361 Demonstrates Superiority To Placebo And Satisfies Rule Of Combinations

The goal of Study DB2113361 was to compare the safety and efficacy of Anoro (UMECH/VI) to its individual components and placebo. Anoro, UMEC, and VI demonstrated significant improvements in trough FEV1 at day 169 compared to placebo. FEV1 improvements was significantly superior for Anoro relative to either

UMEC or vilanterol monotherapy, satisfying FDA's rule of combinations. Additionally, Anoro demonstrated superior improvements in the transition dyspnea index (TDI) relative to UMEC, VI, or placebo. A summary of the efficacy data from DB2113361 is below:

Comparison Of Anoro To Placebo, UMEC, and VI

	Placebo	UMEC (125µg)	VI (25µg)	UMEC/VI (125/25µg)
LS Mean Change (mL) Trough FEV1 (Day 169)	-31	129	93	207
Column vs. placebo Δ from column (mL)		160	124	238
p-value		<0.001	<0.001	0.001
UMEC/VI (125/25µg) Δ from column (mL)		79	114	
p-value		<0.001	<0.001	
TDI Focal Score (Day 168)	0.8	1.2	1.3	1.8
Column vs. placebo Δ from column		0.4	0.5	1
p-value		0.108	0.054	<0.001
UMEC/VI (125/25µg) Δ from column		0.6	0.5	
p-value		0.006	0.019	
LS Mean Change (mL) 0-6h FEV1 (Day 168)	-1.8	160	127	269
Column vs. placebo Δ from column (mL)		178	145	287
p-value		<0.001	<0.001	<0.001
UMEC/VI (125/25µg) Δ from column (mL)		109	142	
p-value		<0.001	<0.001	

Source: Company data

The incidence of on-treatment adverse events was 49% on placebo, 52% on UMEC/VI, 53% on VI, and 53% on UMEC. A single case of potentially drug-related atrial fibrillation occurred in both the VI and UMEC groups; however, no drug-related CV events occurred on UMEC/VI. The most common adverse events were headache and nasopharyngitis. A summary of the safety data from DB2113361 is below:

Safety Comparison Of Anoro To Placebo, UMEC, And VI

	Placebo	UMEC (125µg)	VI (25µg)	UMEC/VI (125/25µg)
Any Adverse Event (n%)	134 (49)	217 (53)	215 (53)	211 (52)
Nasopharyngitis	32 (12)	37 (9)	55 (14)	47 (12)
Headache	32 (12)	37 (9)	41 (10)	41 (10)
Cough	16 (6)	15 (4)	18 (4)	29 (7)
Back pain	13 (5)	17 (4)	10 (2)	10 (2)
Pyrexia	7 (3)	9 (2)	9 (2)	13 (3)
Hypertension	4 (1)	9 (2)	12 (3)	8 (2)
Toothache	7 (3)	12 (3)	10 (2)	4 (<1)
Arthralgia	5 (2)	5 (1)	8 (2)	11 (3)
URI	7 (3)	6 (1)	9 (2)	7 (2)
Dyspnea	9 (3)	5 (1)	10 (2)	4 (<1)
Pain in extremity	5 (2)	8 (2)	12 (3)	3 (<1)
COPD	11 (4)	6 (1)	4 (<1)	6 (1)

Source: Company data

Anoro Demonstrates Superiority To Spiriva In Two Phase III Studies

The goal of Study DB2113374 was to compare the safety and efficacy of two doses of Anoro (UMEC/VI) to UMEC and Spiriva. Anoro 125/25µg demonstrated superior improvements in trough FEV1 and 0-6h FEV versus Spiriva and was numerically, but

not significantly, superior to UMEC alone. A summary of the efficacy data from DB2113374 is below:

Efficacy Comparison Of Anoro To UMEC And Spiriva

	UMEC (125µg)	UMEC/VI (62.5/25µg)	UMEC/VI (125/25µg)	Spiriva (18µg)
Number of Patients	222	217	215	215
LS Mean Change (mL) Trough FEV1 (Day 169)	186	208	223	149
UMEC/VI (62.5/25µg) Δ from column (mL)	22			0.06
p-value	0.377			0.018
UMEC/VI (125/25µg) Δ from column (mL)	37			74
p-value	0.142			0.003
LS Mean Change (mL) 0-6h FEV1 (Day 168)	206	276	282	180
UMEC/VI (62.5/25µg) Δ from column (mL)	70			96
p-value	0.003			<0.001
UMEC/VI (125/25µg) Δ from column (mL)	76			101
p-value	0.003			<0.001

Source: Company data

On-treatment adverse events occurred in 59-62% of patients on UMEC, VI, or the combination compared to 59% of patients on Spiriva. There were no reports of drug-related serious adverse events. A summary of the safety data for Study DB2113374 is presented below:

Safety Comparison Of Anoro To UMEC And Spiriva

	UMEC (125µg)	UMEC/VI (62.5/25µg)	UMEC/VI (125/25µg)	Spiriva (18µg)
Any Adverse Event (n%)	131 (59)	127 (59)	133 (62)	126 (59)
Headache	25 (11)	21 (10)	20 (9)	15 (7)
Nasopharyngitis	6 (3)	14 (6)	16 (7)	17 (8)
URI	17 (8)	6 (3)	10 (5)	14 (7)
Back pain	10 (5)	8 (4)	6 (3)	11 (5)
Cough	14 (6)	5 (2)	8 (4)	6 (3)
Hypertension	9 (4)	1 (<1)	4 (2)	7 (3)
Oropharyngeal pain	8 (4)	3 (1)	6 (3)	3 (1)
Diarrhea	8 (4)	4 (2)	1 (<1)	5 (2)
Gastritis	6 (3)	6 (3)	5 (2)	1 (<1)
Pain in extremity	1 (<1)	7 (3)	6 (3)	4 (2)
UTI	6 (3)	2 (<1)	5 (2)	4 (2)
COPD	2 (<1)	7 (3)	6 (3)	1 (<1)
Influenza	6 (3)	3 (1)	2 (<1)	5 (2)
Lower respiratory tract infection	1 (<1)	9 (4)	3 (1)	2 (<1)
Dyspnea	6 (3)	1 (<1)	0	3 (1)

Source: Company data

The goal of Study DB2113360 was to compare the safety and efficacy of two doses of Anoro (UMEC/VI) to VI and Spiriva. Anoro 62.5/25µg and 125/25µg demonstrated superior improvements in trough FEV1 and 0-6h FEV versus Spiriva and VI alone. A summary of the efficacy data from DB2113360 is below:

Efficacy Comparison Of Anoro To VI And Spiriva

	Placebo	UMEC (125µg)	VI (25µg)	UMEC/VI (125/25µg)
LS Mean Change (mL) Trough FEV1 (Day 169)	-31	129	93	207
Column vs. placebo Δ from column (mL)		160	124	238
p-value		<0.001	<0.001	0.001
UMEC/VI (125/25µg) Δ from column (mL)		79	114	
p-value		<0.001	<0.001	
TDI Focal Store (Day 168)	0.8	1.2	1.3	1.8
Column vs. placebo Δ from column		0.4	0.5	1
p-value		0.108	0.054	<0.001
UMEC/VI (125/25µg) Δ from column		0.6	0.5	
p-value		0.006	0.019	
LS Mean Change (mL) 0-6h FEV1 (Day 168)	-1.8	160	127	269
Column vs. placebo Δ from column (mL)		178	145	287
p-value		<0.001	<0.001	<0.001
UMEC/VI (125/25µg) Δ from column (mL)		109	142	
p-value		<0.001	<0.001	

Source: Company data

The incidence of adverse events was slightly higher for VI and UMEC/VI relative to Spiriva. However, a dose dependent trend in adverse events for UMEC/VI was not observed. A summary of the safety data from Study DB2113360 is below:

Safety Comparison Of Anoro To VI And Spiriva

	VI (125µg)	UMEC/VI (62.5/25µg)	UMEC/VI (125/25µg)	Spiriva (18µg)
Any Adverse Event (n%)	99 (47)	108 (51)	94 (44)	82 (39)
Nasopharyngitis	17 (8)	21 (10)	14 (7)	16 (8)
Headache	21 (10)	20 (9)	14 (7)	9 (4)
URI	5 (2)	8 (4)	7 (3)	8 (4)
Back pain	3 (1)	10 (5)	7 (3)	4 (2)
Cough	4 (2)	7 (3)	7 (3)	5 (2)
Oropharyngeal pain	5 (2)	1 (<1)	6 (3)	2 (<1)
Hypertension	6 (3)	3 (1)	3 (1)	1 (<1)
UTI	2 (<1)	0	0	6 (3)

Source: Company data

Advair Growth Likely Clipped By Next-Generation Drugs, Non-Substitutable Generics

Advair (Seretide ex-U.S.) was the first combination long-acting beta agonist (LABA)/steroid to be launched into the European and U.S. markets. First-line use of Advair in asthma has slowed due to FDA label changes in 2005 regarding the risk of rare but serious exacerbations associated with long-acting beta agonists. FDA revisited the concern with LABAs in December 2008 with a meta-analysis which showed that LABAs were associated with an increased risk of asthma-related events relative to non-LABA treatment. Three of the four drugs (Foradil (NVS), Serevent (GSK), Symbicort (AZN) had positive risk difference estimates for the asthma composite endpoint, but Advair did not; however, only Serevent had a statistically significant estimate. The Joint Advisory Committee endorsed Advair's use in both children and adults with a similar recommendation for Symbicort. In April 2008, FDA approved Advair 250/50 for the reduction of exacerbations and the improvement of lung function in COPD.

Advair sales have been under pressure from generics in E.U. markets and U.S. competitive pressures (pricing, shift to other agents, including Breo). However, Advair was re-instated on the Express Scripts formulary for 2015, reflecting price concessions by Glaxo. We estimate Advair sales of £4.225B (-20%) in 2014, £3.49B in 2015, £3.025B in 2016, £2.03B in 2018, and £1.71B in 2020.

Advair Generics Gaining Some Ground In Europe

Novartis (Sandoz) received approval in Denmark for a non-substitutable Advair generic (Airflusal) in December, 2013, followed by approvals in Germany, Sweden, Hungary, Romania, and Bulgaria (in 10 countries total). Glaxo has filed suit vs. Sandoz in Germany alleging unfair competition due to the same primary packaging color (purple) used for AirFluSal. Teva plans to launch a non-substitutable Advair generic in 2015 in the E.U. and in 2016 in the U.S. Mylan will be starting a Phase III trial in October 2014 for its generic version of Advair (with scheduled completion April 2015). To date, non-substitutable generics have not gained a significant foothold in the market.

FDA Guidance On Regulatory Pathway For Advair Generics Surprisingly Mild; Starts The Clock For U.S. Competition

The long-awaited draft guidance for generic Advair was issued by the FDA on September 9, 2013. The guidelines include 1) in vitro performance looking at particle distribution, 2) equivalent systematic exposure based on PK data, and 3) equivalent local delivery with PK and clinical endpoints. Per the guidance, in vitro studies, including a particle size distribution study, a PK bioequivalence study, and a clinical study with two FEV1 endpoints will be required. Additionally, to make this a "J" filing, the guidance indicates that the devices should be quantitatively and qualitatively similar. Final guidelines could be released at any time.

Overall, the guidelines were in line with our consultant's expectations, although the clinical guidelines were viewed as less onerous. Other comments from our consultant include: 1) the in vitro particle distribution studies look straightforward, but require several iterations of testing and therefore, will take time; 2) the PK BE study looked straightforward; 3) the endpoint in the clinical study of FEV1 at the lowest dose seemed a surprisingly low hurdle to our consultant who had expected the FDA to require data on assay sensitivity between doses and a requirement to establish does response based on mathematical modeling; in the draft guidelines, the higher doses need only show PK data; and 4) key requirement for device is that it must be of "similar size and shape" as the Advair diskus device – this could preclude generics until the expiration of the device patent in 2016.

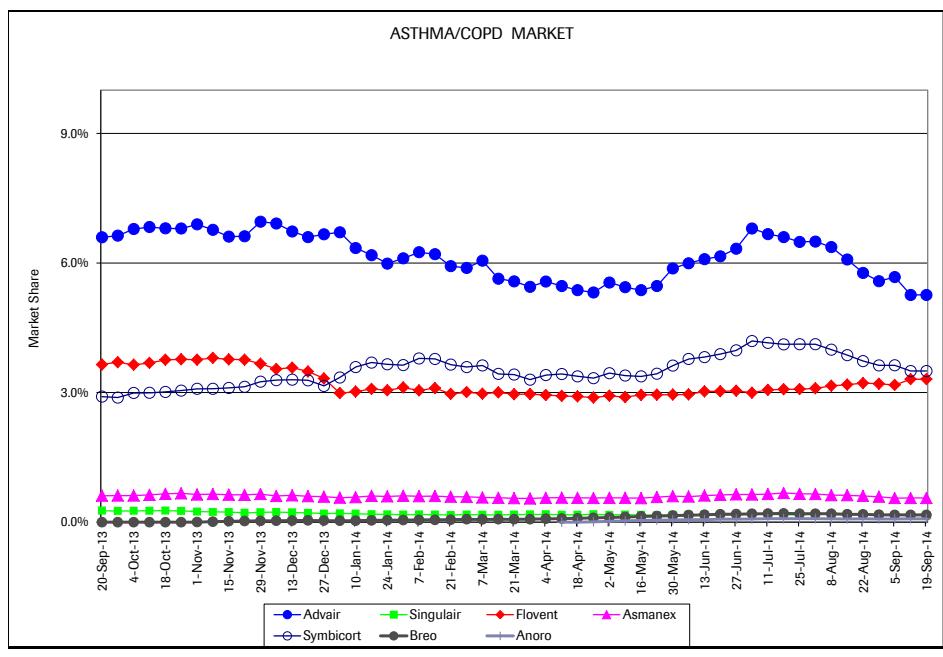
Glaxo Submits Detailed Response To Draft Guidelines

In November 2013, Glaxo filed an extensive (14 pages) and detailed response to the FDA's draft guidelines for generic Advair. The takeaway message from our consultants is that the response is primarily focused on the CMC (chemistry, manufacturing, and control) aspects of the draft. These tests include the demonstration of equivalent product quality through the life of the product (which our consultants interpret to mean "shelf life") and tighter guidelines for particle-size distribution. Our consultants believe that many of Glaxo's CMC recommendations are likely already required of the company by the agency in making site transfers for Advair, and therefore, FDA might look to incorporate these suggestions for the generics as well. Our consultants note that the initial guidelines were vague on the CMC requirements, and therefore, there is significant room for the agency to entertain some of Glaxo's requests for more specificity and stringency on CMC issues.

Glaxo also suggests that the same quality standards should be applied to generics as are applied to Advair; this should include direct comparisons to Advair over time; specs on particle size distribution should be equally rigorous to Advair; Glaxo is willing to publish its USP product monograph (a "recipe") for Advair in the interest of patients. Glaxo also recommends more extensive clinical testing with clinical endpoints strengthened to include COPD, not just asthma, and break out studies by age and disease state. Glaxo suggests that the FEV1 data as required in the draft is not clinically sufficient. Glaxo also seeks stronger comparison testing with PK tests and in vitro tests having greater specifications in the required endpoints. Glaxo also recommends more device testing (air flow resistance, inactive ingredients).

According to our consultants, if Glaxo's comments are adopted, the FDA would require generics to show CMC-related product performance through the shelf life of the product, which is over 18 months. Therefore, generics would have to produce CMC/stability data of perhaps 18 months or more, delaying potential filings. Additionally, the FDA would have to consider Glaxo's response, which could delay the release of final guidelines by 3-6 months.

ASTHMA, COPD MARKET



Source: IMS America

Incruse Gains U.S. Approval

In April 2014, Glaxo received U.S. and E.U. approval for Incruse (umeclidinium), a once-daily, long-acting anticholinergic/anti-muscarinic (and the LAMA agent in Anoro) for use in COPD patients. It will be delivered as part of the Ellipta inhaler. Launch is expected in Q4:14. The approved dose for Incruse is 62.5mcg, slightly higher than the 55mcg amount in Anoro. At ATS 2014 in May, Glaxo presented results from a study demonstrating the safety and efficacy benefits of adding Incruse (62.5mcg and 125mcg doses) to Advair treatment in COPD patients. A statistically significant improvement in trough FEV1 at day 85 (primary endpoint) was seen with the addition of Incruse for both Incruse doses. Headache and nasopharyngitis were the most common adverse reactions. There were fewer COPD exacerbations and CV adverse

events with the Incruse arms; however, three cases of pneumonia were reported in the Incruse arms, and one death was cited as study-drug related. Incruse was filed in Japan in Q2:14. We estimate Incruse sales at £40MM in 2015, £60MM in 2016, £100MM in 2018, and £140MM in 2020.

In June 2014, Glaxo/Theravance reported data from two Phase III studies which demonstrated that Incruse can be a safe and efficacious addition to COPD patients already on Breo/Relvar ("triple therapy"). With a primary endpoint of trough FEV1 at day 85, the addition of Incruse to Breo resulted in a statistically significant improvement in trough FEV1 in a range of 111-128ml for both studies versus placebo + Breo. The side effect profile was similar for all groups, including CV and pneumonia events.

ICS Arnuity In Ellipta Inhaler Gains U.S. Approval

In August 2014, Glaxo received U.S. approval for the 100mcg and 200mcg once daily inhaled doses of Arnuity, the ICS fluticasone furoate , utilizing the Ellipta inhaler, for use in asthma patients 12 years and older. Regulatory filings in other countries are planned for 2014.

Fixed Triple Combo Now In Phase III

A Phase III study (IMPACT) of a fixed dose "closed" triple combo (FF/UMEC/VI) of fluticasone furoate (ICS), vilanterol (LABA), and umeclidinium (LAMA) was initiated in July 2014 for once-daily use in COPD. The trial expects to enroll 10,000 patients with a primary completion date of July 2017 (according to ClinicalTrials.gov). The trial is a 52-week, randomized, 3-arm study comparing FF/UMEC/VI to Breo (FF/VI) and Anoro (UMEC/VI). Primary endpoint is rate of exacerbations.

GSK '081 Novel MABA Provides Dual Functionality As Single Agent

'081 is unique, as it combines the functionality of a LABA and a muscarinic antagonist (LAMA) in a single molecule. Our clinical consultants like the potential opportunity MABAs would provide in combination with an ICS to yield a triple therapy, but as monotherapy, MABA are likely to have a limited role in the treatment of asthma or COPD. We estimate '081 sales of £10MM in 2017, £25MM in 2018, and £75MM in 2020.

MABA Effective In Phase II; Phase III Pre-Clinical Work Initiated At Year End 2013

In May 2012, Glaxo and Theravance reported complete Phase IIb data on '081. All doses of '081 achieved the study's primary trough FEV1 endpoint compared to placebo and showed improvement in FEV1 over salmeterol (weighted mean FEV1 at 0-24hrs and 0-12hrs). The safety profile of '081 appears to be benign with headache, cough, and dysgesia the most frequently observed adverse events. A single serious adverse event occurred in a '081 treated patient (biliary colic), but this event was determined not to be drug related. Preclinical Phase III enabling work with '081 in combination with once-daily fluticasone furoate began late 2013 as the company looks to focus on '081 as the backbone of triple therapy (LABA/LAMA/ICS). Phase III monotherapy trials for '081 have been delayed and revised timing has not been announced.

Phase II Study Met Primary Endpoint Of FEV1

At ERS 2012, Glaxo presented Phase II dose ranging data (total daily dose of 100-800ug) for '081 in patients with moderate-to-severe COPD. The primary endpoint of

the study was mean change from baseline for trough FEV1 on Day-29. A number of secondary endpoints were also evaluated. Treatment with '081 resulted in statistically significant improvements in trough FEV1 at all doses.

'081 Primary Endpoint Analysis

Treatment	Primary Endpoint Analysis-Trough FEV1 At Day 29						
	SAL 50	100 BID	200 BID	400 BID	100 OD	400 OD	800 OD
N	43	47	46	49	45	41	48
LSMean Difference	72mL	173mL	249mL	258mL	155mL	215mL	277mL
95%CI	(0-150)	(100, 250)	(170-320)	(190, 320)	(80, 230)	(140, 290)	(200, 350)
p-value	0.048	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Source: Company data, ERS 2012

Although the study was not powered to detect a reduction in rescue medication use, all doses of '081 significantly reduced the use of rescue medication between weeks 1 and 4.

'081 Rescue Medication Use

Treatment	Analysis Of Rescue Medication Use						
	SAL 50	100 BID	200 BID	400 BID	100 OD	400 OD	800 OD
N	43	50	48	52	48	45	51
LSMean Difference	-0.39	-0.57	-0.56	-0.74	-0.45	-0.65	-0.6
95%CI	(-0.7, -0.1)	(-0.9, -0.3)	(-0.9, -0.2)	(-1.1, -0.4)	(-0.8, -0.1)	(-1.0, -0.3)	(-0.9, -0.2)
p-value	0.026	<0.001	<0.001	<0.001	0.007	<0.001	<0.001

Source: Company data, ERS 2012

Adverse events on '081 were rare and generally in-line with placebo and salmeterol with the exception of headache, cough, and dyspepsia which occurred more frequently in MABA-treated patients. Pre-clinical studies in dogs suggested that '081 may be associated with airway erosion at high doses, although differences in inhalation devices likely caused powder deposition in animals' airways that would not occur in humans.

'081 Treatment Adverse Events

AE	PBO	Summary of On-Treatment Adverse Events						
		SAL 50 (n=81)	100 BID (n=47)	200 BID (n=52)	400 BID (n=54)	100 OD (n=50)	400 OD (n=50)	800 OD (n=52)
Headache	5 (6%)	2 (4%)	2 (4%)	0	5 (9%)	5 (10%)	5 (10%)	2 (4%)
Cough	2 (2%)	0	2 (4%)	4 (8%)	1 (2%)	5 (10%)	5 (10%)	4 (8%)
Dysgeusia	0	0	2 (4%)	3 (6%)	4 (8%)	3 (6%)	2 (4%)	1 (2%)
Nasopharyngitis	3 (4%)	0	1 (2%)	3 (6%)	0	3 (6%)	1 (2%)	0
Back pain	2 (2%)	0	1 (2%)	0	0	0	2 (4%)	0
Dysphonia	2 (2%)	0	0	0	0	0	1 (2%)	2 (4%)
Muscle spasms	0	1 (2%)	1 (2%)	0	2 (4%)	0	0	1 (2%)
Nausea	2 (2%)	0	0	0	0	1 (2%)	1 (2%)	0
Myalgia	1 (1%)	1 (2%)	0	0	0	0	2 (4%)	0
Palpitations	0	1 (2%)	0	0	2 (4%)	0	0	0

Source: Company data, ERS 2012

Adverse events leading to withdraw were rare. One case of Wolff-Parkinson-White and the single case of AV block on '081 were determined to be pre-existing conditions and were unrelated to drug.

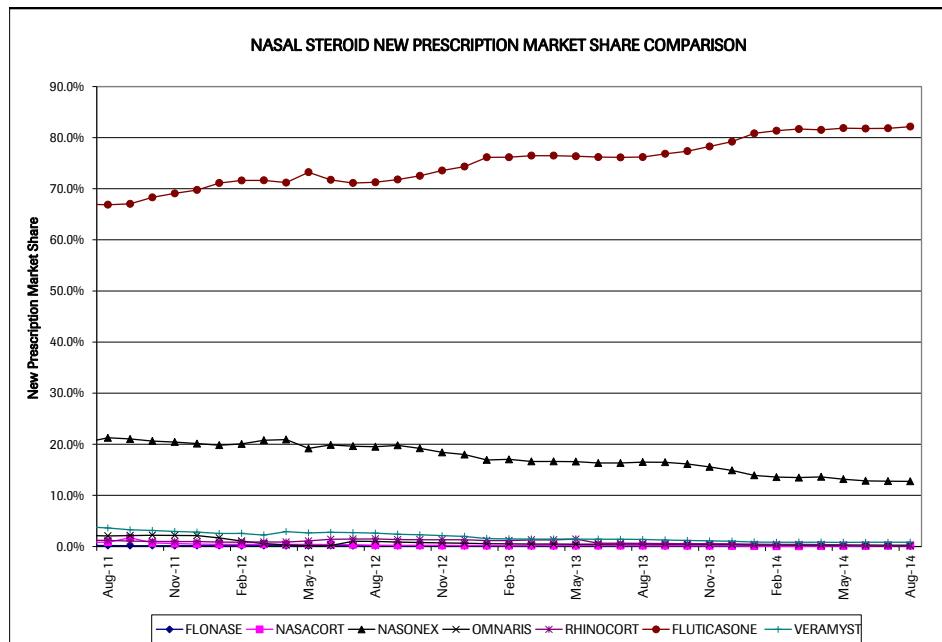
Veramyst Has Subtle Label Differentiation But Fluticasone Generics Dominate The Market

Veramyst (fluticasone furoate), administered as a once-daily nasal formulation, is marketed for the treatment of seasonal and year-round allergy symptoms in adults and children as young as two years. This is a broader label, in that it includes both nasal and ocular symptoms, compared to NasoneX (Merck) which is indicated only for the treatment of the nasal symptoms of seasonal allergic (SAR) and perennial allergic rhinitis. Approval was based on three Phase III studies, two in SAR and one in perennial allergic rhinitis, which highlighted that Veramyst had demonstrated a benefit for ocular symptoms.

In the first Phase III SAR study (presented February 2007) of 302 patients allergic to mountain cedar pollen, Veramyst was associated with a sustained relief in both nasal and eye symptoms for a period of 24 hours. These endpoints achieved statistical significance. In the second SAR study in 299 patients allergic to ragweed, Veramyst demonstrated a statistical improvement in the sustained (24 hours) relief of both nasal and ocular symptoms. The nasal symptoms improved within 8 hours of the 1st dose ($p=0.028$). In the perennial allergic rhinitis (PAR) study, once-daily Veramyst given for four weeks improved the nasal symptoms for a sustained period of 24 hours. The improvement in ocular symptoms associated with SAR and the broader label represent a differentiating feature versus Flonase and NasoneX. However, this distinction was offset in July 2014, as Flonase received OTC approval for symptoms of hay fever or upper respiratory allergies including relief of all nasal and eye-related allergy symptoms. Glaxo expects to launch Flonase Allergy Relief OTC in early 2015.

As of August 2014, Veramyst held a 0.8% NRx share of the allergy market; NRxs were down 36% Y/Y. We forecast Veramyst sales of £260MM (+4%) in 2014, £310MM in 2015, £350MM in 2016, £420MM in 2018, and £490MM in 2020.

Nasal Steroid New Prescription Market Share Comparison



Source: IMS America

Bosatria Expected To Be Filed For Asthma In Q4:14

Bosatria (mepolizumab), an anti-interleukin 5 (IL-5) antibody, reduces the number of eosinophils by inhibiting an immune system signaling through interleukin-5. Results from two studies in the Phase III program (in severe asthma) were released in September, 2014 which demonstrated positive results in exacerbation reduction and decreasing the amount of daily steroid use. We estimate Bosatria sales of £10MM in 2017, £25MM in 2018, and £75MM in 2020.

Phase III Data Supports Expected Late 2014 Filing

In September 2014, results from two Phase III mepolizumab studies were published in the New England Journal of Medicine. MENSA was a 32-week trial evaluating the efficacy of mepolizumab 75mg IV and 100mg SQ every 4-weeks versus placebo on the frequency of clinically significant exacerbations in patients with severe refractory asthma. SIRIUS was a 24-week study which evaluated the use of mepolizumab 100mg SQ as adjunctive therapy every 4-weeks to reduce steroid use in patients with severe refractory asthma.

Mepolizumab Phase III MENSA Results

Endpoints At Week 32	Placebo	Mepolizumab (75mg IV)	Mepolizumab (100mg SC)
Annualized rate of severe asthma exacerbations (Percent reduction vs. placebo)	1.75	0.93 (47%)	0.81 (53%)
p-value		<0.001	<0.001
FEV1 pre-bronchodilator mL difference from placebo	--	100 mL 0.025	98 mL 0.028
p-value			
FEV1 post-bronchodilator mL difference from placebo	--	146 mL 0.003	138 mL 0.004
SGRQ score* difference from placebo	--	6.4	7.0
p-value		<0.001	<0.001
ACQ-5 score** difference from placebo	--	0.42	0.44
p-value		<0.001	<0.001

*A change of 4 points is considered clinically relevant

**A change of 0.5 points is considered clinically relevant

Source: Company data

Mepolizumab Phase III SIRIUS Results

Reduction In OCS Dose	Mepolizumab (% of patients)	Placebo (% of patients)
90 - 100%	23	11
75 - <90%	17	8
50 - <75%	13	15
>0 - 50%	10	11
No decrease	36	56

Source: Company data

The Phase III program also includes safety extension trials to further access treatment of subsequent asthma attacks.

Phase II Data Show Mepolizumab May Have A Role In Poorly Controlled Asthma Patients

At ERS 2012, Glaxo presented a 52-week, 616 patient Phase II trial comparing mepolizumab plus standard of care to standard of care alone for the treatment of refractory asthma (>2 exacerbations in past 12-months) in patients >12 years old with eosinophilic asthma. The diagnosis of eosinophilic asthma was made if blood eosinophils were >300/uL, sputum eosinophils were >3%, or if lung function rapidly deteriorated following <25% reduction in steroid dose. Patients were predominantly middle aged (mean age 46-50 years), had 60-80% predicted FEV1, and had experienced an average of 3-7 exacerbations per year prior to entering the study. The primary endpoint was reduction in rate of clinically significant exacerbations, defined as an episode requiring systemic corticosteroids, hospitalization, or ED visit.

Mepolizumab reduced exacerbations by ~50% over the course of the study. No dose response relationship was observed, with all doses significantly reducing exacerbations, hospitalizations, and emergency room visits. Mepolizumab was associated with an 8-fold reduction in blood eosinophils. No impact on symptom scores or quality-of-life measures were observed.

Mepolizumab Exacerbations Data

Dose	N	% Reduction In Exacerbations	p-value
75mg	153	48 (31-61)	<0.001
250mg	152	39 (19-54)	<0.002
750mg	156	52 (36-64)	<0.003

Source: Company data, ERS 2012

Mepolizumab was associated with an equivalent rate of adverse events and serious adverse events compared to placebo. Three deaths occurred in the trial (2 at 250mg dose and 1 at 750mg dose).

Mepolizumab Safety Data

Dose	AEs	SAEs
Placebo	77%	16%
75mg	82%	12%
250mg	82%	16%
750mg	78%	13%

Source: Company data, ERS 2012

In February 2014, Glaxo announced it started a Phase III trial (ME115921) of mepolizumab in eosinophilic granulomatosis with polyangiitis (EGPA), a rare disease characterized by widespread vasculitis that can affect multiple organs including the heart, lungs, skin, GI tract, and kidneys. The treatment goal is to induce and maintain remissions while reducing use of corticosteroids and immunosuppressants.

Vaccines

Cervarix Performance Modest

Cervarix, like Gardasil, is a three-dose HPV vaccine regimen administered at 0, 1, and 6 months. However, Cervarix is made with only two viral vectors (HPV16 and HPV18; 20ug of each) and AS04, a novel adjuvant. ASO4 is a detoxified endotoxin designed to boost the immune response and may result in faster onset of protection, a more durable response against HPV 16/18, as well as cross-protection against other high-risk HPV strains.

Based on clinical data presented, Cervarix appears to be more potent than Merck's Gardasil, have better cross-protection, but does not prevent non-cervical lesions. The potency advantage may afford longer protection and alleviate the need for a booster vaccine. However, our vaccine consultants believe that this will take many years to unfold and are unclear if a booster dose will even be necessary given that, at the time it may be required, female sexual activity is low and concomitantly so is the cancer risk. In September 2011, a report in the British Medical Journal from the U.K.'s Health Protection Agency concluded that Gardasil is more cost effective and even if the vaccines were priced the same that Gardasil is a better choice because it offers protection against a broader spectrum of HPV serotypes. Prior to November 2011, the U.K.'s NICE only offered Cervarix; however, following a tender process, NICE will now only endorse the use of Gardasil. NICE cited Cervarix's lack of protection against genital warts as the primary driver of the switch.

In February 2012, FDA's Pediatric Advisory Committee observed an increase in the risk of febrile seizure with concomitant administration of the 2010-11 flu vaccine with Cervarix and recommended further refinement of febrile seizure risk and continued routine pharmacovigilance when administering these vaccines. In October 2012, the CHMP adopted a positive opinion recommending granting marketing authorization for Cervarix in patients from the age of 9 years for the prevention of premalignant cervical lesions and cervical cancer. In February 2013, the CHMP granted a positive opinion for Cervarix to extend its therapeutic indication to the prevention of premalignant genital vulvar and vaginal lesions causally related to certain oncogenic HPV types. We estimate Cervarix sales of £195MM (+13%) in 2014, £270MM in 2015, £315MM in 2016, £405MM in 2018, and £495MM in 2020.

Comparison Of Glaxo's Cervarix And Merck's Gardasil's U.S. Labels

Prevention of:	Cervarix	Gardasil
<u>Females</u>		
Cervical cancer	Ages 10-25; types 16 and 18	Age 9-26; types 16 and 18
Vulvar cancer	No	Age 9-26; types 16 and 18
Vaginal cancer	No	Age 9-26; types 16 and 18
Cervical intraepithelial neoplasia	Ages 10-25; types 16 and 18	Age 9-26; types 6, 11, 16 and 18
Adenocarcinoma in situ	Ages 10-25; types 16 and 18	Age 9-26; types 6, 11, 16 and 18
Vulvar intraepithelial neoplasia	No	Age 9-26; types 6, 11, 16 and 18
Vaginal intraepithelial neoplasia	No	Age 9-26; types 6, 11, 16 and 18
Genital warts	No	Age 9-26; types 6 and 11
<u>Males</u>		
Genital warts	No	Age 9-26; types 6 and 11

Source: Product labels

Comparison Of Gardasil And Cervarix's Effectiveness Regardless Of Current Or Prior Infection With Vaccine Or Non-Vaccine HPV Types

	Gardasil	Cervarix
CIN 2/3 AIS	% Reduction (95% CI)	% Reduction (95% CI)
Prophylactic efficacy	42.7% (23.7, 57.3)	70.2% (54.7, 80.9)

Women regardless of current or prior exposure to vaccine or non-vaccine HPV types 18.4% (7.0, 28.4) 30.4% (16.4, 42.1)

*Includes all subjects who had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1 and were naïve to 14 common HPV types at Day 1 ; for Gardasil patients received at least 1 dose

Source: Cowen and Company; Gardasil Label; GlaxoSmithKline Data

Final results of Cervarix's pivotal HPV 008 study presented at the 2009 IPV meeting demonstrated a 92.9% protection against HPV-16/18 precancerous lesions and 98.4% in sero and cytology negative females aged 15-25. Overall vaccine efficacy against CIN II+ was 30.4% regardless of serologic and cytological and 70.2% in sero and cytology negative patients. GlaxoSmithKline believes that these overall efficacy data suggest a significant cross-protection advantage over Gardasil's cross-protection data.

GlaxoSmithKline has not presented data on the prevention against precancerous vulvar lesions or genital warts. Our physician experts believe the cross-protection claim will be difficult to substantiate and is unlikely to play a significant role in a physician's choice between Gardasil and Cervarix. Merck failed to garner an approval for Gardasil's sBLA for cross-protection and decided against pursuing the claim further. At IPV 2009, Glaxo presented the much awaited head-to-head immunogenicity data versus Gardasil. At one month post the last vaccination, Cervarix resulted in a significantly higher neutralizing antibody response (measured from sera and cervicovaginal secretions) and memory B cell response than Gardasil. Rates of solicited symptoms were higher for Cervarix. The clinical relevance of these data is unknown.

Rotarix Offers Advantages Over Merck's RotaTeq; PCV-1 Finding A Hiccup

Rotarix is a two dose, oral, monovalent, live attenuated vaccine indicated for the prevention of rotavirus gastroenteritis in infants and children caused by G1 and non-G1 types (G3, G4, and G9). By comparison, Merck's RotaTeq, a three-dose, live, oral pentavalent vaccine, is indicated for the G1, G2, G3 and G4 serotypes. Rotarix's WAC is \$205 for the two vaccines. This is a 4% discount to Merck's three-dose RotaTeq which costs \$213.51 per course. Our vaccine consultant believes that Rotarix's two-dose (1mL each) schedule may be favored over RotaTeq's three-dose (2mL each) regimen for compliance reasons but we have limited visibility into the contracting that may have transpired for RotaTeq.

In March 2010, the FDA recommended the temporary suspension of Rotarix following the detection of porcine circovirus type 1 (PCV1) DNA in the vaccine; however, the FDA allowed the use of Rotarix to resume in June 2010. The EMEA's CHMP stated that no action was necessary at that time, but requested that GSK provide further information. A Vaccine's Advisory Committee in May 2010 concluded that the benefits of Rotarix outweigh the theoretical risk of a PCV1 infection. PCV has never been associated with disease in humans. The advisory meeting documents noted that RotaTeq is not only contaminated with PCV1 but also PCV2. The PCV1 fragments in RotaTeq are smaller than seen in Rotarix. However, PCV2 is a more virulent strain in pigs and therefore potentially poses a greater theoretical risk. Our consultant believes that the source of contamination is the cell culture used to manufacture the vaccines. FDA did not suspend RotaTeq supply.

In June 2013, ACIP (Advisory Committee on Immunization Practices) reviewed new data showing an increased risk of intussusception (a type of bowel blockage) after receiving Rotarix, and to a lesser degree, RotaTeq. The estimated incidence range is 0.7 to 5.4 extra cases per 100,000 children who receive the vaccine. However, the data also showed a marked decrease in hospitalizations and deaths from rotavirus infections which ACIP believes far outweighs the intussusception risk and thus continues to strongly recommend the vaccination. We estimate Rotarix sales of £410MM (+9%) in 2014, £460MM in 2015, £510MM in 2016, £610MM in 2018, and £710MM in 2020.

Rotarix Vs. RotaTeq Comparison

Company	Merck/SanofiAventis	GlaxoSmithKline
Valencies	G1, G2, G3, G4, G9P1A	G1P
Dose	3 x 2mL	2 x 1mL
Schedule	1st dose: 6-12 weeks 2nd dose: 4-10 week interval 3rd dose: 4-10 week interval; no later than 32 weeks	1st dose: 6 weeks 2nd dose after 4 weeks prior to 24 weeks
Indications where approved	Prevention of rotavirus gastroenteritis caused by G1, G2, G3, and G4 serotypes	Prevention of rotavirus gastroenteritis caused by G1, G3, G4, and G9 serotypes
Price per course (WAC)	\$225.60	\$213.15

Source: fda.gov, product labels, www.emea.europa.eu, PriceRx

Synflorix Marketed In The E.U. But Faces Competition From Prevnar 13

Synflorix is a conjugated 10 valent vaccine with significant protection against *Streptococcus pneumoniae* and non-typable *H. influenza* (NTHI). Synflorix uses NTHI as the active carrier protein. NTHI and Streptococcus pneumonia are responsible for approximately 40% of otitis media infections. Current Hib vaccines only cover the encapsulated forms of Haemophilus influenzae (Type B). Phase III data presented at the 6th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD) demonstrated Synflorix efficacy in children. Synflorix provides broader coverage against invasive disease, compared to Prevnar-7, as it includes three additional pneumococcal strains - 1, 5 and 7F - that are not currently vaccine preventable. These strains cause a significant number of severe childhood invasive diseases, accounting for 5-25% of all cases in different regions of the world and are an increasingly prominent cause of serious disease in Europe. In March 2009, the E.C. approved Synflorix, for active immunization against invasive disease and otitis media caused by *Streptococcus pneumoniae* in infants and children from six weeks up to two years of age. The recommendation did not include an indication for non-typable HiB otitis media, negating any potential advantage over Pfizer's Prevnar 13. GlaxoSmithKline has stated it designed Synflorix's manufacturing process to keep the cost of goods low. A low cost vaccine is likely to change the value proposition and is better suited for emerging markets.

In November 2009, Glaxo was awarded prequalification by the WHO. Prequalification is a service provided by the WHO to facilitate access to medicines in less-affluent countries. A WHO prequalification will facilitate rapid access by developing countries. In September 2012, Glaxo announced the submission of a new application seeking approval for Synflorix in an additional indication in the E.U., targeting prevention of invasive pneumococcal disease (IPD) in infants <2 years of age. In November 2012, Glaxo published data in the Lancet suggesting that Synflorix was highly effective (93-100%) at preventing IPD in infants as part of a 2 +1 vaccination program. In December 2013, Synflorix was approved for use in infants/children age 6 weeks to 5 years old. We forecast Synflorix sales of £435MM (+7%) in 2014, £460MM in 2015, £480MM in 2016, £520MM in 2018, and £560MM in 2020.

Comparison Of Pneumococcal Vaccines

	Prevnar	Synflorix	Prevnar 13
Company	Pfizer	Glaxo	Pfizer
Approved	WW	Ex-U.S.	WW
Serotypes	4 6B 9V 14 18C 19F 23F	1 4 5 6B 7F 9V 14 18C 23F	1 <u>3</u> 4 5 6A 6B 7F 9V 14 18C <u>19A</u> 19F 23F
Carrier protein	CRM197	Non-typeable <i>H. influenza</i>	CRM 197

Bold = additional serotypes vs. Prevnar

Underlined= additional serotypes vs. Prevnar and Synflorix

Source: Company data

MenHibrix An Option For Infants

MenHibrix was approved in the U.S. in June 2012. It covers sero groups C and Y and also Haemophilus b. It is approved on a 4 dose regimen in children 6 weeks to 18 months. MenHibrix does not have the A and W sero groups but it is conveniently given on the pediatric vaccine schedule, providing protection from 2 months of age.

Because it is combined with Hib, it will not require an additional shot. Glaxo believes that the C and Y strains are responsible for 90%+ of the meningococcal infections in the U.S. and therefore the vaccine is unlikely disadvantaged by excluding the A and W serotypes. Menhibrix may be used for routine vaccination against Hib, likely at the patient's expense. The protection from MenCY may be of short duration (4-5 years) and booster doses are likely needed to maintain protection until the 11-12 year-old dose. We forecast MenHibrix sales of £5MM in 2016, £15MM in 2018, and £25MM in 2020.

Nimenrix Approved In E.U.

In February 2012, Glaxo announced that the CHMP issued a positive opinion recommending marketing authorization for Nimenrix, its MenACWY-TT quadrivalent vaccine, for active immunization against invasive meningococcal disease caused by *N. meningitidis* serogroups A,C,W-135, and Y. The CHMP recommendation was based on immunogenicity and safety data from more than 8,000 patients >1 year old. Nimenrix's clinical program included 17 clinical studies that were conducted in 17 countries worldwide. In April 2012, the EMA granted marketing authorization for Nimenrix. We estimate Nimenrix sales of £25MM in 2014, £70MM in 2015, £150MM in 2016, £250MM in 2018, and £350MM in 2020.

Pediatric Vaccine Business Substantial But U.S. Competition Heating Up

Pediarix is indicated for active immunization against diphtheria, tetanus, pertussis (whooping cough), all known subtypes of hepatitis B virus, and poliomyelitis caused by poliovirus Types 1, 2, and 3 as a three-dose primary series in infants born of HBsAg-negative mothers, beginning as early as 6 weeks of age. Increased competition in the DTPa sector in the U.S. has clipped sales. We estimate Pediarix/Infanrix sales of £865MM (flat) in 2014, £925MM in 2015, £985MM in 2016, £1,105MM in 2018, and £1,225MM in 2020.

Hepatitis Vaccine Sales In Decline

Glaxo manufactures both Hepatitis A (Havrix) and recombinant Hepatitis B (Engerix) vaccines. We estimate hepatitis vaccine sales of £550MM (-13%) in 2014, £525MM in 2015, £495MM in 2016, £435MM in 2018, and £375MM in 2020.

Malaria Vaccine Submitted For Approval

In July 2014, Glaxo submitted its malaria vaccine, RTS,S to EMA per a WHO-related protocol, to assess quality, safety, and efficacy of the vaccine, which will be manufactured in the E.U., but intended for use exclusively outside the E.U. The vaccine targets the *Plasmodium falciparum* malaria parasite, which is most prevalent in sub-Saharan Africa (SSA). If a positive opinion is granted by EMA, then WHO may make its recommendation by the end of 2015. The E.U. opinion is also needed for marketing approval in the SSA countries. Glaxo has stated it will ultimately price the vaccine at manufacturing cost plus a 5% mark-up which will be re-invested in vaccine research for other tropical diseases. We estimate RTS,S sales of £10MM in 2017, £20MM in 2018, and £40MM in 2020.

Ebola Vaccine May Begin Small-Scale Use In early 2015

GSK's vaccine candidate against the ebola virus is based on an attenuated strain of chimpanzee cold virus, called chimp adenovirus type 3 (ChAd3). The adenovirus is used as a vector to deliver benign genetic material derived from the Zaire species of Ebola virus (which is responsible for the current outbreak in west Africa). The genetic material allows the recipient's cell to express a protein which prompts an immune response to the Ebola virus. Glaxo's candidate has been fast-tracked and partially funded by an international consortium. Safety studies have begun in the U.S. and UK and the WHO (World Health Organization) hopes to begin small-scale use in West Africa early in 2015, assuming safety trials are successful. There are a number of other vaccines in development, although GSK's vaccine and one from NewLink are the leading two candidates being focused on by WHO. The current ebola outbreak has killed 3,100 people (out of 6,600 infected) in west Africa since last March.

Novartis Vaccines: Led By Meningococcal Vaccines

As part of the asset swap transaction announced in April 2014, Glaxo will acquire Novartis' Vaccine portfolio (excluding influenza vaccines). Key vaccines acquired are the meningitis vaccines Menveo (A,C,Y, and W-135) and Bexsero (meningitis B), which was filed with the FDA in June 2014. Glaxo will pay Novartis upfront cash of \$5.25B and potential future milestones of up to \$1.8B and ongoing royalties for the Vaccines business. We assume the transaction closes at the end of Q2:15.

Novartis has a potentially exciting vaccine pipeline but it has been plagued by setbacks. The meningitis B vaccine (Bexsero) is novel and first-in-class but the development in the U.S. was delayed. However, in mid-June 2014, Bexsero was filed with the FDA; Pfizer's meningitis B vaccine was also filed mid-June. Bexsero was approved for individuals age 2 months and older in the E.U. in January 2013. Menveo, the meningitis A,C,Y,W-135 vaccine, has been launched in the U.S. and competes with the well-established incumbent, Menactra (Sanofi). In addition, it appears that the A,C,Y,W market has contracted, as the large catch-up cohort has been saturated by Menactra thus leaving only the birth cohort for both Menactra and Menveo to pursue. Pseudomonas, Group B Strep, acellular pertussis, respiratory syncytial virus, cytomegalovirus, and *H. Pylori* vaccines are all novel, early and unlikely to be significant U.S. opportunities.

We forecast Glaxo vaccine sales from Novartis vaccines at £325MM in 2015, £600MM in 2016, £700MM in 2018, and £800MM in 2020.

Meningitis B Vaccine Filed In U.S.

Bexsero is approved in 34 countries, including the E.U., Australia, and Canada. In March 2014, the UK vaccine committee recommended Bexsero as part of the routine immunization program. In April 2014, Bexsero received Breakthrough Therapy designation and a rolling BLA submission was filed in mid-June for use in adolescents/young adults ages 10-25. In the past year, Bexsero was provided to two U.S. universities, UCSB and Princeton, under an Investigational New Drug designation in response to meningitis outbreaks. Pfizer also filed a BLA for its meningitis vaccine in mid-June.

The meningococcal B strains are a leading cause of bacterial meningitis throughout the world, particularly among infants, accounting for 72% of meningococcal disease in Europe in 2006. Meningococcal B infection can be a devastating disease that strikes suddenly and can kill children quickly. However, the low incidence of MenB disease in the U.S., approximately 9 per 100,000 infants, provides our physician consultant with concern that the ACIP may not recommend MenB for routine vaccination. Novartis however has highlighted that the ACIP recognizes that Meningitis B is an unmet need, and the disease has significant community awareness.

Bexsero Demonstrated Solid Immune Response In Infants

In June 2011 data from a study in more than 1,800 infants showed that the meningitis B vaccine, Bexsero, induces a robust immune response to meningococcal serogroup B when given alone or when co-administered with other routine vaccines. Infants were randomized to receive Bexsero at 2, 4, and 6 months or at 2, 3, and 4 months with or without routine vaccines (7-valent pneumococcal glyco-conjugate-vaccine and a combined diphtheria-toxoid, tetanus-toxoid, inactivated-polio, acellular-pertussis, hepatitis B and Haemophilus influenza type-b vaccine). Immune response was measured using the human serum bactericidal antibody (hSBA) assay. The study met its primary endpoints, and showed that the majority of infants vaccinated with Bexsero, at either dosing schedule with or without routine vaccines, achieved hSBA >1:5 against all vaccine antigens in tested MenB strains (H44/76, 5/99, NZ98/254). More than 99% of participants receiving Bexsero at 2, 4, and 6 months (concomitantly or without routine-vaccines) or at 2, 3 and 4 months (with routine-vaccines) developed hSBA titers >1:5 against strains 44/76 and 5/99. For NZ98/254 the correlate was reached or exceeded in 79% (2, 4, 6 months with routine-vaccines), 87% (2, 4, and 6 months without routine-vaccines) and 81% (2, 3, and 4 months with routine vaccines). Data also show that responses to the routine vaccine antigens,

when co-administered with Bexsero, were generally similar, except for a slightly lower immune response to pneumococcal serotype 6B, which was not clinically meaningful.

Menveo Approved For Infants/Children 2 Months and Older

In August 2013, the FDA granted approval for Menveo (meningococcal conjugate vaccine covering sero groups A, C, Y, and W-135) to be given to infants and toddlers from 2 months of age. Menveo was approved in February 2010 for use in adolescents and adults (ages 11-55 years) and in January 2011 for use in children 2-10 years. The indication for infants as young as 2 months makes Menveo the only vaccine covering four sero groups in this age group. Menveo had competed with Glaxo's MenHibrix (covers meningoicoccal sero groups C and Y and influenza), although the Hib component is a differentiating factor. Menveo's advantage in adolescents is less clear despite demonstrating higher antibody titers in a head-to-head study versus Sanofi's Menactra. The clinical relevance of higher titers is unclear.

Several Novel Antibacterial Vaccines In Development But All Early

Novartis has three novel bacterial vaccines that are in development: *P. aeruginosa* (Phase II/III); Group B *S. Pneumoniae* (GBS) (Phase I); and *H. Pylori* (Phase I). The pseudomonas vaccine (IC43) is being developed in partnership with Valneva, and is aimed predominantly at the U.S. nosocomial market where ICU/burn patients are at risk to develop pseudomonas infections. Pseudomonas can be fatal given limitations of current antibacterial therapy. The pivotal Phase II/III program began in March 2012 and is a randomized, placebo-controlled double-blind study that will enroll up to 800 ventilated intensive-care unit patients in 40 sites over 5 European countries. Interim data, from 394 patients provided in October 2013, showed the vaccine met its pre-specified futility criterion on the primary endpoint of all-cause mortality at day 28 versus placebo. The difference was considered clinically meaningful and in line with results from prior studies. No concerns in safety profile were reported. In March 2014, Novartis and Valneva announced they will continue the trial and enroll an additional ventilated intensive care 400 patients. Preliminary results are expected late 2015/early 2016.

Novartis's GBS vaccine is being developed to cover 85% of the strains. Despite active surveillance in pregnancy for GBS, it is still responsible for 2,750 cases of neonatal sepsis in the U.S. The GBS vaccine is therefore ideal for childbearing women but it is unclear how a broad vaccination would be justified given reasonably effective antibiotics to treat GBS. The *H. pylori* vaccine is being developed for the Far East where gastric ulcers and cancers are significant problems compared to in the U.S.

HIV

Pfizer, GlaxoSmithKline, And Shionogi In HIV Joint Venture

In November 2009, Pfizer and GlaxoSmithKline formed a JV (ViiV) focused solely on research, development and commercialization of HIV medicines. ViiV has a marketed product portfolio which includes Combivir and Kivexa (GSK) and Selzentry/Celsentri (PFE). ViiV has a pipeline of medicines, including compounds in Phase II. ViiV contracts R&D and manufacturing services directly from Glaxo and Pfizer, entered into a new research alliance agreement with Glaxo and Pfizer, and invests in Pfizer and Glaxo's programs for discovery research and development of HIV medicines. ViiV has exclusive rights of first negotiation in relation to any new HIV-related medicines developed by either Glaxo or Pfizer. Pfizer holds a 13.5% equity interest in the new company, and Glaxo a 76.5% equity interest. In November 2012, ViiV Healthcare acquired the exclusive global rights to the Shionogi integrase portfolio through an

equity transaction by which Shionogi became a 10% shareholder in ViiV. Pfizer accounts for its share as an equity method investment. We forecast HIV sales of £1.51B (+9%) in 2014, £2.01B in 2015, £2.355B in 2016, £3.155B in 2018, and £4.025B in 2020, largely driven by the expected strong growth of Tivicay.

In June 2014, ViiV entered into an agreement with Janssen (JNJ) for the development of a single-tablet formulation of dolutegravir (Tivicay) and Janssen's rilpivirine (Endurant). This is ViiV's first external collaboration to co-develop Tivicay with another drug. The two-drug combo will be evaluated as an HIV maintenance therapy for patients already virally suppressed on a three drug regimen. A fixed-dose formulation for pediatric use will also be evaluated. Studies are expected to begin by Q1:15

Tivicay Approved With Favorable Label

In August 2013, the FDA approved Tivicay (dolutegravir) for use in HIV patients in combination with other antiretroviral agents. Tivicay was approved in the E.U. in January 2014. It was approved for both treatment-naïve and treatment-experienced patients, including those treated with other INSTI's. Tivicay's label relative to Isentress indicates fewer side effects. Tivicay is indicated for children at least 12 years old, while Isentress can be given in 2 yr olds and up. Tivicay is priced at a 9% premium to Isentress. We estimate Tivicay sales of £295MM in 2014, £775MM in 2015, £1,100MM in 2016, £1,800MM in 2018, and £2,500MM in 2020.

Trumeq (Dolutegravir Combo Tablet) Receives EU Approval

In September 2014, ViiV received EU approval for Trumeq, a once-daily, single tablet formulation of dolutegravir (Tivicay), and abacavir +lamivudine (Epzicom/Kivexa) in HIV infected adults/children >12yrs. The combo was filed in the U.S. in October 2013; regulatory submissions have also been made in Canada, Australia, and Brazil.

Dolutegravir Efficacy Solid, As Expected, In SPRING-2

In SPRING-2, dolutegravir was non-inferior to raltegravir on the primary endpoint of viral suppression (88% for dolutegravir vs. 86% for raltegravir; response rates independent of which NRTI was used). For patients with high baseline viral loads (HIV-1 RNA >100,000 c/mL), the response rates were 82% for dolutegravir compared to 75% for raltegravir. Patients on dolutegravir did not develop integrase resistance mutations or NRTI resistance mutations (compared to 1 integrase mutation and 4 NRTI mutations in the raltegravir group). Tolerability for dolutegravir was similar to that of raltegravir with the most common adverse events being nausea, headache, nasopharyngitis, and diarrhea. No grade 3 elevations in serum creatinine were observed in either treatment arm. Dolutegravir may be differentiated from GILD's QUAD by once-daily dosing, superior GI tolerability, a potentially cleaner renal profile, the lack of a requirement for a boosting agent, and an impressive resistance profile. The study will continue through 96-weeks to evaluate the tolerability, long-term safety, antiviral and immunologic activity, and viral resistance profile of dolutegravir.

Superior Viral Suppression Driven By Improved Tolerability In SINGLE

In July 2012, Glaxo reported top-line data from dolutegravir's Phase III SINGLE study comparing dolutegravir (50mg) + abacavir/lamivudine to Bristol/Gilead's Atripla (tenofovir/emtricitabine/efavirenz) in treatment naïve adults with HIV-1. Dolutegravir demonstrated statistically superior viral suppression compared to Atripla, driven by improved tolerability translating to fewer dropouts in the dolutegravir-containing arm. As demonstrating superiority as part of a three-drug combination is a high hurdle, we had anticipated dolutegravir to be non-inferior to Atripla in SINGLE. Superior efficacy

and tolerability compared to Atripla is a positive given that Gilead's QUAD demonstrated non-inferior efficacy and inferior GI- and renal-tolerability versus Atripla in Study 102.

At 48 weeks, 88% of patients on the dolutegravir regimen were virologically suppressed compared to 81% of patients on Atripla; the difference in treatment effect was statistically significant ($p=0.003$). Differences in efficacy were driven by improved tolerability and a lower dropout rate in the dolutegravir-containing arm (2% of patients dropped out in dolutegravir arm vs. 10% in Atripla arm). The most frequent adverse events in the Atripla arm were CNS-related (41%). CNS-related events occurred in only 15% of patients in the dolutegravir-containing arm. The rates of GI-related adverse events were similar between treatment groups (22% in both dolutegravir and Atripla arms).

While both Gilead's QUAD and dolutegravir demonstrated reductions in CNS-related adverse events compared to Atripla in head-to-head studies, the QUAD increased the rate of GI- and renal-related adverse events. Our consultants believe the lack of a boosting agent in dolutegravir-containing regimens likely is responsible for its improved tolerability profile compared to the QUAD.

Additional Phase III Studies

- **VIKING-3** — a study which assessed the antiviral activity and safety of dolutegravir containing regimen in 183 antiretroviral therapy-experienced adults with current or historical failure on an integrase inhibitor (INSTI) containing regimen. The proportion of patients who were subsequently virally suppressed with the addition of Tivicay to their background regimen was 63% at week 24. However, poor virologic response was seen in patients on Tivicay twice daily along with an integrase inhibitor.
- **SAILING** — was a 48-week non-inferiority study in 719 antiretroviral experienced, integrase-naïve HIV patients who were failing on current therapy. The study compared once-daily dolutegravir to twice-daily raltegravir, each added to an investigator selected background regimen consisting of at least one fully active agent plus no more than one second single agent. Interim data (24-weeks) showed 79% of dolutegravir patients were virologically suppressed (HIV-1 RNA <50 c/ml) vs. 70% in the raltegravir group.
- **FLAMINGO** — a 96-week study in treatment-naïve HIV-1 patient to assess antiviral activity of dolutegravir compared to darunavir/ritonavir with fixed-dose dual nucleoside reverse Transcriptase Inhibitor. In September 2013, 48-week data showed dolutegravir superior to DRV/r.

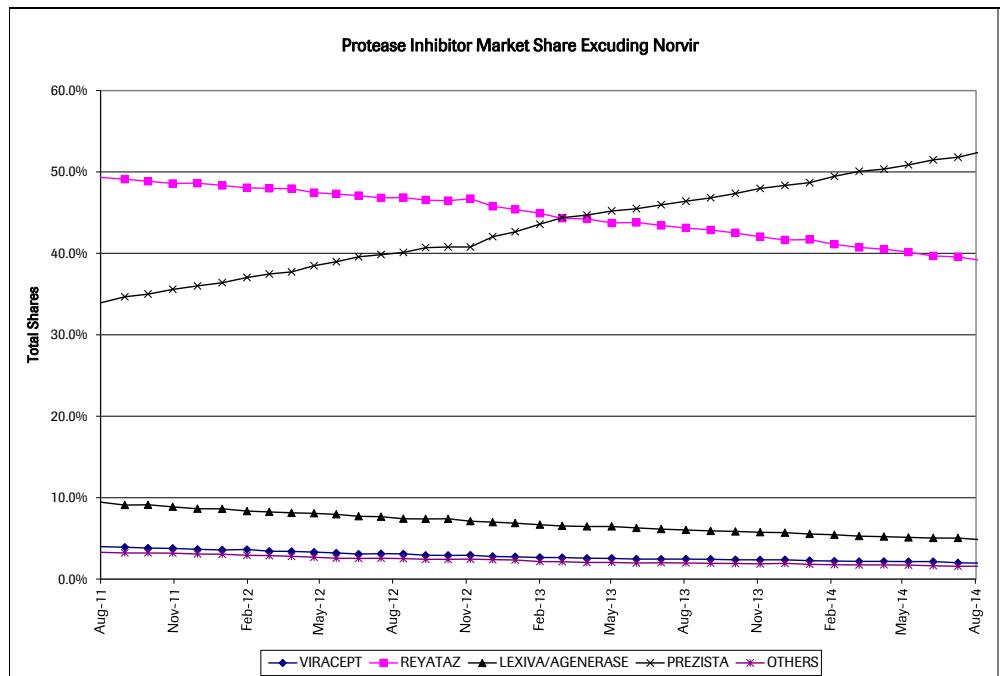
Lexiva Won't Challenge Kaletra Or Reyataz

Lexiva, GlaxoSmithKline's protease inhibitor for the treatment of HIV infection, is a prodrug of agenerase. Lexiva is approved for use with ritonavir in the E.U. under the brand name Telzir. Lexiva's relatively low pill burden and dosing flexibility have allowed it to modestly penetrate the HIV protease inhibitor market. In June 2008 Glaxo acquired the rights to future royalties from sales of Lexiva and Agenerase for \$160MM in cash.

Lexiva is unaffected by antacids, including proton pump inhibitors (PPIs). Antacids have been found to have a dramatic effect on some PIs, significantly reducing absorption, and substantially reducing levels of the drug in the bloodstream. Lexiva

may be dosed in three different ways: two 700mg tablets twice daily; two 700mg tablets once daily in combination with two 100mg capsules of ritonavir; or one 700mg tablet BID in combination with one 100mg capsule of ritonavir BID.

In general, our physician consultants view Lexiva as a good drug, but unlikely to unseat Abbott's Kaletra or Bristol-Myers' Reyataz as the preferred protease inhibitor. Our physician consultants believe that Kaletra may be more potent (although results from the KLEAN study comparing Lexiva + ritonavir BID to Kaletra BID therapy showed them comparable), while Reyataz offers a lower pill-count (two 200mg capsules once daily). Furthermore, Agenerase's drug interactions may prevent Lexiva from playing much of a role in salvage regimens that use two or more protease inhibitors. Competition also is increasing for PIs in salvage regimens from Boehringer Ingelheim's Aptivus and J&J/Tibotec's Prezista. Our physician experts believe Prezista is the most promising PI for inclusion in salvage regimens. In June 2007, the FDA approved a Lexiva oral suspension for children 2-18 years. We forecast Lexiva sales of £95MM (-16%) in 2014, £95MM in 2015 and 2016, £100MM in 2018, and £110MM in 2020.



Source: IMS

Zeffix No Longer The Gold Standard

Zeffix/Epivir-HBV (lamivudine) is identical to lamivudine but formulated at one-third (100mg once per day) the dose. Zeffix blocks viral replication by inhibiting HBV polymerase, the enzyme that copies the HBV's DNA genome into RNA and then back into DNA. While the drug is very well tolerated, its poor resistance profile has limited long-term use. Specifically, studies have shown 15-30% of patients develop resistance within one year of treatment. That proportion increases to 70% by five years of treatment. Viral breakthrough is often associated with an elevation in ALT levels, which in some cases can lead to hepatic decompensation and even death. Competition in the U.S. and Europe from Gilead's Hepsera and Bristol-Myers Squibb's Baraclude also has pressured sales due to emerging Zeffix resistance. We estimate

Zeffix/Epivir sales at £205MM (-9%) in 2014, £210MM in 2015, £215MM in 2016, £235MM in 2018, and £255MM in 2020.

Metabolic/Cardiovascular Drugs

Tanzeum Approved In U.S. But Lagging The GLP-1 Competition, May Have Niche Potential

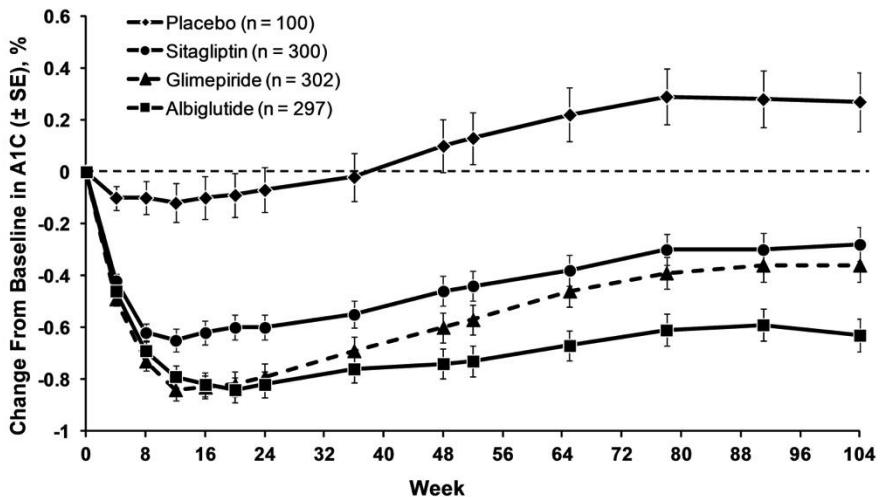
GlaxoSmithKline's Tanzeum/Eperzan (albiglutide) is a GLP-1 agonist that is administered once weekly. Eperzan was approved in the EU in March 2014 and Tanzeum in the U.S. in April 2014. The company believes Eperzan can target the users of high amounts of insulin. The label indicates that in patients on insulin, the insulin dose may need to be reduced when Tanzeum is started, to lessen the risk of hypoglycemia. GSK believes "insulin sparing" is a key differentiating factor among the GLP-1s and could help it gain payor/provider traction. Tanzeum will be priced at \$326/month for both the 30mg and 50mg doses. We estimate Tanzeum/Eperzan sales of £20MM in 2014, £110MM in 2015, £200MM in 2016, £300MM in 2018, and £400MM in 2020.

Unlike the competitors' GLP 1 agonists, Tanzeum/Eperzan is bound to human albumin in order to extend its half-life. Human albumin causes an immune reaction in rodents resulting in the inability to do preclinical testing in these species. Glaxo has done its testing in primates. This precludes a direct comparison of the c-cell carcinomas seen with Novo's liraglutide in rodents. Glaxo stated that there have been no thyroid findings in the preclinical or clinical development program for albiglutide to date. Albiglutide is being evaluated as monotherapy and in combination regimens against both placebo and active comparators including metformin, sulfonylurea, TZD, insulin, and a DPP-IV inhibitor. The primary endpoint in all trials is change in baseline HbA1C with secondary endpoints including change in weight.

Albiglutide Demonstrates Improvements Over Glimepiride And Sitagliptin In HARMONY-3

HARMONY-3 was a 3-year randomized trial comparing the safety and efficacy of albiglutide+metformin to metformin+placebo, metformin+glimepiride, or metformin+sitagliptin. The primary endpoint was difference in A1c from baseline. Albiglutide demonstrated superiority to glimepiride and sitagliptin on A1c and FPG, but failed to demonstrate superior weight loss compared to placebo.

**Figure. Model-Adjusted¹ Change From Baseline in A1C Through Week 104
(Intent-to-Treat; Last Observation Carried Forward²)**



¹ANCOVA model adjusted for baseline A1C, region, history of prior MI, and age category.

A prespecified statistical testing procedure was performed for Albi vs. PBO followed by Albi vs active control for noninferiority and subsequent superiority

²Last observation prior to study discontinuation or hyperglycemia rescue

Source: Cowen and Company

HARMONY-4 Results Mixed Versus Lantus

HARMONY-4 was a 3-year Phase III study comparing the safety and efficacy of albiglutide to Sanofi's Lantus in patients who were uncontrolled on a regimen of metformin +/- a sulfonylurea. If necessary, patients were up titrated from albiglutide 30mg to albiglutide 50mg. Glargin was titrated per prespecified criteria. While albiglutide demonstrated numerically inferior A1c lowering compared to Lantus, the difference was not statistically significant. Albiglutide was significantly inferior to Lantus on lowering FPG, but delivered superior weight loss relative to glargin.

Table. Week 52 Model-Adjusted Change From Baseline Least Square Mean For Key Efficacy Parameters

	Albiglutide (n = 496)	Glargine (n = 239)
A1C, LS Mean ^a (SE), %	-0.67 (0.04)	-0.79 (0.06)
P value (noninferiority)	.0086	
P value (superiority)	.1463	
FPG, LS mean (SE), mg/dL	-15.7 (2.30)	-37.1 (3.31)
P value	< .0001	
Weight, LS mean (SE), kg	-1.05 (0.17)	+1.56 (0.25)
P value	< .0001	

^aLast observation prior to study discontinuation or hyperglycemia rescue carried forward. Treatment comparison based on ANCOVA model was adjusted for baseline A1C, region, history of prior MI, age category, and background antidiabetic therapy.

Source: Cowen and Company

Albiglutide Inferior To TDZ In HARMONY-5

HARMONY-5 was a 52-week Phase III trial comparing the safety and efficacy of albiglutide in combination with metformin and glimepiride to placebo plus metformin and glimepiride and pioglitazone plus metformin and glimepiride. Albiglutide

demonstrated superior A1c reductions relative to placebo, but was inferior when compared to pioglitazone. Similar results were obtained on the FPG endpoint. A greater number of GI events were observed in albiglutide treated patients relative to pioglitazone treated patients.

Table. Efficacy (Adjusted Mean Difference From Baseline [SE]) and Adverse Event (%) Findings at 52 Weeks

	Albiglutide (n=269)	Pioglitazone (n=273)	Placebo (n=115)
A1C (%)	-0.55 (0.06)	-0.80 (0.06) ^a	+0.33 (0.08) ^b
FPG (mg/dL)	-12.4 (2.9)	-31.4 (2.9) ^b	+11.5 (4.4) ^b
Weight (kg)	-0.4 (0.2)	+4.4 (0.2) ^b	-0.4 (0.4) ^c
Adverse events (% participants)			
Diarrhea/nausea/vomiting	8.9/9.6/2.6	5.4/4.3/1.8	2.6/3.5/0.9
Injection site reactions	12.9	3.2	3.5
Documented symptomatic/ severe hypoglycemia ^d	13.7/0.4	25.3/1.1	7.0/0.0

^aLast observation prior to study discontinuation or hyperglycemia rescue carried forward. Treatment comparison based on ANCOVA model was adjusted for baseline A1C, region, history of prior MI, and age category; *P* (noninferiority) not significant (albiglutide not noninferior to pioglitazone)

^b*P*<.0001 vs albiglutide; ^cNot significant; ^dEvents prior to addition of hyperglycemia rescue meds.

Source: Cowen and Company

HARMONY-6 Shows Albiglutide Non-Inferior To Lispro

In HARMONY-6, albiglutide met its primary endpoint of non-inferior HbA1c reduction compared to pre-prandial insulin lispro after 26-weeks when both drugs were given on top of insulin glargine. Albiglutide demonstrated an HbA1c reduction of 0.82% compared to a reduction of 0.66% for lispro insulin (*p*<0.0001 for non-inferiority). The proportion of patients achieving a clinically meaningful HbA1c target level (ADA goal of <7.0%) by week 52 was 45% in the albiglutide group compared to 30% in the lispro arm (*p*=NS). Fasting plasma glucose decreased from baseline in both study arms throughout the 52-week period (-27mg/dL in the albiglutide arm compared to 16mg/dL in the lispro arm). Weight change from baseline was -0.73kg in the albiglutide arm and +0.81kg in the lispro insulin arm (*p*<0.0001 for treatment difference). The most common side effects in the albiglutide arm were nausea (13% for albiglutide vs. 2.1% for lispro insulin) and vomiting (7% for albiglutide vs. 1.4% for lispro insulin).

Albiglutide Did Not Meet Primary Endpoint in Harmony 7

Albiglutide's Phase III HARMONY-7 trial compared albiglutide (50mg once weekly) to Novo's Victoza (liraglutide, 1.8mg QD). In HARMONY-7, albiglutide demonstrated a statistically significant lowering of HbA1c from baseline (*p*<0.001), but did not meet the pre-specified primary endpoint of non-inferiority to Victoza (0.78% lowering of HbA1c vs. 0.99% for Victoza; 95% CI, 0.08-0.34%). Weight loss with albiglutide was less than what was observed for Victoza (-0.62kg vs. -2.21kg for Victoza); however, albiglutide appeared to be more tolerable (9.9% of patients with nausea on albiglutide

vs. 29.9% of patients on Victoza; 5% of patients with vomiting on albiglutide vs. 9.3% on Victoza).

The absolute difference in HbA1c reduction between albiglutide and Victoza in HARMONY-7 (0.21%) was similar to the absolute difference in HbA1c lowering between Bydureon (ALMN) and Victoza in DURATION-6 (0.22%), suggesting comparable glycemic control for Bydureon and albiglutide. However, Bydureon appears to offer a superior weight loss profile (-2.58kg for Bydureon vs. -3.58kg for Victoza in DURATION-6 vs. -0.62kg for albiglutide vs. -2.21kg for Victoza in HARMONY-7).

Albiglutide Superior To Sitagliptin In HARMONY-8

HARMONY-8 was a 52-week study comparing albiglutide to sitagliptin in 507 patients with type 2 diabetes and renal impairment. At the 26-week time point, albiglutide showed a statistically significant reduction in HbA1c from baseline (8.08% for albiglutide vs. 8.22% for sitagliptin) and superiority vs. sitagliptin (0.83% for albiglutide vs. 0.52% for sitagliptin, $p=0.0003$). At 26-weeks, weight loss for albiglutide was statistically greater than for sitagliptin (-0.79kg vs. -0.19kg, $p=0.0281$). Nausea and vomiting rates were comparable across the albiglutide and sitagliptin treatment arms.

Secondary Analysis Shows Blood Glucose Remains Low At 3 Years

At ADA 2014 GSK presented data for four of the HARMONY studies (1,2, 4, and 5) that demonstrated blood glucose lowering at 3 years (on continued once weekly dosing) that was consistent with results reported at year one (primary endpoint). Most common AEs included nausea, diarrhea, and injection site reactions.

Comparison Of Bydureon, Eperzan and Trulicity To Victoza In Phase III Trials

	DURATION-6	HARMONY-7	AWARD-6
Drug	Bydureon (exenatide); 2mg once weekly	Eperzan (albiglutide); 50mg once weekly	Trulicity (dulaglutide); 1.5mg once weekly
Comparator	Victoza (liraglutide); forced titration to 1.8mg QD	Victoza (liraglutide); forced titration to 1.8mg QD	Victoza (liraglutide) 1.8mg QD
Enrollment	911	841	599
Duration	26 weeks	32 weeks	26 weeks
HbA1c reduction	1.26% vs. 1.48% for Victoza; did not meet prespecified non-inferiority endpoint	0.78% vs. 0.99% for Victoza; did not meet prespecified non-inferiority endpoint	Met non-inferiority endpoint; 1.42% vs 1.36% for Victoza
Mean treatment difference	0.21% (95% CI -0.08 to 0.33) not meeting upper limit CI <0.25%	0.21% (95% CI 0.08 to 0.34) p-non-inferiority = 0.0846	-0.06% (95% CI -0.19 to 0.07) p-non-inferiority <0.0001
Weight loss	-2.58kg vs. -3.58kg for Victoza	-0.62kg vs. -2.21kg for Victoza	-2.9kg vs. -3.6kg for Victoza
Nausea	9.3% vs. 20.4% for Victoza	9.9% vs. 29.2% for Victoza	20% vs 18% for Victoza
Vomiting	3.7% vs. 10.7% for Victoza	5% vs. 9.3% for Victoza	7% vs 8% for Victoza

Source: Company data

Darapladib STABILITY And SOLID Results Disappointing But Not Surprising

Tyrosa (darapladib) blocks Lp-PLA2, an enzyme that helps process a form of LDL-C into atherosclerotic plaques and produces signals within the plaques that promote inflammation. Several studies have documented the strong association of Lp-PLA2 with coronary heart disease and stroke in the general population, regardless of total cholesterol or other markers of inflammation. Patients who might benefit from darapladib are those at risk for or who have unstable plaques before or after myocardial infarction or ischemic stroke. These patients would be identified using the PLAC test, which measures plasma Lp-PLA2, and is approved as an aid in predicting risk for CHD and ischemic stroke associated with atherosclerosis. Darapladib was discovered by GSK based on Human Genome Science technology. GlaxoSmithKline is advancing in Phase II rilapladib as a back-up compound. The failure of Anthera's SPLA2 inhibitor, varespladip, in acute ACS increases uncertainty around the anti-inflammatory hypothesis in ACS. However, short-term and long-term inflammation may differentially affect the vasculature and cardiovascular outcomes. We forecast darapladib sales of £10MM in 2020.

STABILITY: Two Secondary Endpoints Achieved Significance While Five, Including Stroke And Total All-Cause Mortality, Missed

In November 2013, GSK released top-line results from its 15,500-patient pivotal Phase III trial, STABILITY. This is an event driven trial (~1,500 events) in patients with stable chronic coronary heart disease. The study did not meet the primary endpoint of time to first occurrence of any MACE (heart attack, stroke, CV death). The result was not surprising as our physician consultants have been consistently skeptical

Full STABILITY results were presented at ACC 2014. Two secondary endpoints achieved significance – reduction in major coronary events ($p=0.045$) and reduction in total coronary events ($p=0.02$) – while five others did not. Importantly, both stroke and total all-cause mortality failed to achieve significance. Of the two endpoints that achieved significance, the reduction in major coronary events appears to have been driven by a reduction in nonfatal MI, and the reduction in total coronary events appears to have been driven by a reduction in nonfatal MI and any coronary revascularization procedure. Any adverse event leading to discontinuation of study drug occurred in 19.8% of darapladib patients and 13.5% of control group patients. Diarrhea, and feces, urine and skin odor, were common reasons. Darapladib was also associated with a reduction in GFR.

SOLID-TIMI 52: Darapladib Also Missed Endpoint

SOLID-TIMI 52 was the second Phase III study of darapladib but studied acute coronary syndrome. Darapladib did not achieve the primary endpoint of a reduction of major coronary events versus placebo when added to standard of care. Safety was consistent with that in STABILITY. The primary endpoint in SOLID-TIMI 52 was time to first occurrence of any event from the composite of coronary heart disease death, MI and urgent coronary revascularisation.

Lovaza Sales In Decline Due To Generics

In November 2007, GlaxoSmithKline acquired Reliant, primarily for their triglyceride-lowering drug Lovaza. Despite containing omega-3 fatty acids that are available as over the counter agents, Lovaza is only available by prescription to treat adult patients with triglycerides greater than or equal to 500 mg/dL only. Lovaza has a proprietary formulation that contains highly purified (>90%) omega-3 oils. In clinical trials it has

demonstrated its benefit across all lipid parameters and has been tested both as monotherapy and in combination with Simvastatin but is only indicated as an adjunct to diet to reduce triglyceride levels in adult patients with very high (>500 mg/dL) triglyceride levels. Results from the GISSI Heart Failure study presented at ESC 2008 showed that 1 g/d dose of Lovaza reduced all-cause mortality and hospital admissions for cardiovascular reasons in patients with chronic heart failure. Data presented at the 2010 Heart Rhythm Society demonstrated that Lovaza failed to reduce AF or atrial flutter in patients undergoing CABG. A study presented at AHA 2010 did not show a benefit for Lovaza in reducing the recurrence of symptomatic AF in patient groups on high-dose Lovaza compared to placebo.

On April 8, 2014, Teva received FDA approval for a generic Lovaza and already claims 50%+ TRx share. We forecast Lovaza sales of £155MM (-73%) in 2014, £30MM in 2015, £25MM in 2016, £30MM in 2018, and £40MM in 2020.

Lovaza In Patients With Very High TG Levels (>500 mg/dL)

Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (>500 mg/dL)

	LOVAZA N=42		Placebo N=42		Difference
	BL	%Change	BL	%Change	
TG	816	-44.9	788	6.7	-51.6
Non-HDL-C	271	-13.8	292	-3.6	-10.2
TC	296	-9.7	314	-1.7	-8
VLDL-C	175	-41.7	175	-0.9	-40.8
HDL-C	22	9.1	24	0	9.1
LDL-C	89	44.5	108	-4.8	49.3

Source: Lovaza Label

CNS

Lamictal Franchise In Decline

Lamictal (lamotrigine) has proven particularly effective in treating partial-onset and generalized-onset epilepsy. However, Lamictal needs to be titrated carefully since many patients develop a serious skin rash if the dose is escalated too quickly; physicians often titrate Lamictal over the course of months before achieving the appropriate treatment level. Lamictal is indicated for the treatment of epilepsy (monotherapy and adjunctive therapy) and bipolar disorder in patients who have not responded to standard therapies. Lamictal has an indication for long-term management of bipolar disorder to delay the relapse/recurrence of depressive episodes. It is also used for neuropathic pain, prevention of migraine headaches and for the adjunctive treatment of primary generalized tonic-clonic seizures. In September, 2006, the FDA issued a warning concerning the increased risk of cleft lip/cleft palate in infants of mothers using Lamictal during the first three months of pregnancy. In July 2008, an FDA advisory panel voted to reject the Agency's proposal to make manufacturers of 11 epilepsy drugs put a Black Box warning label on their products. The FDA had recommended the Black Box warning because studies showed the drugs had nearly double the risk of suicide compared to placebo, although in absolute terms it was still quite small. The panel did however, recommend the warning should be increased, but not to the Black Box level. In December 2008, FDA announced that it was adding a label warning on the heightened suicide risk for users of antiepileptic drugs, including suicidal thoughts and behaviors (suicidality). The FDA

also required that manufacturers draw up Medication Guides that outline the risks and can be given to patients and their families when the medications in question are prescribed.

The Lamictal patent was set to expire in 2009 in the U.S. but GlaxoSmithKline and Teva settled and Teva launched its generic in mid-2008. GlaxoSmithKline had filed Lamictal XR, an extended-release version of Lamictal, for the treatment of epilepsy in 11/06 in an effort to extend the franchise. However after several not-approvable letters, it was finally approved in June 2009, too late to convert the franchise. In December 2012, GSK finalized the sale of its Australian portfolio of "Classic Brands," which includes Lamictal, to Aspen Global for £163.8MM. We estimate Lamictal sales of £505MM (-9%) in 2014, £465MM in 2015, £395MM in 2016, £320MM in 2018, and £315MM in 2020.

Retigabine/Ezogabine Limited By Dosing Profile

Retigabine/ezogabine (Trobalt/Potiga) is a selective potassium channel opener and potentiates the effects of GABA. Retigabine/ezogabine was approved by FDA for the adjunctive treatment of partial onset seizures in June 2011. In December 2011, FDA scheduled retigabine as a class V controlled substance. In January 2011, Glaxo received a positive opinion from the CHMP for retigabine and received marketing authorization in March 2011. In February 2012, Germany's IQWiG determined that retigabine offers no proof of additional efficacy in epilepsy compared with present standard therapies. Our consultants note that retigabine/ezogabine has no particular advantages but its mechanism of action is novel. Its major drawback is dosing three times daily. In May 2013, the CHMP recommended restricting the use of Trobalt only to those for whom other anti-epileptic medicines have proved inadequate. A Phase I study of 5 modified release formulations of retigabine are complete; no further trials are scheduled. We forecast retigabine/ezogabine sales of £10MM in 2014, £20MM in 2015, £25MM in 2016, £35MM in 2018, and £45MM in 2020.

Glaxo licensed worldwide rights to retigabine/ezogabine from Valeant. Under the terms of the agreement, GlaxoSmithKline has worldwide development and commercialization rights to Retigabine, VRX698, and the other back-up compounds from the potassium channel opener discovery program. Glaxo paid Valeant \$125MM upfront and will pay up to \$545MM based on the achievement of certain regulatory, development, and commercialization milestones and the development of additional indications for retigabine.

Losmapimod In Phase II For Neurological Disorders

Losmapimod (GW856553), a p38 kinase inhibitor, is in Phase II development for the treatment of MDD, pain, COPD, and cardiovascular disease. P38 kinase is responsible for the production of some pro-inflammatory molecules, called cytokines. Increased blood levels of these molecules were seen in populations of MDD patients and this was more apparent in subjects with severe symptoms, psychomotor retardation and loss of energy. We estimate losmapimod sales of £10MM in 2017, £25MM in 2018, and £75MM in 2020.

Firategrast A Small Molecule Targeting RRMS

Firategrast ('699) is an anti-VLA small molecule currently in a 350 patient Phase II dose-ranging study in relapsing remitting MS patients. Tysabri (BIIB) targets VLA, supporting the mechanism of action. However, adverse events will need to be closely

followed. Firategrast's original 1200mg bid Phase II study was halted when the original Tysabri PML events were reported. Due to gender differences in the PK profile for firategrast, females are dosed at 900mg BID and males dosed at 1200mg BID. GlaxoSmithKline believes that firategrast's 12-hour half-life versus Tysabri's 11 days half-life offers a safety advantage. GlaxoSmithKline is discussing study design with FDA. However, FDA is concerned about a preclinical nephrotoxicity signal although there have been no signals in animals and humans. Phase II data presented at ECTRIMS 2010 showed that the 900/1200mg doses of firategrast met its primary endpoint of reduction in cumulative Gd-enhancing lesions during the 24 week treatment period when compared to placebo. A non-significant trend towards fewer relapses was observed. After one year post-first dose, there have been no reported cases of PML. We estimate firategrast sales of £10MM in 2017, £25MM in 2018, and £75MM in 2020.

Alzheimer's Programs Early

SB-742457, a 5-HT6 receptor antagonist, is in several Phase II studies in combination or using Aricept as an active control. 5-HT6 receptor antagonist may help improve cognition. GlaxoSmithKline stated that 5HT6 is isolated to the central nervous system and therefore '457 should not result in peripheral side effects. '457 is dosed once-daily and does not require titration. In a 371-patient 24-week dose-ranging Phase II study only the highest 35mg dose separated from placebo when measuring CIBC+ scores but not with the ADAS-cog score. In a 198 patient Aricept controlled study, the 35mg dose showed efficacy similar to Aricept using the CIBC+ and ADAS-cog scores. In both studies, '457 was well tolerated without the peripheral effects seen with acetylcholine receptor inhibitors.

In October 2008, GlaxoSmithKline acquired the rights to develop AFFiRIS's Alzheimer's vaccine program that targets beta-amyloid. The program includes two Phase I vaccines.

Consumer Business Ramped Up With Novartis Joint Venture

As part of the asset swap transactions announced in April 2014, Glaxo will establish a Consumer products joint venture with Novartis. Glaxo will have controlling interest with a 63.5% share. Glaxo's 2013 Consumer revenue was £4.8B; 2013 pro forma combined revenue was £6.5B. We assume the transaction will close at the end of Q2:15. The combination will be the leading global OTC company in a market Glaxo estimates to be \$73B and growing at 4%. We estimate Consumer sales of £4.35B (-9% reflecting divestitures), £5.545B in 2015, £6.85B in 2016, £7.535B in 2018, and £8.245B in 2020.

Below-Average Patent Exposure/Challenges Through 2020

Excluding Advair (compound patent expired in 2010, blister pack patent expires in 2016), many products could encounter generic competition through 2020, placing an estimated 22% of EPS at risk. This is below the industry average exposure of 41%.

GlaxoSmithKline Patent Vulnerability

Company	Drug	Territory	Patent Exp.	Date	Estimated WW Sales (\$MM)	U.S. Sales As % Of Total Sales	Estimated U.S. Sales (\$MM)*		Non-U.S. Sales As % Of Total Sales		Estimated Non-U.S. Sales (\$MM)*		% Total Sales	EPS (#)	% Total EPS
							Total Sales	(\$MM)*	Total Sales	(\$MM)*	Total Sales	(\$MM)*			
GSK	Agenerase	E.U.	2014		£113				48%		£54		0%	£0.00	0%
	Infanrix/Pediarix	E.U.	2014		862				67%		580		2%	0.03	3%
	Relenza	E.U.	2014		25				91%		23		0%	0.00	0%
	Avodart	U.S.	2015		840	34%	283					1%	0.02	2%	
	Epzicom/Kivexa	U.S.	2016		825	36%	294					1%	0.02	2%	
	Trizivir	U.S.	2016		30	14%	4					0%	0.00	0%	
	Trizivir	E.U.	2016		30			86%		26		0%	0.00	0%	
	Avodart	E.U.	2017		715			66%		474		2%	0.03	3%	
	Infanrix/Pediarix	U.S.	2017		985	33%	322					1%	0.02	2%	
	Lexiva	U.S.	2017		95	52%	50					0%	0.00	0%	
	Lovaza	U.S.	2017		25	100%	25					0%	0.00	0%	
	Boostrix	U.S.	2017		400	46%	183					1%	0.01	1%	
	Boostrix	E.U.	2017		400			54%		217		1%	0.01	1%	
	Epzicom/Kivexa	E.U.	2019		970			64%		624		2%	0.03	3%	
	Lexiva	E.U.	2019		100			48%		48		0%	0.00	0%	
	Cervarix	E.U.	2020		450			95%		430		1%	0.02	2%	
	Cervarix	U.S.	2020		450	5%	20					0%	0.00	0%	
	Rotarix	E.U.	2020		660			77%		506		2%	0.03	2%	
	Volibris	E.U.	2020		265			100%		265		1%	0.01	1%	

*Estimated sales in year prior to patent expiration

**Estimated sales in the year generic competition is expected

#Assumes 25% net margin

Source: Company data, FDA Orange Book, Thomson Pharma, Cowen and Company

EPS Down In 2014, Tepid Trends 2015-17 Before Rebound In 2018

Turnover And EPS Estimated To Be Down In 2014

We forecast that 2014 EPS will be down 14% to 93p, on an 8% decline in turnover. 2014 is clipped largely by divestitures (cardiac drugs Arixtra and Fraxiparine and Lucozade/ Ribena drinks) which were completed in most regions in 2014 and a decline in Respiratory sales. Gross PM is forecast to decline 0.6pp to 71.8%, SG&A is estimated to decline 6% to £7.275B, R&D is forecast to also decline 6% to £3.2B, other operating income is expected to be down £87MM to £300MM, net interest payable should decline £67MM to £625MM, tax rate down 1pp to 22% and share count down 22MM shares to 4,809MM with H2 sharecount stable.

GlaxoSmithKline 2014 Guidance Versus Our Estimates

	<u>GSK Guidance</u>	<u>Cowen Estimates</u>
Turnover	Similar to 2013 levels (at CER)	-8% (includes Fx)
R&D	Approx. £3.5B but tracking to £3.2B	£3.2B
Royalties Income	£300MM	£300MM
Net finance expense	In-line with 2013 (£692MM)	£625MM
Tax rate	22%	22%
EPS*	Broadly similar to 2013 (at CER)	-14%
Share repurchase	No repurchases in H2:14; £238MM in H1	4,809MM (-22MM)

*2013 EPS base 108.4p which excludes divestitures; **Revised**

Source: Company data, Cowen and Company

GlaxoSmithKline 2013-15 Segment P&L Buildup (£MM)

	2013			2014E			2015E		
	Turnover	Op Profit	Op. P.M.	Turnover	Op Profit	Op. P.M.	Turnover	Op Profit	Op. P.M.
Pharmaceuticals	20,846	7,153	34.3%	19,098	6,049	31.7%	19,320	6,009	31.1%
Consumer Healthcare	4,756	618	13.0%	4,350	609	14.0%	5,545	832	15.0%
Turnover	25,602	7,771	30.4%	23,448	6,658	28.4%	24,865	6,841	27.5%
Share of assoc. (Qwest)		43			30			40	
Net interest payable		(692)			(625)			(600)	
Profit before tax	7,122	27.8%		6,063	25.9%		6,281	25.3%	
Implied tax rate		23.0%			22.0%			22.0%	
Equity M.I./pref div		250			255			420	
Earnings	5,237	20.5%		4,474	19.1%		4,479	18.0%	
EPS (Basic) (pence)	108.4			93.0			96.0		
% growth		4%			-14%			3%	
EPS (Diluted) (pence)	107.1			91.8			94.6		
% growth		4%			-14%			3%	
Shares in issue (Basic)		4,831			4,809			4,685	
Shares in issue (Diluted)		4,890			4,873			4,755	

Source: Company data, Cowen and Company

Modest EPS Growth 2015-17 Before In Ramp 2018-20

During 2015-20, we forecast turnover growth in a range of 3-7% (2014-20 CAGR +6%) and EPS growth of flat to +10% (2014-20 CAGR +6%). However, EPS gains are estimated to be flat to +4% 2015-17, before expanding to +8-10% 2018-20. Our turnover estimates assume the Novartis transactions are effective starting Q3:15. We forecast Advair declines 14% on a compounded basis and new products contribute an incremental £0.9-1.5B in each year. We look for gross profit margin to erode modestly 2015-17, before improving modestly 2018-2020. Trading profit margin is estimated to decline 1.1pp in 2015 and 0.7pp in 2017 before trending back up. SG&A and R&D spending are forecast to grow roughly in line with sales in 2015-20. Other income is expected to increase £70MM in 2015, then grow by £10MM annually. Net interest payable is expected to trend down by £10MM annually. The tax rate is expected to remain at 22%. Share count is estimated to decrease by 124MM shares in 2015 due to the £4B share repurchase scheme GSK plans with the proceeds of the NVS transactions, then decline by 20MM shares each year 2016-20. All told, Glaxo's forecast 2014-20 EPS CAGR of 6% is in line with the industry average.

Speculation on GlaxoSmithKline 2013-20 EPS Outcomes (p)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2013-16		2013-20	2014-20	Comment
									CGR	CGR			
New Drugs Contribution	1.1p	3.6p	10.1p	16.9p	26.1p	36.4p	48.1p	60.1p	150%	77%	60%	Breo/Relvar, Anoro, Tivicay, Tanzeum/Eperzan, Benlysta most critical	
Advair	27.3	22.0	18.6	16.2	12.4	11.0	9.9	9.3	-16%	-14%	-13%	Branded competitors, generics in EU, generic draft guidance in U.S.	
In Line Drug Contribution	69.7	57.5	56.1	55.2	48.4	48.0	45.9	42.8	-7%	-7%	-5%	ViiV, vaccines+NVS (acq for \$5.25B H2:15), oncology (divest. to NVS for \$14.5B H2:15)	
Pharma EPS	98.1p	83.1p	84.8p	88.4p	87.0p	95.4p	103.9p	112.2p	-3%	2%	5%		
Consumer EPS	10.3	10.0	11.2	11.6	13.1	14.5	16.1	17.8	4%	8%	10%	OTC, Oral Care, Skin Care, Nutritional; 36.5% MI to NVS H2:15	
GSK EPS (basic in pence)	108.4p	93.0p	96.0p	100.0p	100.0p	110.0p	120.0p	130.0p	-3%	3%	6%	Versus industry average of +4%, +6% and +8%	
% Change	4%	-14%	3%	4%	0%	10%	9%	8%					
Average exchange rate	\$1.56	\$1.62	\$1.62	\$1.62	\$1.62	\$1.62	\$1.62	\$1.62				Exchange rate as of 10/01/14	
GSK EPS (\$)	\$3.39	\$3.01	\$3.11	\$3.24	\$3.24	\$3.56	\$3.89	\$4.21	-2%	3%	6%		

Source: Company data, Cowen and Company

GlaxoSmithKline Key Upcoming Events

2014	Clinical	Tafinlar + Mekinist	Phase III full data for COMBI-d by YE 2014/early 2015
	Regulatory	Dolutegravir/Epzicom Incruse (umec) Mepolizumab	E.U. regulatory decision in 2014; U.S. launches underway Launch around year end U.S. filing for severe asthma by year end
	Corporate	Mature products	Possible agreement for sale by year end

Source: Company data

GlaxoSmithKline 2013-20 P&L Buildup (£MM)

	Total Turnover		Gross P.M.			Other op inc			Share of JVs			Net Income		EPS							
	Turnover	% Chg	SG&A	% Sales	R&D	% Sales	Trdng Pft	% Sales	Op Pft	% Sales	Net int.	Pft b/f tax	Tax Rate	MI/Pdiv.	(basic)	% Chg	Shares				
Q1	£6,255	-4%	72.4%	£1,908	30.5%	£855	13.7%	£1,763	28.2%	£113	£1,876	30.0%	£11	-£176	£1,711	22.3%	£68	£1,261	26.1p	3%	4,834
Q2	6,374	0%	73.5%	2,039	32.0%	846	13.3%	1,797	28.2%	82	1,879	29.5%	7	-183	1,703	24.0%	64	1,230	25.3	4%	4,855
Q3	6,274	-2%	72.1%	1,831	29.2%	789	12.6%	1,903	30.3%	94	1,997	31.8%	14	-178	1,833	23.5%	49	1,353	28.0	14%	4,837
Q4	6,700	0%	71.6%	1,971	29.4%	904	13.5%	1,922	28.7%	98	2,020	30.1%	11	-155	1,876	22.1%	69	1,392	29.0	-4%	4,798
2013	£25,602	-15%	72.4%	£7,749	30.3%	£3,394	13.3%	£7,384	28.8%	£387	£7,771	30.4%	£43	-£692	£7,122	23.0%	£250	£5,237	108.4p	4%	4,831
Q1	£5,613	-10%	72.2%	£1,811	32.3%	£784	14.0%	£1,460	26.0%	£70	£1,530	27.3%	£1	-£161	£1,370	22.0%	£62	£1,007	21.0p	-20%	4,802
Q2	5,561	-13%	72.3%	1,922	34.6%	766	13.8%	1,335	24.0%	72	1,407	25.3%	8	-156	1,259	22.0%	61	921	19.1	-24%	4,812
Q3E	5,870	-6%	71.6%	1,750	29.8%	755	12.9%	1,698	28.9%	75	1,773	30.2%	10	-155	1,628	22.0%	65	1,205	25.0	-10%	4,810
Q4E	6,395	-5%	71.1%	1,787	27.9%	895	14.0%	1,865	29.2%	83	1,948	30.5%	11	-153	1,806	22.0%	67	1,342	27.9	-4%	4,810
2014E	£23,450	-8%	71.8%	£7,270	31.0%	£3,200	13.7%	£6,358	27.1%	£300	£6,658	28.4%	£30	-£625	£6,063	22.0%	£255	£4,474	93.0p	-14%	4,809
Q1E	£5,700	2%	71.2%	£1,845	32.4%	£835	14.6%	£1,378	24.2%	£85	£1,463	25.7%	£10	-£150	£1,323	22.0%	£70	£962	20.0p	-5%	4,810
Q2E	5,880	6%	71.3%	2,040	34.7%	815	13.9%	1,337	22.7%	90	1,427	24.3%	10	-150	1,287	22.0%	70	934	19.4	1%	4,810
Q3E	6,465	10%	70.6%	1,845	28.5%	805	12.5%	1,914	29.6%	95	2,009	31.1%	10	-150	1,869	22.0%	140	1,318	28.9	15%	4,560
Q4E	6,820	7%	70.1%	1,995	29.3%	945	13.9%	1,841	27.0%	100	1,941	28.5%	10	-150	1,801	22.0%	139	1,265	27.7	-1%	4,560
2015E	£24,865	6%	70.8%	£7,725	31.1%	£3,400	13.7%	£6,471	26.0%	£370	£6,841	27.5%	£40	-£800	£6,281	22.0%	£420	£4,479	96.0p	3%	4,685
2016P	£26,310	6%	70.5%	£8,020	30.5%	£3,600	13.7%	£6,929	26.3%	£380	£7,309	27.8%	£50	-£590	£6,769	22.0%	£614	£4,666	100.0p	4%	4,665
2017P	£27,140	3%	70.2%	£8,350	30.8%	£3,750	13.8%	£6,952	25.6%	£390	£7,342	27.1%	£55	-£580	£6,817	22.0%	£671	£4,647	100.0p	0%	4,645
2018P	£28,855	6%	70.4%	£8,800	30.5%	£3,950	13.7%	£7,564	26.2%	£400	£7,964	27.6%	£60	-£570	£7,454	22.0%	£728	£5,086	110.0p	10%	4,625
2019P	£30,930	7%	70.6%	£9,505	30.7%	£4,150	13.4%	£8,182	26.5%	£410	£8,592	27.8%	£65	-£560	£8,097	22.0%	£789	£5,526	120.0p	9%	4,605
2020P	£33,115	7%	70.8%	£10,300	31.1%	£4,350	13.1%	£8,795	26.6%	£420	£9,215	27.8%	£70	-£550	£8,735	22.0%	£852	£5,962	130.0p	8%	4,585

Figures reflect IAS19 Employee Benefit accounting change beginning in 2012; 2013 not yet restated for divestitures

Source: Company data, Cowen and Company estimates

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Seretide / Advair - U.S. (lc, ex fx)									475	600		310	375	300	430	
Seretide / Advair - U.S.	2,533	688	708	632	741	2,769	455	528	430	570	1,985	300	370	300	430	1,400
Seretide / Advair - EU (lc, Ex fx)									325	325		300	275	250	255	
Seretide / Advair - EU	1,447	370	376	344	368	1,458	352	348	300	305	1,305	285	270	250	255	1,060
Seretide / Advair - EM	417	106	117	87	119	429	97	98	80	110	385	105	105	90	120	420
Seretide / Advair - Japan		63	70	62	82	277	67	45	60	80	250	70	60	65	85	280
Seretide / Advair - ROW	649	82	87	84	88	341	68	76	75	80	300	75	85	85	85	330
Seretide / Advair	5,046	1,309	1,358	1,209	1,398	5,274	1,039	1,095	945	1,145	4,225	835	890	790	975	3,490
Flixotide / Flovent - U.S. (lc, ex fx)									100	120		130	115	100	125	
Flixotide / Flovent - U.S.	448	129	124	105	124	482	123	106	90	115	435	125	115	100	125	465
Flixotide / Flovent - EU (lc, ex fx)									25	25		25	25	25	25	
Flixotide / Flovent - EU	122	33	29	25	30	117	30	24	25	25	105	25	25	25	20	95
Flixotide / Flovent - EM	55	15	14	12	17	58	12	13	15	20	60	15	15	15	20	65
Flixotide / Flovent - Japan		10	11	9	12	42	7	7	10	10	35	5	5	10	10	30
Flixotide / Flovent - ROW	154	26	24	21	26	97	21	22	20	20	85	20	20	15	15	70
Flixotide / Flovent	779	213	202	172	209	796	193	172	160	190	715	190	180	165	190	725
Ventolin - U.S. (lc, ex fx)									70	85		95	75	70	85	
Ventolin - U.S.	277	76	69	66	80	291	92	73	65	80	310	90	75	70	85	320
Ventolin - EU (lc, ex fx)									25	25		25	25	25	20	
Ventolin - EU	126	33	32	29	33	127	32	30	25	25	110	25	25	25	20	95
Ventolin - EM	171	41	44	39	47	171	38	40	40	50	170	40	50	45	50	185
Ventolin - Japan		2	2	2	3	9	2	1	5	5	15	5	5	5	5	20
Ventolin - ROW	57	10	13	9	12	44	9	11	10	10	40	10	10	10	5	35
Ventolin	631	162	160	145	175	642	173	155	145	170	645	170	165	155	165	655
Veramyst - U.S. (lc, ex fx)									10	10		10	10	15	15	
Veramyst - U.S.	59	11	12	13	6	42	8	7	10	10	35	10	10	15	15	50
Veramyst - EU (lc, ex fx)									20	20		20	20	25	25	
Veramyst - EU	62	17	23	13	16	69	18	23	15	20	75	20	25	20	25	90
Veramyst - EM	63	16	17	20	18	71	17	18	25	20	80	20	20	25	20	85
Veramyst - Japan		32	3	5	9	49	23	7	5	15	50	25	10	10	15	60
Veramyst - ROW	62	4	5	4	5	18	4	3	5	5	15	10	5	5	5	25
Veramyst	246	80	60	55	54	249	70	58	60	70	260	85	70	75	80	310
Flixonase/Flovent - U.S. (lc, ex fx)									0	5		0	0	0	5	
Flixonase/Flovent - U.S.	14	2	1	0	4	7	0	6	0	5	10	0	0	0	5	5
Flixonase/Flovent - EU (lc, ex fx)									5	5		0	10	5	5	
Flixonase/Flovent - EU	32	8	9	7	7	31	0	9	5	5	20	0	10	5	5	20
Flixonase/Flovent - EM	57	13	15	11	10	49	15	5	10	10	40	15	15	15	10	55
Flixonase/Flovent - ROW	30	16	2	1	4	23	10	5	5	5	25	5	5	5	5	20
Flixonase / Flonase	133	39	27	19	25	110	25	25	20	25	95	20	30	25	25	100

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Anoro								5	20	40	65	60	60	100	120	340
Breo/Relvar - U.S. (lc, ex fx)								15	20		25	30	35	40		
Breo/Relvar - U.S.	0	0	0	5	5	5	1	5	15	20	40	25	30	35	40	130
Breo/Relvar - EU (lc, ex fx)								5	10		10	10	15	15	15	
Breo/Relvar - EU	0	0	0	0	0	0	2	3	5	10	20	0	0	15	15	30
Breo/Relvar - EM	0	0	0	0	0	0	0	1	0	0	0	5	5	5	5	20
Breo/Relvar - Japan	0	0	0	3	3	3	1	2	10	15	30	20	25	30	35	110
Breo/Relvar - ROW	0	0	0	0	0	0	0	0	0	0	0	5	5	5	5	20
Breo/Relvar	0	0	0	8	8	8	3	11	30	45	89	55	65	90	100	310
Incruse												5	10	10	15	40
Losmapimod																
2586881																
961081																
Fluticasone Furoate																
Vilanterol																
Dilmapimod																
2190915																
2245035																
Bosatria																
Zyrtec	81	24	17	15	20	76	17	13	15	20	65	15	10	15	20	60
Other respiratory	230	52	23	25	34	134	34	25	20	25	105	25	20	20	20	85
Respiratory	7,291	1,879	1,847	1,640	1,923	7,289	1,554	1,559	1,415	1,730	6,260	1,460	1,500	1,445	1,710	6,115
% Change	0%	2%	2%	-5%	1%	0%	-17%	-16%	-14%	-10%	-14%	-6%	-4%	2%	-1%	-2%
Wellbutrin - U.S. (lc, ex fx)								0	5		5	5	0	0		
Wellbutrin - U.S.	12	5	4	1	6	16	0	7	0	5	10	5	5	0	0	10
Wellbutrin - EU (lc, ex fx)									15	16		15	15	15	15	
Wellbutrin - EU	44	12	13	12	14	51	15	12	15	15	55	15	15	15	15	60
Wellbutrin - EM	28	7	8	7	8	30	5	8	10	10	35	10	10	10	10	40
Wellbutrin - ROW	0	0	1	3	2	0	0	0	5	5	10	0	5	5	5	15
Wellbutrin	84	24	24	23	26	97	20	26	30	35	111	30	35	30	30	125
Treximet - U.S. (lc, ex fx)																
Treximet - U.S.	49	10	10	10	10	40	10	10								
Treximet	49	10	10	10	10	40	10	10								
Trobalt (retigabine)/Potiga (ezogabine)	11	3	3	2	3	11	1	1	5	5	10	0	5	5	10	20
239512																
249320																
Other CNS	188	40	48	43	49	180	40	40	40	45	165	40	40	40	40	160
CNS	1,670	77	85	78	88	328	71	77	75	85	310	70	80	75	80	305
% Change	-3%	-81%	-81%	-80%	-79%	0%	-8%	-9%	-4%	-3%	-5%	-1%	4%	0%	-6%	-2%

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Epzicom/Kivexa - U.S. (lc, ex fx)									70	85		60	65	70	85	
Epzicom/Kivexa - U.S.	243	61	63	65	80	269	59	67	65	80	270	60	65	70	85	280
Epzicom/Kivexa - EU (lc, ex fx)									85	90		85	90	85	90	
Epzicom/Kivexa - EU	285	77	84	79	88	328	82	85	80	85	330	80	90	85	90	345
Epzicom/Kivexa - EM	57	13	23	24	18	78	15	15	25	20	75	20	20	30	25	95
Epzicom / Kivexa - Japan		8	9	9	10	36	9	8	10	10	35	10	10	10	15	45
Epzicom/kivexa- ROW	80	10	14	13	15	52	12	13	15	15	55	15	15	15	15	60
Epzicom / Kivexa	665	169	193	190	211	763	177	188	195	210	770	185	200	210	230	825
Trizivir - U.S. (lc, ex fx)									0	0		0	0	0	0	
Trizivir - U.S.	61	14	13	15	16	58	3	1	0	0	5	0	0	0	0	0
Trizivir - EU (lc, ex fx)									5	5		5	5	5	5	
Trizivir - EU	37	9	8	8	7	32	6	6	5	5	20	5	5	5	5	15
Trizivir - EM	5	0	1	2	1	4	0	1	5	5	10	0	5	5	5	15
Trizivir - Japan		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Trizivir- ROW	4	1	1	1	2	3	2	0	0	0	0	0	0	0	0	0
Trizivir	107	24	23	24	26	97	11	7	10	10	40	5	10	10	5	30
Agenerase / Lexiva - U.S. (lc, ex fx)									15	15		10	10	15	15	
Agenerase / Lexiva - U.S.	68	15	14	15	18	62	11	11	15	15	50	10	10	15	15	50
Agenerase / Lexiva - EU (lc, ex fx)									5	5		5	5	5	5	
Agenerase / Lexiva - EU	33	8	7	6	6	27	6	5	5	5	20	5	5	5	5	15
Agenerase / Lexiva - EM	19	2	6	7	3	18	4	3	5	5	15	5	5	5	5	20
Agenerase / Lexiva - Japan		1	1	1	0	3	1	0	0	0	0	0	5	5	0	10
Agenerase / Lexiva- ROW	7	1	1	0	1	3	0	2	0	0	0	0	0	0	0	0
Agenerase / Lexiva	127	27	29	29	28	113	22	21	25	25	95	20	25	30	20	95
Combivir - U.S. (lc, ex fx)									5	10		5	5	5	5	
Combivir - U.S.	24	11	6	7	11	35	3	3	5	10	20	5	5	5	5	15
Combivir - EU (lc, ex fx)									5	5		5	5	5	5	
Combivir - EU	64	14	10	8	7	39	6	5	5	5	20	5	5	5	0	15
Combivir - EM	79	7	9	8	11	35	5	9	5	5	25	5	5	5	5	20
Combivir - Japan		1	1	1	0	3	1	0	5	0	5	0	5	5	5	15
Combivir- ROW	12	0	1	1	2	4	1	0	0	0	0	0	0	0	0	0
Combivir	179	33	27	25	31	116	16	16	20	20	70	15	20	20	10	65
Epivir - U.S. (lc, ex fx)									0	5		0	0	0	0	5
Epivir - U.S.	8	3	1	3	3	10	2	2	0	5	10	0	0	0	0	5
Epivir - EU (lc, ex fx)									5	0		0	0	5	5	
Epivir - EU	21	4	5	3	4	16	3	3	5	0	10	0	0	5	5	10
Epivir - EM	12	2	4	3	2	11	2	2	5	0	10	0	5	5	0	10
Epivir - ROW	8	2	1	3	0	6	0	0	5	0	5	0	0	0	0	5
Epivir	49	11	11	12	9	43	7	7	15	5	35	5	5	10	10	30

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Tivicay - U.S. (lc, ex fx)									65	85		105	125	145	165	
Tivicay - U.S.	0	0	4	15	19	26	48	60	80	215	100	125	145	165	535	
Tivicay - EU (lc, ex fx)								20	25		30	35	40	45		
Tivicay - EU	0	0	0	0	0	0	4	12	20	25	60	30	35	40	45	150
Tivicay - EM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tivicay - Japan	0	0	0	0	0	0	0	3	5	10	20	15	20	25	30	90
Tivicay - ROW	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Tivicay	0	0	4	15	19	31	64	85	115	295	145	180	210	240	775	
Selzentry - U.S. (lc, ex fx)								15	10		15	15	15	15	10	
Selzentry - U.S.	128	13	15	16	14	58	12	14	15	10	50	15	15	15	10	55
Selzentry - EU (lc, ex fx)								15	15		10	10	15	15	15	
Selzentry - EU	15	17	14	17	63	15	16	15	15	60	10	10	15	15	50	
Selzentry - EM	2	2	1	1	6	1	2	5	0	10	0	5	5	0	10	
Selzentry - Japan	1	1	1	0	3	1	0	5	0	5	0	5	5	0	10	
Selzentry - ROW	6	0	2	5	13	4	6	5	5	20	5	0	5	5	15	
Selzentry	37	35	34	37	143	33	38	45	30	146	30	35	45	30	140	
1265744																
Rescriptor	45	10	0	10	10	30	4	5	5	5	20	5	5	5	5	20
Viracept	29	5	5	5	5	20	5	5	5	0	15	5	5	0	0	10
Other HIV	45	2	16	11	13	42	5	1	10	10	25	5	5	5	5	20
HIV	1,374	318	339	344	385	1,386	311	352	415	430	1,510	420	490	545	555	2,010
% Change	-12%	-5%	-2%	-3%	14%	0%	-2%	4%	21%	12%	9%	35%	39%	31%	29%	33%
Relenza - U.S. (lc, ex fx)								0	0		0	0	0	0	0	
Relenza - U.S.	6	1	7	0	0	6	0	1	0	0	0	0	0	0	0	0
Relenza - EU (lc, ex fx)								0	0		0	0	0	0	0	
Relenza - EU	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Relenza - EM	0	3	0	0	5	8	5	2	0	5	10	0	0	0	5	5
Relenza - ROW	26	16	1	0	51	68	36	1	0	15	50	30	10	10	20	70
Relenza	33	20	-6	0	56	70	41	4	0	20	65	30	10	10	25	75
Zovirax	89	21	20	20	20	81	20	20	15	15	70	15	15	15	15	60
Other Antivirals	21	3	3	2	1	14	5	5	5	5	20	5	5	5	10	25
Antivirals	764	44	17	27	77	165	66	29	20	40	155	50	30	30	50	160
% Change	-9%					0%					-6%					3%
Augmentin - U.S. (lc, ex fx)								0	0		0	0	0	0	0	
Augmentin - U.S.	1	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0
Augmentin - EU (lc, ex fx)								35	45		50	35	30	35		
Augmentin - EU	202	62	45	43	53	203	58	43	35	40	175	50	35	30	35	150
Augmentin - EM	367	103	99	90	101	393	86	97	90	100	375	90	100	95	105	390
Augmentin - Japan	3	3	3	4	13	3	2	5	5	15	5	5	5	5	5	20
Augmentin - ROW	38	7	3	4	6	20	4	6	5	5	20	5	5	5	5	20
Augmentin	608	175	150	140	165	630	152	147	135	150	585	150	145	135	150	580

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
1322322																
Zinnat / Ceftin Etaquine (Tafenoquine)	174	45	42	36	46	169	43	41	40	40	165	40	40	40	40	160
Altabax	7	1	1	1	1	4	0	0	0	5	5	0	0	0	5	5
Other antibacterials	458	118	116	105	114	453	110	110	110	110	440	105	105	105	105	420
Antibacterials	1247	339	309	282	326	1,256	305	298	285	305	1,195	295	290	280	300	1,165
% Change	-10%					0%					-5%					-3%
Tanzeum/Eperzan									5	15	20	20	25	30	35	110
1070806																
1278863																
Boniva income																
Other metabolic	160	45	45	41	43	174	45	45	45	45	180	45	45	45	50	185
Metabolic	166	45	45	41	43	174	45	45	50	60	200	65	70	75	85	295
% Change	-50%	36%	0%	-9%	-10%	0%	0%	0%	22%	40%	15%	44%	56%	50%	42%	48%
Infanrix / Pediarix - U.S. (lc, ex fx)									105	65		75	70	100	65	
Infanrix / Pediarix - U.S.	218	38	72	100	61	271	71	66	95	60	290	75	70	100	65	310
Infanrix / Pediarix - EU (lc, ex fx)									100	100		100	100	100	100	
Infanrix / Pediarix - EU	376	96	103	98	101	398	92	93	95	95	375	95	95	100	100	390
Infanrix / Pediarix - EM	120	28	28	44	32	132	23	31	45	35	135	25	35	50	40	150
Infanrix / Pediarix - Japan	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Infanrix / Pediarix - ROW	61	16	15	16	14	61	16	12	20	15	65	20	15	20	20	75
Infanrix / Pediarix	775	178	218	258	208	862	202	202	255	205	865	215	215	270	225	925
Synforix - EU (lc, ex fx)									15	15		15	15	15	15	
Synflorix - EU	45	12	12	12	12	48	12	9	15	15	50	15	15	15	15	60
Synflorix - EM	334	77	60	66	147	350	49	94	70	160	375	55	95	75	160	385
Synflorix - Japan	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Synflorix - ROW	6	1	2	2	2	7	1	2	5	5	15	0	5	5	5	15
Synflorix	385	90	74	80	161	405	62	105	90	180	435	70	115	95	180	460

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Hepatitis - U.S. (lc, ex fx)									75	50		40	50	65	40	
Hepatitis - U.S.	266	54	73	81	55	263	44	56	70	45	215	40	50	65	40	195
Hepatitis - EU (lc, ex fx)									45	50		45	45	40	40	
Hepatitis - EU	197	46	52	48	52	198	46	47	40	45	180	45	45	40	40	170
Hepatitis - EM	128	24	36	29	34	123	19	30	30	35	115	20	30	30	30	110
Hepatitis - Japan		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hepatitis - ROW	55	15	9	10	11	45	11	9	10	15	45	15	10	10	15	50
Hepatitis	646	139	170	168	152	629	120	142	150	140	550	120	135	145	125	525
Rotarix - U.S. (lc, ex fx)									30	25		25	25	30	30	
Rotarix - U.S.	100	27	25	32	24	108	26	24	25	25	100	25	25	30	30	110
Rotarix - EU (lc, ex fx)									20	15		20	15	25	20	
Rotarix - EU	39	11	16	17	15	59	18	15	20	15	70	20	15	25	20	80
Rotarix - EM	159	31	37	50	46	164	34	51	55	50	190	40	55	60	55	210
Rptarix - Japan		5	6	6	8	25	5	9	5	15	35	5	10	10	10	35
Rotarix - ROW	62	6	3	3	7	19	3	4	5	5	15	5	5	5	10	25
Rotarix	360	80	87	108	100	375	86	103	110	110	410	95	110	130	125	460
Boostrix - U.S. (lc, ex fx)									60	70		35	45	60	70	
Boostrix - U.S.	147	21	41	56	65	183	30	43	55	65	195	35	45	60	70	210
Boostrix - EU (lc, ex fx)									20	20		15	25	25	25	
Boostrix - EU	53	13	19	18	15	65	15	26	20	20	80	15	25	25	25	90
Boostrix - EM	16	4	5	4	7	20	10	18	5	5	40	5	5	10	10	30
Boostrix - Japan		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Boostrix - ROW	22	8	3	5	4	20	5	7	5	10	25	5	5	10	10	30
Boostrix	238	46	68	83	91	288	60	94	85	100	340	60	80	105	115	360
Cervarix - U.S. (lc, ex fx)									5	5		5	5	5	5	
Cervarix - U.S.	6	1	2	2	1	6	1	1	5	5	10	5	5	5	5	20
Cervarix - EU (lc, ex fx)									15	25		15	20	20	25	
Cervarix - EU	53	15	13	14	19	61	15	10	15	25	65	15	20	20	25	80
Cervarix - EM	75	17	25	25	25	92	19	10	30	30	90	25	15	30	30	100
Cervarix - Japan		7	4	0	1	10	0	0	10	15	25	10	10	15	15	50
Cervarix - ROW	136	0	2	0	1	3	0	1	0	5	5	5	5	5	5	20
Cervarix	270	40	46	41	45	172	34	22	60	80	195	60	55	75	80	270
Fluarix / FluLaval - U.S. (lc, ex fx)									115	40		0	0	115	45	
Fluarix / FluLaval - U.S.	88	4	2	104	36	146	0	2	105	40	145	0	0	115	45	160
Fluarix / FluLaval - EU (lc, ex fx)									15	25		0	0	15	30	
Fluarix / FluLaval - EU	43	1	1	16	21	35	0	1	15	25	40	0	0	15	30	45
Fluarix / FluLaval - EM	44	9	5	7	22	43	6	4	10	20	40	10	5	10	25	50
Fluarix / FluLaval - Japan		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fluarix / FluLaval - ROW	25	3	1	15	8	27	3	1	15	10	30	5	5	20	10	40
Fluarix / FluLaval	200	15	7	142	87	251	9	6	145	95	255	15	10	160	110	295

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Pandemic - U.S. (lc, ex fx)									0	0		0	0	0	0	
Pandemic - U.S.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pandemic - EU (lc, ex fx)									0	0		0	0	0	0	
Pandemic - EU	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0
Pandemic - EM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pandemic - ROW	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0
Pandemic	1	0	0	2	0	2	0	0	0	0	0	0	0	0	0	0
Novartis Vaccines														150	175	325
Nimerix (MenACWY-TT)		1	3	3	5	12	3	4	5	15	25	10	15	20	25	70
Menhibrix (Hib-MenCY-TT)																
Varicella zoster																
Tuberculosis																
Mosquirix																
Other vaccines																
Vaccines	2,875	680	786	987	967	3,420	82	88	110	120	400	85	95	95	105	380
% Change	-3%	5%	21%	18%	31%	0%	-3%	-3%	2%	8%	2%	11%	8%	23%	21%	17%
Established Products																
Coreg - U.S. (lc, ex fx)																
Coreg - U.S.	132	32	33	36	29	130	32	29	30	30	120	30	25	25	25	105
Coreg - EU (lc, ex fx)									0	0		0	0	0	0	
Coreg - EU	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Coreg - EM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Coreg - Japan	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Coreg - ROW	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0
Coreg	133	33	33	36	29	131	32	30	30	30	120	30	25	25	25	105
Hepsera - EM																
Hepsera - Japan		21	24	10	15	70	17	16	15	15	65	15	20	10	15	60
Hepsera - ROW	6	6	7	6	6	25	6	4	10	10	30	10	5	10	10	35
Hepsera	126	0	0	-1	2	1	0	1	0	0	0	0	0	0	0	0
Imigran / Imitrex - U.S. (lc, ex fx)																
Imigran / Imitrex - U.S.	72	22	19	21	18	80	24	22	15	15	75	15	15	15	15	60
Imigran / Imitrex - EU (lc, ex fx)									15	15		15	15	15	15	10
Imigran / Imitrex - EU	67	17	16	15	15	63	15	15	15	15	60	15	15	15	15	55
Imigran / Imitrex - EM	7	2	2	1	2	7	2	1	0	0	5	5	5	0	0	10
Imigran / Imitrex - Japan	6	6	6	6	6	24	4	4	5	10	25	5	5	10	10	30
Imigran / Imitrex - ROW	44	1	4	4	5	14	1	2	5	5	15	5	5	5	5	20
Imigran / Imitrex	190	48	47	47	46	188	46	44	40	45	175	45	45	45	40	175

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Lamictal - U.S. (lc, ex fx)									60	60		45	50	45	35	
Lamictal - U.S.	332	66	63	70	77	276	56	60	55	55	225	45	50	45	35	175
Lamictal - EU (lc, ex fx)									25	25		25	20	20	20	
Lamictal - EU	112	28	27	27	28	110	28	26	25	25	105	25	20	20	20	85
Lamictal - EM	75	19	20	19	20	78	18	18	20	20	75	20	20	20	25	85
Lamictal - Japan		18	21	21	23	83	22	18	20	25	85	25	25	25	25	100
Lamictal- ROW	91	2	2	2	4	10	2	2	5	5	15	5	5	5	5	20
Lamictal	610	133	133	139	152	557	126	124	125	130	505	120	120	115	110	465
Lovaza - U.S. (lc, ex fx)									15	5		5	5	5	5	
Lovaza - U.S.	604	147	161	134	139	581	104	27	15	5	150	5	5	5	5	20
Lovaza - Japan	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lovaza - ROW	3	1	0	1	1	3	1	0	0	5	5	5	0	0	5	10
Lovaza	607	148	161	135	140	584	105	27	15	10	155	10	5	5	10	30
Requip - U.S. (lc, ex fx)									0	0		0	0	0	0	
Requip - U.S.	19	2	1	3	1	7	2	2	0	0	5	0	0	0	0	0
Requip - EU (lc, ex fx)									10	10		10	10	10	10	
Requip - EU	76	15	13	13	11	52	11	11	10	10	40	10	10	10	10	40
Requip - EM	14	4	3	4	3	14	3	4	5	5	15	5	5	5	10	25
Requip - Japan		10	12	15	14	51	11	9	15	15	50	10	10	10	15	45
Requip- ROW	55	0	0	0	0	0	1	0	0	0	0	0	0	0	5	10
Requip	164	31	29	36	29	125	28	26	30	30	115	25	25	30	40	120
Serevent - U.S. (lc, ex fx)									10	10		5	10	10	10	
Serevent - U.S.	51	13	12	13	13	51	9	9	10	10	40	5	10	10	10	35
Serevent - EU (lc, ex fx)									10	10		10	10	10	10	
Serevent - EU	64	14	14	13	14	55	13	13	10	10	45	10	10	10	5	35
Serevent - EM	3	1	1	1	1	4	1	1	0	5	5	0	0	5	5	10
Serevent - Japan		3	4	3	3	13	3	2	5	0	10	5	5	5	0	15
Serevent - ROW	27	2	2	2	0	6	1	1	0	5	5	0	0	0	5	5
Serevent	145	33	33	32	31	129	27	26	25	30	110	20	25	30	25	100
Paxil/Seroxat - U.S. (lc, ex fx)									0	5		0	0	0	0	5
Paxil/Seroxat - U.S.	0	0	0	0	0	0	0	0	0	5	5	0	0	0	5	5
Paxil/Seroxat - EU (lc, ex fx)									10	15		5	10	10	10	
Paxil/Seroxat - EU	57	14	15	12	12	53	12	10	10	15	45	5	10	10	10	35
Paxil/Seroxat - EM	84	23	21	16	19	79	17	13	15	15	60	10	15	15	15	55
Paxil/Seroxat - Japan		32	37	34	35	138	25	24	25	25	100	20	20	20	20	80
Paxil/Seroxat - ROW	233	4	6	2	3	15	1	2	5	5	15	0	5	5	5	15
Paxil/Seroxat	374	73	79	64	69	285	55	49	55	65	225	35	50	50	55	190

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Valtrex - U.S. (lc, ex fx)									10	10		5	10	10	5	
Valtrex - U.S.	35	11	9	10	15	45	6	8	10	10	35	5	10	10	5	30
Valtrex - EU (lc, ex fx)									10	5		5	5	5	5	
Valtrex - EU	33	7	7	8	7	29	7	8	10	5	30	5	5	5	5	20
Valtrex - EM	37	9	10	11	10	40	9	7	10	15	40	10	10	15	15	50
Valtrex - Japan		26	28	26	22	102	14	12	15	15	55	10	10	10	10	40
Valtrex - ROW	147	2	1	0	5	8	1	2	0	5	10	0	0	0	5	5
Valtrex	252	55	55	55	59	224	37	37	45	50	170	30	35	40	40	145
Zeffix - U.S. (lc, ex fx)									5	5		0	0	5	5	
Zeffix - U.S.	15	3	4	3	3	13	1	1	5	5	10	0	0	5	5	10
Zeffix - EU (lc, ex fx)									5	0		5	0	0	0	
Zeffix - EU	16	3	3	3	3	12	2	2	5	0	10	5	0	0	0	5
Zeffix - EM	188	47	44	16	33	140	38	33	25	35	130	40	40	30	35	145
Zeffix - Japan		4	4	4	4	16	3	3	5	5	15	5	5	5	5	20
Zeffix - ROW	24	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
Zeffix	243	57	55	27	43	182	45	40	40	45	170	50	45	40	45	180
Total Established Products		638	656	586	621	2,501	524	424	430	460	1,838	390	400	400	415	1,605
% Chg.							-18%	-35%	-27%	-26%	-26%	-26%	-6%	-7%	-10%	-13%
Promacta - U.S. (lc, ex fx)									25	25		25	25			
Promacta - U.S.	54	16	19	19	19	73	18	21	25	25	90	25	25			50
Promacta - EU (lc, ex fx)									20	20		15	20			
Promacta - EU	36	11	13	15	16	55	16	18	20	20	75	15	20			35
Promacta - EM	12	5	5	6	6	22	5	7	10	10	30	10	10			20
Promacta - Japan		6	8	8	8	30	8	7	8	10	35	8	10			20
Promacta - ROW	28	2	0	1	3	6	1	2	2	5	10	2	5			5
Promacta	130	40	45	49	52	186	48	55	65	70	240	60	70			130
Tykerb - U.S. (lc, ex fx)									10	10		10	15			
Tykerb - U.S.	68	15	15	14	11	55	10	11	10	10	40	10	15			25
Tykerb - EU (lc, ex fx)									20	20		20	20			
Tykerb - EU	87	21	21	21	19	82	18	18	20	20	75	20	20			40
Tykerb - EM	54	10	11	12	14	47	10	13	15	15	55	10	10			20
Tykerb - Japan		4	5	4	4	17	3	1	5	5	15	5	5			10
Tykerb - ROW	30	2	1	2	1	6	1	2	5	5	15	5	5			10
Tykerb	239	52	53	53	49	207	42	45	55	55	195	50	55			105

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Hycamtin - U.S. (lc, ex fx)									0	0		0	0	0	0	
Hycamtin - U.S.	6	2	3	2	3	10	0	2	0	0	0	0	0	0	0	0
Hycamtin - EU (lc, ex fx)									5	0		0	0	0	0	
Hycamtin - EU	19	2	3	2	3	10	0	2	5	0	5	0	0	0	0	0
Hycamtin - EM	12	1	2	0	3	6	5	1	5	5	15	5	5	5	5	10
Hycamtin - ROW	9	2	1	0	0	1	0	0	0	0	0	0	0	0	0	0
Hycamtin	46	7	7	4	9	27	5	5	10	5	25	5	5	5	5	10
Votrient/Patorma - U.S. (lc, ex fx)	183								40	45		40	40			
Votrient/Patorma - U.S.		33	36	36	39	144	37	42	35	45	160	40	40			80
Votrient/Patorma - EU (lc, ex fx)									45	45		45	50			
Votrient/Patorma - EU		26	30	39	35	130	37	39	40	40	155	45	50			95
Votrient/Patorma - EM		7	9	10	11	37	9	12	10	10	40	10	10			20
Votrient/Patorma - Japan		2	2	3	2	9	2	4	5	5	15	5	5			10
Votrient/Patorma - ROW		3	2	3	3	11	2	4	5	5	15	5	5			10
Votrient/Patorma		71	79	91	90	331	87	101	95	105	388	105	110			215
Tafinlar - U.S. (lc, ex fx)									20	25		30	35			
Tafinlar - U.S.	0	1	4	6	11		11	14	20	25	70	30	35			65
Tafinlar - EU (lc, ex fx)									20	25		30	35			
Tafinlar - EU	0	0	0	4	4		10	16	20	25	71	30	35			65
Tafinlar - EM	0	0	0	0	0		0	0	0	0	0	0	0			0
Tafinlar - Japan	0	0	0	0	0		0	0	0	0	0	0	0			0
Tafinlar - ROW	0	0	0	1	1		1	3	0	0	4	0	5			5
Tafinlar	0	1	4	11	16		22	33	40	50	145	60	75			135
Mekinist - U.S. (lc, ex fx)									20	25		30	35			
Mekinist - U.S.	0	0	3	7	10		13	15	20	25	45	30	35			65
Mekinist - EU (lc, ex fx)									0	0		0	0			
Mekinist - EU	0	0	0	0	0		0	0	0	0	0	0	0			0
Mekinist - EM	0	0	0	0	0		0	0	0	0	0	0	0			0
Mekinist - Japan	0	0	0	0	0		0	0	0	0	0	0	0			0
Mekinist - ROW	0	0	0	0	0		0	1	0	0	0	0	0			0
Mekinist	0	0	3	7	10		13	16	20	25	74	30	35			65
Arzerra - U.S. (lc, ex fx)	60								15	15		20	20			
Arzerra - U.S.	10	10	13	13	46		10	7	15	15	30	20	20			40
Arzerra - EU (lc, ex fx)									10	10		10	10			
Arzerra - EU	11	7	4	5	27		5	5	10	10	20	10	10			20
Arzerra - EM	0	0	0	0	0		0	0	0	0	30	0	0			20
Arzerra - Japan	0	0	0	0	0		1	0	0	0	0	0	0			0
Arzerra - ROW	0	0	0	1	1		0	0	0	0	1	0	0			0
Arzerra	21	17	18	19	75		16	12	25	25	78	30	30			60

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Mapatumumab																
2110183																
Foretinib																
MAGE-A3																
Other Oncology/emesis	140	30	31	27	29	117	28	28	25	25	105	20	20			40
Oncology	2,810	221	233	249	266	969	261	295	335	360	1,250	360	400			760
% Change	4%	23%	19%	22%	21%	0%	18%	27%	35%	35%	29%	38%	36%			-39%
Floлан - U.S. (lc, ex fx)																
Floлан - U.S.	33	7	7	5	6	25	5	6	5	5	20	5	5	5	5	10
Floлан - EU (lc, ex fx)																
Floлан - EU	23	5	5	4	4	18	5	3	5	5	20	5	5	5	5	25
Floлан - EM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Floлан - ROW	79	15	16	16	13	60	8	8	20	20	55	20	20	20	20	80
Floлан	135	27	28	25	23	103	18	18	30	30	95	30	30	30	30	130
Voliris - U.S. (lc, ex fx)																
Voliris - U.S.																
Voliris - EU (lc, ex fx)																
Voliris - EU	73	20	20	21	21	82	20	24	25	25	95	25	25	25	25	100
Voliris - EM	9	3	2	3	3	11	5	6	5	0	15	5	5	5	5	20
Voliris - ROW	45	11	15	12	16	54	13	10	15	15	55	15	15	15	20	65
Voliris	127	34	37	36	40	147	38	39	45	40	160	45	45	45	50	185
Other	233	52	62	64	67	245	50	42	60	60	210	50	60	60	65	235
Rare Diseases	495	113	127	125	130	495	106	99	135	130	470	125	135	135	155	550
% Change	7%	7%	15%	-9%	-8%	0%	-6%	-22%	8%	0%	-5%	18%	37%	0%	19%	17%
Avodart - U.S. (lc, ex fx)																
Avodart - U.S.	317	75	84	73	80	312	59	67	75	85	285	50	60	70	40	220
Avodart - EU (lc, ex fx)																
Avodart - EU	228	66	68	67	72	273	71	70	65	70	275	70	70	70	80	290
Avodart - EM	84	24	27	26	27	104	26	27	30	30	115	30	35	35	35	135
Avodart - Japan	25	28	28	33	114	31	22	25	30	110	30	25	30	35	120	
Avodart - ROW	161	13	14	13	14	54	12	13	15	15	55	15	15	15	20	65
Avodart	790	203	221	207	226	857	199	199	210	230	840	195	205	220	210	830

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Fraxiparine - EU (lc, ex fx)																
Fraxiparine - EU	145															
Fraxiparine - EM	87	19	24	19	21	83	5	7	10	10	30	5	10	10	10	35
Fraxiparine - ROW	1															
Fraxiparine	233	19	24	19	21	83	5	7	10	10	30	5	10	10	10	35
Arixtra - U.S. (lc, ex fx)																
Arixtra - U.S.	68															
Arixtra - EU (lc, ex fx)																
Arixtra - EU	91															
Arixtra - EM	28	8	9	5	6	28	5	2	5	5	15	5	5	5	10	25
Arixtra - ROW	8															
Arixtra	195	8	9	5	6	28	5	2	5	5	15	5	5	5	10	25
Vesicare - U.S. (lc, ex fx)																
Vesicare - U.S.	174															
Vesicare - EU (lc, ex fx)																
Vesicare - EU	0															
Vesicare - EM	1															
Vesicare - ROW	0															
Vesicare	175															
Losmapimod																
Tyrosa																
Other Cardiovascular	298	73	73	68	65	279	32	25	30	30	115	25	25	25	25	100
Cardio./Urogenital	2,431	303	327	299	318	1,247	241	233	255	275	1,005	230	245	260	255	990
% Change	7%	-58%	-43%	-47%	-44%	0%	-20%	-29%	-15%	-14%	-19%	-5%	5%	2%	-7%	-1%
Benlysta - U.S.	65	27	35	39	33	134	34	37	40	45	155	50	55	60	65	230
Benlysta - EU	2	2	2	2	2	8	3	3	5	5	15	10	10	10	10	40
Benlysta - ROW	5	0	1	1	2	4	1	1	0	0	0	0	0	0	0	0
Benlysta (belimumab)	70	29	38	42	37	146	38	41	45	50	175	60	65	70	75	270
Firatagras																
933776																
Ofatumumab																
Sirukumab																
Ozanezumab																
Camicinal																

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
2245840																
2586148																
2941266																
Zantac	142	27	29	26	29	111	25	25	25	25	100	25	25	20	20	90
Entereg																
Retosiban																
Denosumab income	39	10	12	15	15	52	16	7	5	5	35	5	5	5	5	20
Other	1,149	195	257	274	306	1,032	201	217	225	250	895	175	175	200	225	775
Other	3,412	261	336	357	387	1,341	280	290	300	330	1,200	265	270	295	325	1,155
% Change	-6%	-14%	8%	-2%	-8%	0%	7%	-14%	-16%	-15%	-11%	-5%	-7%	-2%	-2%	-4%
Bactroban - U.S. (lc, ex fx)																
Bactroban - U.S.	51	8	5	9	7	29	5	3	5	10	25	5	5	5	5	20
Bactroban - EU (lc, ex fx)																
Bactroban - EU	26	6	6	6	6	24	5	5	5	5	20	5	5	5	5	20
Bactroban - EM	39	9	11	11	7	38	5	8	10	10	35	10	10	10	10	40
Bactroban - ROW	8	2	2	0	3	7	5	1	0	5	10	0	0	5	5	10
Bactroban	124	25	24	26	23	98	20	17	20	30	85	20	20	25	25	90
Soriatane - U.S. (lc, ex fx)																
Soriatane - U.S.	79	20	19	15	2	56	5	5	5	5	20	5	5	5	0	15
Soriatane - EU (lc, ex fx)												0	0	0	0	
Soriatane - EU	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Soriatane - EM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Soriatane - ROW	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0
Soriatane	79	20	19	16	2	57	5	5	5	5	20	5	5	5	0	15
Dermovate - U.S. (lc, ex fx)																
Dermovate - U.S.																
Dermovate - EU (lc, ex fx)																
Dermovate - EU	18	6	6	5	5	22	5	5	5	5	20	5	5	5	5	20
Dermovate - EM	36	13	14	13	14	54	11	11	15	15	50	15	15	15	15	60
Dermovate - ROW	21	3	5	5	5	18	5	6	5	5	20	5	5	5	5	20
Dermovate	75	22	25	23	24	94	21	22	25	25	95	25	25	25	25	100
Duac - U.S. (lc, ex fx)																
Duac - U.S.	38	4	3	4	4	15	4	1	0	0	5	5	0	0	0	5
Duac - EU (lc, ex fx)												10	10	5	10	10
Duac - EU	24	7	7	7	8	29	5	7	10	10	30	5	10	10	10	35
Duac - EM	13	4	4	4	4	16	5	5	5	5	20	5	5	5	5	20
Duac - ROW	12	2	4	3	3	12	0	1	5	5	10	0	5	5	5	15
Duac	87	17	18	18	19	72	14	12	20	20	65	15	20	20	20	75
Other	485	115	120	111	103	450	110	115	105	100	430	105	110	100	95	410
Dermatology	850	199	206	194	171	770	170	171	175	180	695	170	180	175	165	690
% Change	-5%	-7%	-2%	-3%	-24%	0%	-15%	-17%	-10%	5%	-10%	0%	5%	0%	-8%	-1%

Source: Cowen and Company

GlaxoSmithKline 2013-20 Quarterly Product Sales Buildup (£MM) (continued)

	2012	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
TOTAL PHARMACEUTICALS	£24,890	£5,004	£5,186	£5,084	£5,573	£20,846	£4,486	£4,539	£4,765	£5,300	£19,098	£4,505	£4,785	£4,825	£5,205	£19,320
% Change	-3%	-4%	2%	-1%	3%	-16%	-10%	-12%	-6%	-5%	-8%	0%	5%	1%	-2%	1%
OTC	2,008	499	448	464	454	1,865	416	366	425	445	1,650	450	400	930	930	2,710
% Change	-8%	-7%	-8%	-3%	-10%	-7%	-17%	-18%	-8%	-2%	-12%	8%	9%	NM	NM	NM
Oral Care	1,797	480	481	476	447	1,884	457	434	450	450	1,790	490	475	480	480	1,925
% Change	5%	4%	9%	6%	0%	5%	-5%	-10%	-5%	1%	-5%	7%	9%	7%	7%	8%
Nutritional Healthcare	1,050	175	162	160	130	627	170	151	155	125	600	175	155	160	130	620
% Change	2%	-35%	-40%	-42%	-45%	-40%	NM	NM	NM	NM	NM	3%	3%	3%	4%	3%
Skin Health	255	97	97	90	96	380	84	71	75	75	305	80	65	70	75	290
% Change	-25%	47%	62%	41%	48%	49%	-13%	-27%	-17%	-22%	-20%	-5%	-8%	-7%	0%	-5%
TOTAL CONSUMER HEALTHCARE	5,110	£1,251	£1,188	£1,190	£1,127	4,756	£1,127	£1,022	£1,105	£1,095	£4,350	£1,195	£1,095	£1,640	£1,615	£5,545
% Change	-3%	-6%	-5%	-6%	-10%	-7%	-10%	-14%	-7%	-3%	-9%	6%	7%	NM	NM	NM
TOTAL GSK	£30,000	£6,255	£6,374	£6,274	£6,700	£25,602	£5,613	£5,561	£5,870	£6,395	£23,450	£5,700	£5,880	£6,465	£6,820	£24,865
% Change	-3%	-4%	0%	-2%	0%	-15%	-10%	-13%	-6%	-5%	-8%	2%	6%	10%	7%	6%

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
Seretide / Advair - U.S (lc, ex fx)												
Seretide / Advair - U.S	2,533	2,769	1,985	1,400	1,100	500	400	300	200	-32%	-31%	FDA Draft Guidance increases risk of generics; combo pat. Exp. 9/10; blister strip patent 2016
Seretide / Advair - EU (lc, Ex fx)												
Seretide / Advair - EU	1,447	1,458	1,305	1,060	800	600	400	200	100	-35%	-32%	Generics in many markets
Seretide / Advair - EM	417	429	385	420	475	515	500	550	600	8%	5%	
Seretide / Advair - Japan	277	250	280	300	320	340	360	380	7%	5%		
Seretide / Advair - ROW	649	341	300	330	350	370	390	410	430	6%	3%	Japan launch 2007
Seretide / Advair	5,046	5,274	4,225	3,490	3,025	2,305	2,030	1,820	1,710	-14%	-15%	Flovent/Serevent combination in Diskus inhaler
Flixotide / Flovent - U.S. (lc, ex fx)												
Flixotide / Flovent - U.S.	448	482	435	465	485	505	525	545	565	4%	2%	36.0% share 7/14
Flixotide / Flovent - EU (lc, ex fx)												
Flixotide / Flovent - EU	122	117	105	95	85	75	65	55	45	-13%	-13%	
Flixotide / Flovent - EM	55	58	60	65	70	75	80	85	90	7%	6%	
Flixotide / Flovent - Japan	42	35	30	25	20	15	10	5	-28%	-26%		
Flixotide / Flovent - ROW	154	97	85	70	60	50	40	30	20	-21%	-20%	
Flixotide / Flovent	779	796	715	725	725	725	725	725	725	0%	-1%	
Ventolin - U.S. (lc, ex fx)												
Ventolin - U.S.	277	291	310	320	345	365	385	405	425	5%	6%	
Ventolin - EU (lc, ex fx)												
Ventolin - EU	126	127	110	95	80	70	60	50	40	-16%	-15%	
Ventolin - EM	171	171	170	185	195	205	215	225	235	6%	5%	
Ventolin - Japan	9	15	20	25	30	35	40	45	20%	26%		
Ventolin - ROW	57	44	40	35	30	25	20	15	10	-21%	-19%	
Ventolin	631	642	645	655	675	695	715	735	755	3%	2%	
Veramyst - U.S. (lc, ex fx)												
Veramyst - U.S.	59	42	35	50	60	65	70	75	80	15%	10%	0.8% share 7/14
Veramyst - EU (lc, ex fx)												
Veramyst - EU	62	69	75	90	100	110	120	130	140	11%	11%	
Veramyst - EM	63	71	80	85	90	95	100	105	110	5%	6%	
Veramyst - Japan	49	50	60	70	80	90	100	110	110	14%	12%	
Veramyst - ROW	62	18	15	25	30	35	40	45	50	22%	16%	
Veramyst	246	249	260	310	350	385	420	455	490	11%	10%	Fluticasone furoate; glucocorticoid receptor agonist; allergic rhinitis
Flixonase/Flonase - U.S. (lc, ex fx)												
Flixonase/Flonase - U.S.	14	7	10	5	5	5	5	5	5	-11%	-5%	
Flixonase/Flonase - EU (lc, ex fx)												
Flixonase/Flonase - EU	32	31	20	20	20	20	20	20	20	0%	-6%	
Flixonase/Flonase - EM	57	49	40	55	60	65	70	75	80	12%	7%	
Flixonase/Flonase - ROW	30	23	25	20	15	10	5	5	5	-24%	-20%	
Flixonase / Flonase	133	110	95	100	100	100	100	105	110	2%	0%	Generics clip

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
Anoro			65	340	650	900	1250	1500	1750	73%	NM	Muscarinic acetylcholine antagonist/LABA; COPD; rollout underway WW
Breo/Relvar - U.S. (lc, ex fx)												
Breo/Relvar - U.S.	5	40	130	210	300	400	500	600	57%	NM	Long acting beta 2 agonist/steroid; asthma/COPD in EU, COPD in U.S., asthma in Japan; SUMMIT mortality trial in '15 key	
Breo/Relvar - EU (lc, ex fx)												
Breo/Relvar - EU	0	20	30	80	110	140	170	200				
Breo/Relvar - EM	0	0	20	40	60	80	100	120				
Breo/Relvar - Japan	3	30	110	200	250	300	350	400	54%	NM		
Breo/Relvar - ROW	0	0	20	40	60	80	100	120				
Breo/Relvar	8	89	310	570	780	1,000	1,220	1,440	59%	NM		
Incruse			40	60	80	100	120	140				
Losmapimod					10	25	50	75	NM	NM	Umeclidinium (UMEC); COPD; approved US and EU 4/14	
2586881					10	25	50	75	NM	NM	856553; P38 alpha kinase inhibitor; oral; COPD; ACS; Phase II	
961081					10	25	50	75	NM	NM	Recombinant human ACE2; acute lung injury; Phase II	
Fluticasone Furoate					10	25	50	75	NM	NM	MABA; Muscarinic acetylcholine antagonist, beta2 agonist; COPD; Phase II	
Vilanterol					10	25	50	75	NM	NM	Glucocorticoid agonist; asthma; filed 10/23/13	
Dilmapimod					10	25	50	75	NM	NM	COPD; Phase III	
2190915					10	25	50	75	NM	NM	P38 kinase inhibitor; acute respiratory distress syndrome; Phase II	
2245035					10	25	50	75	NM	NM	5-lipoxygenase activating protein (FLAP) inhibitor; asthma; Phase II	
Bosatria					10	25	50	75	NM	NM	Toll-like 7 agonist; asthma; Phase II	
Zyrtec	81	76	65	60	55	50	45	40	35	-10%	-8%	Mepolizumab; anti-IL5 monoclonal antibody; severe asthma; Phase III
Other respiratory	230	134	105	85	75	65	55	45	35	-17%	-17%	Antihistamine; rest of world only
Respiratory	7,291	7,289	6,260	6,115	6,285	6,175	6,665	7,215	7,865	4%	1%	
% Change	0%	0%	-14%	-2%	3%	-2%	8%	8%	9%			
Wellbutrin - U.S. (lc, ex fx)												
Wellbutrin - U.S.	12	16	10	10	10	10	10	10	10	0%	-6%	
Wellbutrin - EU (lc, ex fx)												
Wellbutrin - EU	44	51	55	60	65	70	75	80	85	8%	8%	
Wellbutrin - EM	28	30	35	40	45	50	55	60	65	11%	12%	
Wellbutrin - ROW	0	0	10	15	20	25	30	35	40	26%	NM	
Wellbutrin	84	97	111	125	140	155	170	185	200	10%	11%	
Treximet - U.S. (lc, ex fx)												
Treximet - U.S.	49	40										Patent expires 2017
Treximet	49	40										Imitrex + naprosyn; sold to Pernix for \$250MM; closes 8/1/14
Trobalt (retigabine)/Potiga (ezogabine)	11	11	10	20	25	30	35	40	45	28%	22%	Neuronal potassium channel opener; partial seizures; approved in EU and U.S.; with Valeant
239512						10	25	50	75	NM	NM	Histamine H3 antagonist; MS, dementia, schizophrenia; Phase II
249320						10	25	50	75	NM	NM	Myelin-associated glycoprotein monoclonal AB; stroke, MS; Phase II
Other CNS	188	180	165	160	150	140	130	120	110	-7%	-7%	
CNS	1,670	328	310	305	315	345	385	445	505	8%	6%	
% Change	-3%	0%	-5%	-2%	3%	10%	12%	16%	13%			

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
Epzicom/Kivexa - U.S. (lc, ex fx)												
Epzicom/Kivexa - U.S.	243	269	270	280	295	310	320	330	340	4%	3%	Abacavir + lamivudine
Epzicom/Kivexa - EU (lc, ex fx)												
Epzicom/Kivexa - EU	285	328	330	345	360	375	390	405	420	4%	4%	
Epzicom/Kivexa - EM	57	78	75	95	105	115	125	135	145	12%	9%	
Epzicom / Kivexa - Japan	36	35	45	50	55	60	65	70	70	12%	10%	
Epzicom/kivexa- ROW	80	52	55	60	65	70	75	80	85	8%	7%	
Epzicom / Kivexa	665	763	770	825	875	925	970	1,015	1,060	5%	5%	Competes with Gilead's Truvada; Teva challenged 2018 patent
Trizivir - U.S. (lc, ex fx)												
Trizivir - U.S.	61	58	5	0	0	0	0	20	0	NM	NM	Abacavir + zidovudine + lamivudine
Trizivir - EU (lc, ex fx)												
Trizivir - EU	37	32	20	15	10	5	5	5	5	-21%	-23%	
Trizivir - EM	5	4	10	15	20	25	30	35	40	26%	39%	
Trizivir - Japan	0	0	0	0	0	0	0	0	0			
Trizivir- ROW	4	3	0	0	0	0	0	0	0	NM	NM	
Trizivir	107	97	40	30	30	30	35	60	45	2%	-10%	Combination of Ziagen and Combivir
Agenerase / Lexiva - U.S. (lc, ex fx)												
Agenerase / Lexiva - U.S.	68	62	50	50	45	40	35	30	25	-11%	-12%	
Agenerase / Lexiva - EU (lc, ex fx)												
Agenerase / Lexiva - EU	33	27	20	15	10	10	5	5	5	-21%	-21%	
Agenerase / Lexiva - EM	19	18	15	20	25	30	35	40	45	20%	14%	
Agenerase / Lexiva - Japan	3	0	10	15	20	25	30	35	NM	42%		
Agenerase / Lexiva- ROW	7	3	0	0	0	0	0	0	0	NM	NM	
Agenerase / Lexiva	127	113	95	95	95	100	100	105	110	2%	0%	Protease inhibitor
Combivir - U.S. (lc, ex fx)												
Combivir - U.S.	24	35	20	15	10	5	5	5	5	-21%	-24%	Pressured by generic competition
Combivir - EU (lc, ex fx)												
Combivir - EU	64	39	20	15	10	5	5	5	5	-21%	-25%	Pressured by generic competition
Combivir - EM	79	35	25	20	15	10	5	5	5	-24%	-24%	
Combivir - Japan	3	5	15	20	25	30	35	40	41%	45%		
Combivir- ROW	12	4	0	0	0	0	0	0	0	NM	NM	
Combivir	179	116	70	65	55	45	45	50	55	-4%	-10%	Fixed dose combination of Epivir and Retrovir
Epivir - U.S. (lc, ex fx)												
Epivir - U.S.	8	10	10	5	5	5	5	5	5	-11%	-9%	Patent expired 5/10
Epivir - EU (lc, ex fx)												
Epivir - EU	21	16	10	10	5	5	5	5	5	-11%	-15%	
Epivir - EM	12	11	10	10	10	10	10	10	10	0%	-1%	
Epivir - ROW	8	6	5	5	5	5	5	5	5	0%	-3%	
Epivir	49	43	35	30	25	25	25	25	25	-5%	-7%	

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
Tivicay - U.S. (lc, ex fx)												
Tivicay - U.S.	19	215	535	750	1000	1250	1500	1750	42%	NM	HIV integrase inhibitor; rollout underway; Tri (+abacavir+lamivudine) in PIII	
Tivicay - EU (lc, ex fx)												
Tivicay - EU	0	60	150	200	250	300	350	400				
Tivicay - EM	0	0	0	0	0	0	0	0				
Tivicay - Japan	0	20	90	150	200	250	300	350				
Tivicay - ROW	0	0	0	0	0	0	0	0				
Tivicay	19	295	775	1,100	1,450	1,800	2,150	2,500	43%	NM	Dolutegravir	
Selzentry - U.S. (lc, ex fx)												
Selzentry - U.S.	128	58	50	55	60	65	70	75	80	8%	5%	Maraviroc; CCR5 inhibitor; approved for treatment resistant; Phase III for treatment naïve; from Pfizer
Selzentry - EU (lc, ex fx)												
Selzentry - EU	63	60	50	45	40	35	30	25	-14%	-12%		
Selzentry - EM	6	10	10	10	10	10	10	10	0%	8%		
Selzentry - Japan	3	5	10	10	10	10	10	10	12%	19%		
Selzentry - ROW	13	20	15	15	15	15	15	15	-5%	2%		
Selzentry	143	146	140	140	140	140	140	140	-1%	0%		
1265744						10	25	50	75	NM	NM	HIV integrase inhibitor; long acting IV form; Phase II
Rescriptor	45	30	20	20	15	10	5	5	5	-21%	-23%	From Pfizer
Viracept	29	20	15	10	5	5	5	5	5	-17%	-18%	Protease inhibitor; patent expiration 4/14; from Pfizer
Other HIV	45	42	25	20	15	10	5	5	5	-24%	-26%	
HIV	1,374	1,386	1,510	2,010	2,355	2,750	3,155	3,610	4,025	18%	16%	
% Change	-12%	0%	9%	33%	17%	17%	15%	14%	11%			
Relenza - U.S. (lc, ex fx)												
Relenza - U.S.	6	6	0	0	0	0	0	0	0	NM	NM	
Relenza - EU (lc, ex fx)												
Relenza - EU	1	0	0	0	0	0	0	0	0	NM	NM	
Relenza - EM	0	8	10	5	5	5	5	5	5	NM	NM	
Relenza - ROW	26	68	50	70	70	70	70	70	70	6%	0%	
Relenza	33	70	65	75	75	75	75	75	75	2%	1%	Manufacturing 60MM packs but ramping to 190MM over time; L10 per pack
Zovirax	89	81	70	60	50	40	30	20	10	-28%	-26%	Off patent
Other Antivirals	21	14	20	25	30	35	40	45	50	16%	20%	
Antivirals	764	165	155	160	155	150	145	140	135	-2%	-3%	
% Change	-9%	0%	-6%	3%	-3%	-3%	-3%	-3%	-4%			
Augmentin - U.S. (lc, ex fx)												
Augmentin - U.S.	1	1	0	0	0	0	0	0	0	NM	NM	
Augmentin - EU (lc, ex fx)												
Augmentin - EU	202	203	175	150	125	100	75	50	25	-28%	-26%	
Augmentin - EM	367	393	375	390	405	420	435	450	465	4%	2%	
Augmentin - Japan	13	15	20	20	20	20	20	20	20	5%	6%	
Augmentin - ROW	38	20	20	20	15	15	10	10	5	-21%	-18%	
Augmentin	608	630	585	580	545	535	520	510	495	-3%	-3%	

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
1322322					50	75	100	125	150	NM	NM	Polypeptide deformylase inhibitor; bacterial infections; Phase II
Zinnat / Ceftin	174	169	165	160	155	150	145	140	135	-3%	-3%	Older antibiotic
Etaquine (Tafenoquine)					10	20	30	40	50	NM	NM	Malaria prophylaxis (adults); 8-aminoguinoine; Phase II
Altabax	7	4	5	5	5	5	5	5	5	NM	NM	Broad spectrum topical antiinfective
Other antibacterials	458	453	440	420	400	380	360	340	320	-5%	-5%	
Antibacterials	1247	1,256	1,195	1,185	1,165	1,165	1,160	1,160	1,155	-1%	-1%	
% Change	-10%	0%	-5%	-3%	0%	0%	0%	0%	0%			
Tanzeum/Eperzan			20	110	200	250	300	350	400	NM	NM	GLP1; type 2 diabetes; 7 of 8 studies met endpoints; US launch Q3, EU launch H2; 30-35% discount to competitors
1070806						10	25	50	75	NM	NM	IL-18 Mab; type 2 diabetes; Phase II
1278863						10	25	50	75	NM	NM	Prolyl hydroxylase inhibitor; anemia associated with chronic renal disease; PAD; Phase II
Boniva income										NM	NM	Bisphosphonate; OUS; agreement terminated in most EU markets
Other metabolic	160	174	180	185	190	195	200	205	210	3%	3%	
Metabolic	166	174	200	295	390	465	550	655	760	25%	23%	
% Change	-50%	0%	15%	48%	32%	19%	18%	19%	16%			
Infanrix / Pediarix - U.S. (lc, ex fx)												
Infanrix / Pediarix - U.S.	218	271	290	310	330	350	370	390	410	6%	6%	May get boost from SNY's Pentacel manufacturing issue
Infanrix / Pediarix - EU (lc, ex fx)												
Infanrix / Pediarix - EU	376	398	375	390	405	420	435	450	465	4%	2%	
Infanrix / Pediarix - EM	120	132	135	150	165	180	195	210	225	9%	8%	
Infanrix / Pediarix - Japan		0	0	0	0	0	0	0	0	NM	NM	
Infanrix / Pediarix - ROW	61	61	65	75	85	95	105	115	125	12%	11%	
Infanrix / Pediarix	775	862	865	925	985	1,045	1,105	1,165	1,225	6%	5%	Globorix (conjugated DTP + hep B + influenza b + Neisseria meningitis)
Synforix - EU (lc, ex fx)												
Synflorix - EU	45	48	50	60	65	70	75	80	85	9%	9%	
Synflorix - EM	334	350	375	385	395	405	415	425	435	3%	3%	
Synflorix - Japan		0	0	0	0	0	0	0	0	NM	NM	
Synflorix - ROW	6	7	15	15	20	25	30	35	40	18%	28%	
Synflorix	385	405	435	460	480	500	520	540	560	4%	5%	10 valent S. Pneumonia and non-typable H. Influenza prophylaxis; approved in EU; not pursuing in U.S.

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
Hepatitis - U.S. (lc, ex fx)												
Hepatitis - U.S.	266	263	215	195	175	155	135	115	95	-13%	-14%	
Hepatitis - EU (lc, ex fx)												
Hepatitis - EU	197	198	180	170	160	150	140	130	120	-7%	-7%	
Hepatitis - EM	128	123	115	110	105	100	95	90	85	-5%	-5%	
Hepatitis - Japan	0	0	0	0	0	0	0	0	0	NM	NM	
Hepatitis - ROW	55	45	45	50	55	60	65	70	75	9%	8%	
Hepatitis	646	629	550	525	495	465	435	405	375	-6%	-7%	Hepatitis A (Havrix) and recombinant Hepatitis B (Engerix)
Rotarix - U.S. (lc, ex fx)												
Rotarix - U.S.	100	108	100	110	120	130	140	150	160	8%	6%	
Rotarix - EU (lc, ex fx)												
Rotarix - EU	39	59	70	80	90	100	110	120	130	11%	12%	
Rotarix - EM	159	164	190	210	230	250	270	290	310	9%	10%	
Rptarix - Japan	25	35	35	40	45	50	55	60	60	9%	13%	
Rotarix - ROW	62	19	15	25	30	35	40	45	50	22%	15%	
Rotarix	360	375	410	460	510	560	610	660	710	10%	10%	Rotavirus vaccine
Boostrix - U.S. (lc, ex fx)												
Boostrix - U.S.	147	183	195	210	230	250	270	290	310	8%	8%	
Boostrix - EU (lc, ex fx)												
Boostrix - EU	53	65	80	90	100	110	120	130	140	10%	12%	
Boostrix - EM	16	20	40	30	35	40	45	50	55	5%	16%	
Boostrix - Japan	0	0	0	0	0	0	0	0	0	NM	NM	
Boostrix - ROW	22	20	25	30	35	40	45	50	55	14%	16%	
Boostrix	238	288	340	360	400	440	480	520	560	9%	10%	Booster immunization against tetanus, diphtheria and pertussis
Cervarix - U.S. (lc, ex fx)												
Cervarix - U.S.	6	6	10	20	25	30	35	40	45	28%	33%	
Cervarix - EU (lc, ex fx)												
Cervarix - EU	53	61	65	80	90	100	110	120	130	12%	11%	
Cervarix - EM	75	92	90	100	110	120	130	140	150	9%	7%	
Cervarix - Japan	10	25	50	65	80	95	110	125	125	31%	43%	
Cervarix - ROW	136	3	5	20	25	30	35	40	45	44%	47%	Japan weak in 2013
Cervarix	270	172	195	270	315	360	405	450	495	17%	16%	HPV vaccine; U.S. and EU rollouts progressing slowly
Fluarix / FluLaval - U.S. (lc, ex fx)												
Fluarix / FluLaval - U.S.	88	146	145	160	170	180	190	200	210	6%	5%	34MM doses in 2011, 25MM in 2012
Fluarix / FluLaval - EU (lc, ex fx)												
Fluarix / FluLaval - EU	43	35	40	45	50	55	60	65	70	10%	10%	
Fluarix / FluLaval - EM	44	43	40	50	55	60	65	70	75	11%	8%	
Fluarix / FluLaval - Japan	0	0	0	0	0	0	0	0	0	NM	NM	
Fluarix / FluLaval - ROW	25	27	30	40	45	50	55	60	65	14%	13%	
Fluarix / FluLaval	200	251	255	295	320	345	370	395	420	9%	8%	Flulaval (inactivated split) approved

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
Pandemic - U.S. (lc, ex fx)												
Pandemic - U.S.	0	0	0	0	0	0	0	0	0	NM	NM	
Pandemic - EU (lc, ex fx)												
Pandemic - EU	1	1	0	0	0	0	0	0	0	NM	NM	
Pandemic - EM	0	0	0	0	0	0	0	0	0	NM	NM	
Pandemic - ROW	0	1	0	0	0	0	0	0	0	NM	NM	
Pandemic	1	2	0	0	0	0	0	0	0	NM	NM	H1N1; H5N1 inactivated split monovalent; Phase III
Novartis Vaccines			325	600	650	700	750	800	NM	NM		
Nimerix (MenACWY-TT)	12	25	70	150	200	250	300	350	55%	NM		Acquired from NVS for \$5.25B+\$1.8B in milestones; Bexsero key U.S., launched in EU
Menhibrix (Hib-MenCY-TT)				5	10	15	20	25	NM	NM		Conjugated Neisseria meningitis groups A,C,W & Y prophylaxis; Phase III
Varicella zoster					10	25	50	75	NM	NM		Recombinant; varicella zoster prevention; Phase III in 2015
Tuberculosis					10	20	30	40	NM	NM		Recombinant; tuberculosis prophylaxis; Phase II
Mosquirix					10	20	30	40	NM	NM		Malaria prophylaxis; Phase III study in Africa
Other vaccines	424	400	380	360	340	320	300	280	-6%	-6%		
Vaccines	2,875	3,420	3,480	4,070	4,620	4,945	5,275	5,615	5,955	9%	8%	
% Change	-3%	0%	2%	17%	14%	7%	7%	6%	6%			
Established Products												
Coreg - U.S. (lc, ex fx)												
Coreg - U.S.	132	130	120	105	95	85	75	65	55	-12%	-12%	
Coreg - EU (lc, ex fx)												
Coreg - EU	0	0	0	0	0	0	0	0	0	NM	NM	
Coreg - EM	0	0	0	0	0	0	0	0	0	NM	NM	
Coreg - Japan	0	0	0	0	0	0	0	0	0	NM	NM	
Coreg - ROW	1	1	0	0	0	0	0	0	0	NM	NM	
Coreg	133	131	120	105	95	85	75	65	55	-12%	-12%	
Hepsera - EM		70	65	60	55	50	45	40	35	-10%	-9%	
Hepsera - Japan		25	30	35	40	45	50	55	60	12%	13%	
Hepsera - ROW	126	1	0	0	0	0	0	0	0	NM	NM	
Hepsera	126	96	95	95	95	95	95	95	95	0%	0%	Adefovir; chronic hepatitis B; with Gilead
Imigran / Imitrex - U.S. (lc, ex fx)												
Imigran / Imitrex - U.S.	72	80	75	60	50	40	30	20	10	-29%	-26%	Generics launched to all forms
Imigran / Imitrex - EU (lc, ex fx)												
Imigran / Imitrex - EU	67	63	60	55	50	45	40	35	30	-11%	-10%	
Imigran / Imitrex - EM	7	7	5	10	15	25	30	35	40	41%	28%	
Imigran / Imitrex - Japan		24	25	30	35	35	40	40	45			
Imigran / Imitrex- ROW	44	14	15	20	25	30	35	40	45	20%	18%	
Imigran / Imitrex	190	188	175	175	175	175	175	170	170	0%	-1%	Migraine

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
Lamictal - U.S. (lc, ex fx)												
Lamictal - U.S.	332	276	225	175	100	50	25	15	5	-47%	-44%	XR lost exclusivity in U.S. end 2012; XR represents 56% of U.S. sales
Lamictal - EU (lc, ex fx)												
Lamictal - EU	112	110	105	85	65	45	25	15	5	-40%	-36%	
Lamictal - EM	75	78	75	85	90	95	100	105	110	7%	5%	
Lamictal - Japan												
Lamictal - Japan	83	85	100	115	125	135	145	150	150	10%	9%	
Lamictal- ROW	91	10	15	20	25	30	35	40	45	20%	24%	Japan launch 2007
Lamictal	610	557	505	465	395	345	320	320	315	-8%	-8%	Patent litigation settlement with Teva allowed generic chewable in 6/05 and solid tab in 7/08
Lovaza - U.S. (lc, ex fx)												
Lovaza - U.S.	604	581	150	20	10	5	5	5	5	-43%	-49%	Teva generic holds 50%+ TRx share
Lovaza - Japan		0	0	0	0	0	0	0	0			
Lovaza - ROW	3	3	5	10	15	20	25	30	35	38%	NM	
Lovaza	607	584	155	30	25	25	30	35	40	-20%	-32%	Omega-3-acid ethyl esters; very high triglycerides; new competition and market declining
Requip - U.S. (lc, ex fx)												
Requip - U.S.	19	7	5	0	0	0	0	0	0	NM	NM	
Requip - EU (lc, ex fx)												
Requip - EU	76	52	40	40	30	20	10	5	5	-29%	-29%	
Requip - EM	14	14	15	25	30	35	40	45	50	22%	20%	
Requip - Japan												
Requip - ROW	51	0	50	45	40	35	30	25	20			
Requip	55	0	0	10	15	20	25	30	35	NM	NM	
Requip	164	125	115	120	115	110	105	105	110	-1%	-2%	RLS indication boosts; patent exp: 12/07 (cmpd), 5/08 (PD use), 5/08 (RLS exclusivity); Teva challenged CR
Serevent - U.S. (lc, ex fx)												
Serevent - U.S.	51	51	40	35	30	25	20	15	10	-21%	-21%	
Serevent - EU (lc, ex fx)												
Serevent - EU	64	55	45	35	25	15	10	5	5	-31%	-29%	
Serevent - EM	3	4	5	10	15	20	25	30	35	38%	36%	
Serevent - Japan												
Serevent - Japan	13	10	15	15	15	15	15	15	15	7%	2%	
Serevent - ROW	27	6	5	5	5	5	5	5	5	NM	-3%	
Serevent	145	129	110	100	90	80	75	70	70	-7%	-8%	Label warnings clip; patent expired 8/08 but no ANDA filings to date
Paxil/Seroxat - U.S. (lc, ex fx)												
Paxil/Seroxat - U.S.	0	0	5	5	5	5	5	5	5	0%	NM	
Paxil/Seroxat - EU (lc, ex fx)												
Paxil/Seroxat - EU	57	53	45	35	25	15	10	5	5	-31%	-29%	
Paxil/Seroxat - EM	84	79	60	55	45	35	25	15	5	-34%	-33%	
Paxil/Seroxat - Japan												
Paxil/Seroxat - Japan	138	100	80	60	40	20	10	5				
Paxil/Seroxat - ROW	233	15	15	15	10	5	5	5	0	NM	NM	
Paxil/Seroxat	374	285	225	190	145	100	65	40	20	-33%	-32%	Generics clip

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
Valtrex - U.S. (lc, ex fx)												
Valtrex - U.S.	35	45	35	30	25	20	15	10	5	NM	NM	
Valtrex - EU (lc, ex fx)												
Valtrex - EU	33	29	30	20	15	10	5	5	5	-26%	-22%	
Valtrex - EM	37	40	40	50	55	60	65	70	75	11%	9%	
Valtrex - Japan		102	55	40	30	20	10	5	5	-33%	-35%	
Valtrex - ROW	147	8	10	5	5	5	5	5	5	NM	NM	
Valtrex	252	224	170	145	130	115	100	95	95	-9%	-12%	Shingles/genital herpes; generics launched 11/09
Zeffix - U.S. (lc, ex fx)												
Zeffix - U.S.	15	13	10	10	10	10	10	10	10	0%	-4%	
Zeffix - EU (lc, ex fx)												
Zeffix - EU	16	12	10	5	5	5	5	5	5	-11%	-12%	
Zeffix - EM	188	140	130	145	155	165	175	185	195	7%	5%	
Zeffix - Japan		16	15	20	20	20	20	20	20	5%	3%	
Zeffix - ROW	24	0	0	0	0	0	0	0	0	NM	NM	
Zeffix	243	182	170	180	190	200	210	220	230	5%	3%	Lamivudine; hepatitis B; compound patent expires 5/10
Total Established Products	2,501	1,838	1,605	1,455	1,330	1,250	1,215	1,200		-7%	-10%	
% Chg.			-26%	-13%	-9%	-9%	-6%	-3%	-1%			
Promacta - U.S. (lc, ex fx)												
Promacta - U.S.	54	73	90	50								
Promacta - EU (lc, ex fx)												
Promacta - EU	36	55	75	35								
Promacta - EM	12	22	30	20								
Promacta - Japan		30	35	20								
Promacta - ROW	28	6	10	5								
Promacta	130	186	240	130								
Tykerb - U.S. (lc, ex fx)												
Tykerb - U.S.	68	55	40	25								
Tykerb - EU (lc, ex fx)												
Tykerb - EU	87	82	75	40								
Tykerb - EM	54	47	55	20								
Tykerb - Japan		17	15	10								
Tykerb - ROW	30	6	15	10								
Tykerb	239	207	195	105								

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
Hycamtin - U.S. (lc, ex fx)												
Hycamtin - U.S.	6	10	0	0								
Hycamtin - EU (lc, ex fx)												
Hycamtin - EU	19	10	5	0								
Hycamtin - EM	12	6	15	10								
Hycamtin - ROW	9	1	0	0								
Hycamtin	46	27	25	10								
Votrient/Patorma - U.S. (lc, ex fx)	183											
Votrient/Patorma - U.S.		144	160	80								
Votrient/Patorma - EU (lc, ex fx)												
Votrient/Patorma - EU	130		155	95								
Votrient/Patorma - EM	37		40	20								
Votrient/Patorma - Japan	9		15	10								
Votrient/Patorma - ROW	11		15	10								
Votrient/Patorma	331		388	215								
Tafinlar - U.S. (lc, ex fx)												
Tafinlar - U.S.	11		70	65								
Tafinlar - EU (lc, ex fx)												
Tafinlar - EU	4		71	65								
Tafinlar - EM	0		0	0								
Tafinlar - Japan	0		0	0								
Tafinlar - ROW	1		4	5								
Tafinlar	16		145	135								
Mekinist - U.S. (lc, ex fx)												
Mekinist - U.S.	10		45	65								
Mekinist - EU (lc, ex fx)												
Mekinist - EU	0		0	0								
Mekinist - EM	0		0	0								
Mekinist - Japan	0		0	0								
Mekinist - ROW	0		0	0								
Mekinist	10		74	65								
Arzerra - U.S. (lc, ex fx)	60											
Arzerra - U.S.		46	30	40								
Arzerra - EU (lc, ex fx)												
Arzerra - EU	27		20	20								
Arzerra - EM	0		30	20								
Arzerra - Japan	0		0	0								
Arzerra - ROW	1		1	0								
Arzerra	75		78	60								

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
Mapatumumab												
2110183												
Foretinib												
MAGE-A3												
Other Oncology/emeisis	140	117	105	40								
Oncology	2,810	969	1,250	760								Sold to Novartis for \$16B, \$1.5B of which keyed to COMBI-d trial
% Change	4%	0%	29%	-39%								
Flolan - U.S. (lc, ex fx)												
Flolan - U.S.	33	25	20	25	30	35	40	45	50	16%	10%	
Flolan - EU (lc, ex fx)												
Flolan - EU	23	18	20	25	30	35	40	45	50	16%	16%	
Flolan - EM	0	0	0	0	0	0	0	0	0	0	0	
Flolan - ROW	79	60	55	80	90	100	110	120	130	15%	12%	
Flolan	135	103	95	130	150	170	190	210	230	16%	12%	Pulmonary arterial hypertension
Voliris - U.S. (lc, ex fx)												
Voliris - U.S.												
Voliris - EU (lc, ex fx)												
Voliris - EU	73	82	95	100	110	120	130	140	150	8%	9%	
Voliris - EM	9	11	15	20	25	30	35	40	45			
Voliris - ROW	45	54	55	65	70	75	80	85	90	9%	8%	
Voliris	127	147	160	185	205	225	245	265	285	10%	10%	Pulmonary arterial hypertension
Other	233	245	210	235	245	255	265	275	285	5%	2%	
Rare Diseases	495	495	470	550	600	650	700	750	800	9%	7%	
% Change	7%	0%	-5%	17%	9%	8%	8%	7%	7%			
Avodart - U.S. (lc, ex fx)												
Avodart - U.S.	317	312	285	220	50	25	5	5	5	-49%	-45%	Patent expires 2015; Teva can launch via settlement in Q4:15
Avodart - EU (lc, ex fx)												
Avodart - EU	228	273	275	290	305	75	50	25	10	-42%	-38%	Patent expires 2017
Avodart - EM	84	104	115	135	155	175	195	215	235	13%	12%	
Avodart - Japan		114	110	120	130	140	150	160	170	8%	6%	
Avodart - ROW	161	54	55	65	75	85	95	105	115	13%	11%	
Avodart	790	857	840	830	715	500	495	510	535	-7%	-7%	BPH; good growth despite finasteride generics; prostate cancer filing

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
Fraxiparine - EU (lc, ex fx)												
Fraxiparine - EU	145											
Fraxiparine - EM	87	83	30	35	40	45	50	55	60	12%	-5%	
Fraxiparine - ROW	1											
Fraxiparine	233	83	30	35	40	45	50	55	60	12%	-5%	Sold to Aspen Group for 700MM, except for China, India, Pakistan
Arixtra - U.S. (lc, ex fx)												
Arixtra - U.S.	68											
Arixtra - EU (lc, ex fx)												
Arixtra - EU	91											
Arixtra - EM	28	28	15	25	30	35	40	45	50	22%	9%	
Arixtra - ROW	8											
Arixtra	195	28	15	25	30	35	40	45	50	22%	9%	Sold to Aspen Group for 700MM, except for China, India, Pakistan
Vesicare - U.S. (lc, ex fx)												
Vesicare - U.S.	174											
Vesicare - EU (lc, ex fx)												
Vesicare - EU	0											
Vesicare - EM	1											
Vesicare - ROW	0											
Vesicare	175											Astellas terminated agreement via option
Losmapimod						10	25	50	75	NM	NM	856553; p38 kinase inhibitor; atherosclerosis; Phase II
Tyrisa									10	NM	NM	Darpladib; Lp-PLA2 inhibitor; atherosclerosis; CV studies failed; DME Phase III
Other Cardiovascular	298	279	115	100	80	60	40	20	10	-33%	-38%	
Cardio/Urogenital	2,431	1,247	1,005	990	865	650	650	680	740	-5%	-7%	
Benlysta - U.S.	65	134	155	230	300	350	400	450	500	22%	21%	GSK recorded full sales beginning in Q3:12
Benlysta - EU	8	15	40	80	150	200	250	300	300	65%	68%	
Benlysta - ROW	5	4	0	0	0	0	0	0	0			
Benlysta (belimumab)	70	146	175	270	380	500	600	700	800	29%	28%	Anti-BLS Ab; SLE; Phase III vasculitis; IV; SQ in PIII; Phase II myasthenia gravis
Firategrast						10	25	50	75	NM	NM	Dual alpha4 integrin antagonist (VLA4); multiple sclerosis; Phase II
933776						10	25	50	75	NM	NM	Monoclonal AB; geographic atrophy; Phase II
Ofatumumab						10	25	50	75	NM	NM	CD20 human monoclonal AB; SQ; multiple sclerosis; Phase II
Sirukumab						10	25	50	75	NM	NM	IL-6 AB; SQ; RA; Phase III
Ozanezumab						10	25	50	75	NM	NM	NOGO-A; ALS; Phase II
Camicinal						10	25	50	75	NM	NM	Motilin receptor antagonist; delayed gastric emptying; Phase II

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
2245840						10	25	50	75	NM	NM	SIRT1; psoriasis; Phase II
2586148						10	25	50	75	NM	NM	JAK1 inhibitor; SLE and psoriasis; Phase II
2941266						10	25	50	75	NM	NM	Chemokine receptor antagonist 1; RA; Phase II
Zantac	142	111	100	90	80	70	60	50	40	-14%	-14%	Off patent
Entereg										NM	NM	I.V. mu-opioid antagonist for post operative ileus, returned rights to chronic opioid dysfunction indication
Retosiban						20	30	40	50	NM	NM	Oxytocin antagonist; threatened pre-term labor; Phase II
Denosumab income	39	52	35	20	25	30	35	40	45	4%	-2%	Osteoporosis; rights in EM, some ROW; AMGN took back EU in 4/14
Other	1,149	1,032	895	775	700	600	500	400	300	-17%	-16%	
Other	3,412	1,341	1,200	1,155	1,185	1,310	1,450	1,680	1,910	8%	5%	
% Change	-6%	0%	-11%	-4%	3%	11%	11%	16%	14%			
Bactroban - U.S. (lc, ex fx)												
Bactroban - U.S.	51	29	25	20	15	10	5	5	5	-24%	-22%	
Bactroban - EU (lc, ex fx)												
Bactroban - EU	26	24	20	20	20	20	20	20	20	0%	-3%	
Bactroban - EM	39	38	35	40	40	40	40	40	40	2%	1%	
Bactroban - ROW	8	7	10	10	10	10	10	10	10	0%	5%	
Bactroban	124	98	85	90	85	80	75	75	75	-2%	-4%	
Soriatane - U.S. (lc, ex fx)												
Soriatane - U.S.	79	56	20	15	10	5	5	5	5	-21%	-29%	
Soriatane - EU (lc, ex fx)												
Soriatane - EU	0	0	0	0	0	0	0	0	0	NM	NM	
Soriatane - EM	0	0	0	0	0	0	0	0	0	NM	NM	
Soriatane - ROW	0	1	0	0	0	0	0	0	0	NM	NM	
Soriatane	79	57	20	15	10	5	5	5	5	-21%	-29%	
Dermovate - U.S. (lc, ex fx)												
Dermovate - U.S.												
Dermovate - EU (lc, ex fx)												
Dermovate - EU	18	22	20	20	20	20	20	20	20	0%	-1%	
Dermovate - EM	36	54	50	60	65	70	75	80	85	9%	7%	
Dermovate - ROW	21	18	20	20	20	20	20	20	20	0%	2%	
Dermovate	75	94	95	100	105	110	115	120	125	5%	4%	
Duac - U.S. (lc, ex fx)												
Duac - U.S.	38	15	5	5	5	5	5	5	5	0%	-15%	Generic competition
Duac - EU (lc, ex fx)												
Duac - EU	24	29	30	35	40	45	50	55	60	12%	11%	
Duac - EM	13	16	20	20	20	20	20	20	20	0%	3%	
Duac - ROW	12	12	10	15	15	15	15	15	20	12%	8%	
Duac	87	72	65	75	80	85	90	95	105	8%	6%	
Other	485	450	430	410	390	370	350	330	310	-5%	-5%	
Dermatology	850	770	695	690	670	650	635	625	620	-2%	-3%	Stiefel dermatological business acquisition closed 7/22/09; 70% of sales Rx, 30% of sales OTC
% Change	-5%	0%	-10%	-1%	-3%	-3%	-2%	-2%	-1%			

Source: Cowen and Company

GlaxoSmithKline 2013-20 Annual Product Sales Buildup (£MM) (continued)

	2012	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comment
TOTAL PHARMACEUTICALS	£24,890	£20,846	£19,098	£19,320	£19,460	£19,935	£21,320	£23,040	£24,870	4%	3%	
% Change	-3%	-16%	-8%	1%	1%	2%	7%	8%	8%			
OTC	2,008	1,865	1,650	2,710	3,825	4,025	4,225	4,425	4,625	19%	14%	Reflects 126MM of non-strategic turnover divested 1/12; 185MM divested in Q2:12; 60MM fgn and Alli to be rebuilt - sales of 93MM in 2011; includes NVS Consumer JV (approx \$3B in revenue annually)
% Change	-8%	-7%	-12%	NM	NM	5%	5%	5%	5%			
Oral Care	1,797	1,884	1,790	1,925	2,075	2,200	2,300	2,425	2,550	6%	4%	
% Change	5%	5%	-5%	8%	8%	6%	5%	5%	5%			
Nutritional Healthcare	1,050	627	600	620	640	660	680	700	720	3%	2%	Lucozade and Ribena divested YE 2013; 455MM in sales is sold, representing U.K. and Ireland
% Change	2%	-40%	NM	3%	3%	3%	3%	3%	3%			
Skin Health	255	380	305	290	310	320	330	340	350	2%	-1%	
% Change	-25%	49%	-20%	-5%	7%	3%	3%	3%	3%			
TOTAL CONSUMER HEALTHCARE	5,110	4,756	£4,350	£5,545	£6,850	£7,205	£7,535	£7,890	£8,245	11%	8%	
% Change	-3%	-7%	-9%	NM	NM	5%	5%	5%	4%			
TOTAL GSK	£30,000	£25,602	£23,450	£24,865	£26,310	£27,140	£28,855	£30,930	£33,115	6%	4%	
% Change	-3%	-15%	-8%	6%	6%	3%	6%	7%	7%			

Source: Cowen and Company

GlaxoSmithKline Summary Balance Sheet 2013-20 (£MM)

	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Assets:								
Inventories	£3,900	£4,150	£4,550	£4,550	£4,750	£5,000	£5,350	£5,700
Trade and other receivables	5,442	4,950	5,250	5,500	5,650	6,000	6,450	6,900
Liquid investments	66	100	100	100	100	100	100	100
Cash and cash equivalents	5,534	2,638	2,745	2,637	2,266	1,920	1,551	1,206
Other Current Assets	285	250	250	300	300	300	350	400
Total current assets	15,227	12,088	12,895	13,087	13,066	13,320	13,801	14,306
Property, plant and equipment (net)	8,872	8,700	9,200	9,750	10,050	10,700	11,450	12,250
Goodwill	4,205	4,000	4,000	4,000	3,900	3,800	3,700	3,500
Other Intangible Assets	9,283	8,500	8,600	8,600	8,500	8,400	8,300	8,200
Investments in associates	323	325	325	325	325	325	325	325
Other investments	1,202	1,200	1,200	1,200	1,200	1,200	1,200	1,200
Deferred tax assets	2,084	2,100	2,100	2,100	2,100	2,100	2,100	2,100
Other non-current assets	890	800	800	800	800	800	800	800
Total non-current Assets	26,859	25,625	26,225	26,775	26,875	27,325	27,875	28,375
Total Assets	£42,086	£37,713	£39,120	£39,862	£39,941	£40,645	£41,676	£42,681
Liabilities:								
Short-term borrowings	(2,789)	(3,000)	(3,000)	(3,000)	(3,000)	(3,000)	(3,000)	(3,000)
Trade and other payables	(8,317)	(6,900)	(7,550)	(7,950)	(8,300)	(8,800)	(9,450)	(10,000)
Current tax payable	(1,452)	(1,125)	(1,225)	(1,325)	(1,350)	(1,400)	(1,475)	(1,600)
Short-term provisions	(1,119)	(1,125)	(1,225)	(1,325)	(1,350)	(1,400)	(1,475)	(1,600)
Total current liabilities	(13,677)	(12,150)	(13,000)	(13,600)	(14,000)	(14,600)	(15,400)	(16,200)
Long-term borrowings	(15,456)	(14,500)	(14,250)	(14,000)	(13,750)	(13,500)	(13,250)	(13,000)
Deferred tax provision	(693)	(700)	(700)	(700)	(700)	(700)	(700)	(700)
Pensions and other post-employment benefits	(2,189)	(2,300)	(2,500)	(2,500)	(2,500)	(2,500)	(2,500)	(2,500)
Provisions and Other non-current liabilities	(2,259)	(2,000)	(2,000)	(2,000)	(2,000)	(2,000)	(2,000)	(2,000)
Total non-current liabilities	(20,597)	(19,500)	(19,450)	(19,200)	(18,950)	(18,700)	(18,450)	(18,200)
Total Liabilities	-£34,274	-£31,650	-£32,450	-£32,800	-£32,950	-£33,300	-£33,850	-£34,400
Net Equity	£7,812	£6,063	£6,670	£7,062	£6,991	£7,345	£7,826	£8,281

Source: Company data, Cowen and Company

GlaxoSmithKline Working Capital Analysis 2013-20 (£MM)

	2013A	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Inventories	£3,900	£4,150	£4,550	£4,550	£4,750	£5,000	£5,350	£5,700
COGS	£7,075	£6,611	£7,269	£7,761	£8,088	£8,541	£9,093	£9,670
Inventory Turns	1.8	1.6	1.6	1.7	1.7	1.7	1.7	1.7
Months	6.6	7.5	7.5	7.1	7.1	7.1	7.1	7.1
Accounts Receivable	£5,442	£4,950	£5,250	£5,500	£5,650	£6,000	£6,450	£6,900
Sales	£25,602	£23,448	£24,865	£26,310	£27,140	£28,855	£30,930	£33,115
Receivables Days	77.6	77.0	77.0	76.0	76.0	76.0	76.0	76.0
Other Current Assets	£285	£250	£250	£300	£300	£300	£350	£400
% of Sales	1.1%	1.0%	1.0%	1.1%	1.1%	1.1%	1.1%	1.1%
Accounts Payable	£8,317	£6,900	£7,550	£7,950	£8,300	£8,800	£9,450	£10,000
COGS	£7,075	£6,611	£7,269	£7,761	£8,088	£8,541	£9,093	£9,670
Payables Days	429	380	380	375	375	375	380	377
Other Current Liabilities	£2,571	£2,250	£2,450	£2,650	£2,700	£2,800	£2,950	£3,200
% of COGS	36%	34%	34%	34%	34%	33%	33%	33%
Net Working Capital (Ex. Cash, Debt)	-£1,261	£200	£50	-£250	-£300	-£300	-£250	-£200

Source: Company data, Cowen and Company

GlaxoSmithKline Cash Flow Analysis 2013-20 (£MM)

	2013A	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Operating Activity								
Operating Profit	£5,237	£4,474	£4,479	£4,666	£4,647	£5,086	£5,526	£5,962
Depreciation & Amort.	1,415	1,400	1,350	1,350	1,350	1,400	1,400	1,400
Changes in working capital (net)	504	(1,461)	150	300	50	-	(50)	(50)
Taxes paid	(1,277)	(1,334)	(1,382)	(1,489)	(1,500)	(1,640)	(1,781)	(1,922)
Others Net	1,343	1,200	1,200	1,300	1,300	1,400	1,400	1,500
Net Cash Flow Provided By Operations	£7,222	£4,279	£5,798	£6,127	£5,847	£6,246	£6,495	£6,890
Investing Activities								
Capital Expenditure	-£1,188	-£1,100	-£1,100	-£1,100	-£1,100	-£1,100	-£1,100	-£1,100
Proceeds from sale of property plant and equipment	182	-	4,600	-	-	-	-	-
Purchase of equity investments-net	(74)	-	-	-	-	-	-	-
Asset Sales (net)	2,280	-	-	-	-	-	-	-
Purchase of business/intangibles net	(760)	-	-	-	-	-	-	-
Others (net)	84	-	-	-	-	-	-	-
Net Cash Flow Provided By Investing	£524	-£1,100	£3,500	-£1,100	-£1,100	-£1,100	-£1,100	-£1,100
Financing Activities								
Proceeds from own shares/ employee share options	-	-	-	-	-	-	-	-
Issue of share capital	585	100	-	-	-	-	-	-
Purchase of Treasury shares	(1,504)	(300)	(4,100)	-	-	-	-	-
Increase in long and short term loans	1,913	700	-	-	-	-	-	-
Repayment of long and short term loans	(1,872)	(1,000)	-	-	-	-	-	-
Dividends paid to GSK shareholders	(3,680)	(3,797)	(3,816)	(3,960)	(3,944)	(4,316)	(4,690)	(5,059)
Dividends paid to minority interests	(238)	(200)	(200)	(200)	(200)	(200)	(200)	(200)
Other	(1,477)	(500)	(300)	(200)	(200)	(200)	(100)	(100)
Net Cash Provided By Financing	-£6,273	-£5,772	-£9,191	-£5,135	-£5,119	-£5,491	-£5,765	-£6,134
Net cash flow after financing	1,473	(2,593)	107	(108)	(371)	(345)	(370)	(344)
Exchange adjustments	(148)	-	-	-	-	-	-	-
Increase / (decrease) in cash	£1,325	-£2,593	£107	-£108	-£371	-£345	-£370	-£344
Cash at beginning of period	£3,906	£5,231	£2,638	£2,745	£2,637	£2,266	£1,920	£1,551
Cash at end of period	£5,231	£2,638	£2,745	£2,637	£2,266	£1,920	£1,551	£1,206

Source: Company data, Cowen and Company

DCF Analysis

9/26/14												
Assumptions												
Share Price	\$47		<i>Output</i>									
			Equity Value									
			Estimated Share Price									
			\$117,425									
Discount Rate	8.0%		Net Cash (\$MM)									
Shares Outstanding (000)	4,810		Enterprise Value (\$MM)									
			\$138,415									

GSK DCF

£ MM	2013E	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2021P	2022P	2023P	2024P	2025P	Terminal
Total Revenues	£25,602	£23,448	£24,865	£26,310	£27,140	£28,855	£30,930	£33,115	£35,102	£36,857	£38,700	£40,635	£42,667	
% Change	-15%	-8%	+6%	+6%	+3%	+6%	+7%	+7%	+6%	+5%	+5%	+5%	+5%	+5%
Cost of Goods	£7,075	£6,611	£7,269	£7,761	£8,088	£8,541	£9,093	£9,670	£10,250	£10,689	£11,223	£11,784	£12,373	
Gross Profit	£18,527	£16,837	£17,596	£18,549	£19,052	£20,314	£21,837	£23,445	£24,852	£26,168	£27,477	£28,851	£30,293	
Gross Margin - Total	72.4%	71.8%	70.8%	70.5%	70.2%	70.4%	70.6%	70.8%	70.8%	71.0%	71.0%	71.0%	71.0%	
SG&A	£7,749	£7,270	£7,725	£8,020	£8,350	£8,800	£9,505	£10,300	£10,882	£11,426	£11,803	£12,394	£13,013	
% of Revs	30.3%	31.0%	31.1%	30.5%	30.8%	30.5%	30.7%	31.1%	31.0%	31.0%	30.5%	30.5%	30.5%	
R&D	£3,394	£3,200	£3,400	£3,600	£3,750	£3,950	£4,150	£4,350	£4,598	£4,791	£5,031	£5,283	£5,547	
% of Revs	13.3%	13.6%	13.7%	13.7%	13.8%	13.7%	13.4%	13.1%	13.1%	13.0%	13.0%	13.0%	13.0%	
Operating Expenses	£11,143	£10,470	£11,125	£11,620	£12,100	£12,750	£13,655	£14,650	£15,480	£16,217	£16,834	£17,676	£18,560	
% of Revenues	43.5%	44.7%	44.7%	44.2%	44.6%	44.2%	44.1%	44.2%	44.1%	44.0%	43.5%	43.5%	43.5%	
Other operating income/(expense)	£387	£300	£370	£380	£390	£400	£410	£420	£430	£440	£450	£470	£480	
Operating Income	£7,771	£6,667	£6,841	£7,309	£7,342	£7,964	£8,592	£9,215	£9,802	£10,391	£11,092	£11,645	£12,213	
% Operating Margin	30.4%	28.4%	27.5%	27.8%	27.1%	27.6%	27.8%	27.8%	27.9%	28.2%	28.7%	28.7%	28.6%	
Non-operating income	43	30	40	50	55	60	65	70	75	80	85	90	95	
EBIT	£7,814	£6,697	£6,881	£7,359	£7,397	£8,024	£8,657	£9,285	£9,877	£10,471	£11,177	£11,735	£12,308	
% of Revs	30.5%	28.6%	27.7%	28.0%	27.3%	27.8%	28.0%	28.0%	28.1%	28.4%	28.9%	28.9%	28.8%	
D&A	1,415	1,400	1,350	1,350	1,350	1,400	1,400	1,400	1,450	1,450	1,500	1,500	1,550	
EBITDA	9,229	8,097	8,231	8,709	8,747	9,424	10,057	10,685	11,327	11,921	12,677	13,235	13,858	
Net Interest Income (Expense)	(692)	(625)	(600)	(590)	(580)	(570)	(560)	(550)	(540)	(530)	(520)	(510)	(500)	
Pre-Tax Income	7,122	6,072	6,281	6,769	6,817	7,454	8,097	8,735	9,337	9,941	10,657	11,225	11,808	
Taxes	£1,636	£1,334	£1,382	£1,489	£1,500	£1,640	£1,781	£1,922	£2,173	£2,304	£2,459	£2,582	£2,708	
Income Tax Rate	23.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	22.0%	
Minority Interest	250	255	420	614	671	728	789	852	900	900	925	925	950	
Net Income	£5,237	£4,483	£4,479	£4,666	£4,647	£5,086	£5,526	£5,962	£6,264	£6,738	£7,273	£7,718	£8,150	
% of Revs	20.5%	19.1%	18.0%	17.7%	17.1%	17.6%	17.9%	18.0%	17.8%	18.3%	18.8%	19.0%	19.1%	
NOPAT	£6,179	£5,363	£5,499	£5,869	£5,897	£6,384	£6,875	£7,364	£7,704	£8,168	£8,718	£9,153	£9,600	
Adjustments:														
Capex	-£1,188	-£1,100	-£1,100	-£1,100	-£1,100	-£1,100	-£1,100	-£1,100	-£1,100	-£1,050	-£1,050	-£1,100	-£1,100	
Depreciation & Amortization	£1,415	£1,400	£1,350	£1,350	£1,400	£1,400	£1,400	£1,400	£1,450	£1,450	£1,500	£1,500	£1,550	
Change In Working Capital	£504	-£1,461	£150	£300	£50	£0	-£50	-£50	-£50	-£50	-£50	-£50	-£50	
Operating Free Cash Flow	£5,968	£3,322	£4,879	£5,216	£4,947	£5,386	£5,776	£6,212	£6,564	£7,088	£7,673	£8,068	£8,550	£107,553

Source: Cowen and Company

GLAXOSMITHKLINE R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Arthritis/Inflammation							
Sirukumab				.			IL-6 human MAB; rheumatoid arthritis; with Janssen Biologics
3196165			.				Granulocyte macrophage colony-stimulating factor; rheumatoid arthritis
3117391		.					Macrophage targeted histone deacetylase inhibitor; rheumatoid arthritis
Cancer/Oncology/Hematology							
Revolade/Promacta			.	.	Feb-14		Thrombopoietin receptor agonist; filed in U.S. for severe aplastic anemia; PIII myelodysplastic syndromes
Mekinist + Tafinlar			.	.			Combo therapy, PIII for adjuvant melanoma; approved in U.S. (PIII in EU) for metastatic melanoma
Foretinib		.					1363089; C-met kinase inhibitor; NSCLC
Mekinist + Tafinlar + panitumumab		.					Combo therapy for colorectal cancer
Ronacaleret		.					Calcium receptor antagonist; allogenic hematopoietic stem cell mobilization
Tafinlar		.					Dabrafenib; BRAF protein kinase inhibitor; approved for metastatic melanoma; PII for NSCLC
2110183		.	.				AKT protein kinase inhibitor; PI multiple myeloma; PII Langerhan cell histiocytosis; ovarian cancer
2141795 + trametinib		.					AKT protein kinase inhibitor + MEK1/2 inhibitor; cancer
2256098		.					Focal adhesion kinase inhibitor; cancer
2636771		.					Phosphatidylinositol 3-kinase (PI3) inhibitor; cancer
3052230		.					Fibroblast growth factor ligand trap; cancer
525762		.					Bromodomain inhibitor; NUT gene midline carcinoma
Votrient + MK-3475		.					Multi-kinase angiogenesis inhibitor + PD-1 monoclonal antibody; renal cell cancer
Cardiovascular							
Losmapimod (856553)		⇒	.				P38 kinase inhibitor; acute coronary syndrome; PIII LATITUDE study began June, 2014
1278863			.				Prolyl hydroxylase inhibitor; anemia associated with chronic renal disease; peripheral arterial disease
2881078		.					Selective androgen receptor modulator; heart failure
Central Nervous System							
239512		.					H3 receptor antagonist; multiple sclerosis
249320		.					Myelin-associated glycoprotein monoclonal antibody; stroke
Arzerra		.					Ofatumumab; anti-CD20 human monoclonal antibody; relapsing remitting multiple sclerosis
Rilapladib		.					Lp-PLA2 inhibitor; Alzheimer's disease
2647544		.					Lp-PLA2 inhibitor; Alzheimer's disease
Contraception/Women's Health							
Retosiban (221149)		.					Oxytocin antagonist; threatened pre-term labor
Dermatologic							
Toctino		.					Alitretinoin; retinoic acid receptor modulator; chronic hand eczema
2586184		.					Chronic psoriasis; with Galapagos
2894512		.					Non-steroidal anti-inflammatory; atopic dermatitis, psoriasis
Ofatumumab		.					Pemphigus vulgaris
1940029		.					Stearoyl CoA desaturase 1 inhibitor (topical); acne vulgaris
Diabetes							

GLAXOSMITHKLINE R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
2330672		.					iBAT inhibitor; Type II diabetes
Gastrointestinal							
Camicinal		.					Delayed gastric emptying; motilin receptor agonist
Gene Therapy							
Mepolizumab			.				IL-5 monoclonal antibody; eosinophilic granulomatosis with polyangiitis
2696273		.	.	.			Ex-vivo stem cell gene therapy; adenosine deaminase severe combined immune deficiency (ADA-SCID); EU
1223249 (ozanezumab)		.	.				NOGO-A monoclonal antibody; amyotrophic lateral sclerosis
2398852		.					SAP monoclonal antibody
2696274		.					Ex-vivo stem cell gene therapy; metachromatic leukodystrophy
2696275		.					Ex-vivo stem cell gene therapy; Wiscott-Aldrich syndrome
Immunological							
Benlysta			.				Subcutaneous formulation, SLE; ANCA positive vasculitis; PII myasthenia gravis; transplant rejection
2586184		.					JAK1 inhibitor; SLE + psoriasis; PI ulcerative colitis
2618960		.					IL7 receptor monoclonal antibody; autoimmune disease
Infectious Disease							
Dolutegravir Trii					Oct-13		HIV integrase inhibitor + abacavir + lamivudine FDC
Relenza			.				Neuramidase inhibitor; iv formulation; treatment of influenza in hospitalized patients
1265744		.					HIV Integrase inhibitor; HIV infections; ViiV Healthcare
1322322		.					Novel class antibacterial agent; bacterial infections
2140944	⇒	.					Type 2 topoisomerase inhibitor; bacterial infections
Tafenoquine		.					Malaria prophylaxis (adults); 8-aminoguinoiline
2838232		.					Antiviral maturation inhibitor; HIV infections
2878175		.					NS5B polymerase inhibitor
Ophthalmology							
933776		.					Monoclonal antibody; geographic atrophy secondary to age-related macular degeneration
Darapladib		.					Lp-PLA2 inhibitor; diabetic macular edema
Respiratory							
Relvar/Breo			.		2014E		Asthma; approved in EU; PIII COPD mortality outcomes
Vilanterol			.				COPD; positive data from UMEC/VI plus FF/VI program support monotherapy development
Bosatria		.	.				Mepolizumab; anti-IL5 monoclonal antibody; PIII severe asthma, COPD; PII nasal polypsis
2245035		.					Toll-like receptor 7 agonist
2339345	⇒	.					Sodium channel blocker; cough
2586881		.					Recombinant human angiotensin converting enzyme; acute lung injury
961081		.					Muscarinic antagonist beta2 agonist; COPD; positive PII efficacy data in Feb. 2012; awaiting resolution of tax issue to move to PIII
Fluticasone furoate + umeclidinium		.					Combo therapy for asthma
Losmapimod		.					p38 kinase inhibitor (oral); COPD
2126458		.					Phosphoinositide 3 kinase inhibitor; idiopathic pulmonary fibrosis
2256294		.					Soluble epoxide hydrolase inhibitor; COPD

GLAXOSMITHKLINE R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
2269557		.					Phosphoinositide 3 kinase inhibitor; asthma + COPD
2793660		.					Cathepsin C inhibitor; bronchiectasis
2862277		.					Tumor necrosis factor receptor-1 domain antibody; acute lung injury
Danirixin		.					1325756; CXCR2 antagonist; COPD
Fluticasone furoate + vilanterol + umeclidinium		.					Combo therapy for COPD
Vaccines							
Herpes zoster				.			Shingles prophylaxis
MMR				.			Live attenuated; measles, mumps, rubella prophylaxis; U.S.
Mosquirix				.			Malaria prophylaxis; PIII study ongoing in Africa
MAGE-A3		.					PIII melanoma; PII bladder cancer
HIV immunotherapy			.				Recombinant; HIV disease immunotherapy
Nimenrix			.				MenACWY prophylaxis; approved in EU
PRAME immunotherapeutic	⇒	.					Recombinant; resectable non-small cell lung cancer
S. pneumoniae pediatric		.					Streptococcus pneumonia prophylaxis
Tuberculosis		.					Recombinant; tuberculosis prophylaxis
WT1 immunotherapeutic	⇒	.					Recombinant; treatment of breast cancer
Hepatitis C		.					Recombinant viral vector; hepatitis C virus prophylaxis
HIV prophylaxis		.					HIV prophylaxis
NTH1		.					Recombinant; non-typeable hemophilus influenza prophylaxis
RSV		.					Recombinant viral vector; respiratory syncytial virus prophylaxis
RSV		.					Recombinant; respiratory syncytial virus prophylaxis; maternal immunization
Wound Healing							
1278863		.					Prolyl hydroxylase inhibitor (topical); wound healing
Total Drugs In Development	0	29	37	15	2		83

Progress since last update in bold; movement marked by arrow

Investor Relations Contacts: Tom Curry 215-751-5419

Jeff McGloughlin 215-751-7002



Price: \$59.28 (09/30/2014)
Price Target: \$62.00 (Prior \$59.00)

MARKET PERFORM (2)

Steve Scala, R.Ph., CFA

617.946.3923
steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA

617.946.3857
kathy.miner@cowen.com

Jean Perreault

617.946.3967
jean.perreault@cowen.com

Key Data

Symbol	NYSE: MRK
52-Week Range:	\$61.33 - 44.62
Market Cap (MM):	\$171,001.0
Net Debt (MM):	\$7,574.0
Cash/Share:	\$5.97
Dil. Shares Out (MM):	2,884.6
Enterprise Value (MM):	\$180,831.0
ROIC:	NA
ROE (LTM):	NA
BV/Share:	\$16.68
Dividend:	\$1.76
Yield:	2.97%

FY (Dec) 2013A 2014E 2015E

Earnings Per Share			
Q1	\$0.85	\$0.88A	\$0.80
Q2	\$0.84	\$0.85A	\$0.84
Q3	\$0.92	\$0.88	\$0.90
Q4	\$0.88	\$0.89	\$0.96
Year	\$3.49	\$3.50	\$3.50
P/E	17.0x	16.9x	16.9x

Diluted non-GAAP EPS excludes restructuring costs, purchase accounting adjustments, acquisition-related costs and certain other significant items.

Consensus EPS	\$3.49	\$3.49	\$3.58
---------------	--------	--------	--------

Consensus source: Thomson Reuters

Revenue (MM)

Year	\$44,033.0	\$42,400.0	\$38,630.0
Prior Year	-	-	\$38,710.0
EV/S	4.1x	4.3x	4.7x

Merck

Risk/Reward Appears Balanced

The Cowen Insight

Potential upside from immune oncology and asset disposal are offset by near-term competitive pressures in key franchises and a pipeline facing challenges.

Merck appears to face several obstacles/risks, including Januvia's tepid prescription trends in a very competitive market; IMPROVE-IT results; the anticipated launch of key new products into generic-dominated markets (suvorexant, odanacatib); and uncertainty around the outlook for its success in immune oncology. Use of proceeds from the pending sale of Consumer (assumed close by year end) add uncertainty. All told, our projection of 5% 2014-20 EPS CAGR is below the group average. We believe risks balance opportunities and therefore remain Market Perform on Merck stock.

EPS Flat In 2014; Long-Term Growth Below Average

We forecast flat EPS in 2014 of \$3.50 on a 4% decline in revenue. EPS are projected to remain flat in 2015 and grow 9% in 2016, before flattening in 2017 due to the Vytorin/Zetia patent expiration. EPS growth should resume in 2018-20, forecast at 7-8%.

Januvia Forecast To Grow In 2014 But Decline Modestly Thereafter

We forecast Januvia sales at \$5.945B (+2%) in 2014 and \$5.875B (-1%) in 2015, with continuing decline thereafter, to \$5.6B in 2018 and \$5.4B in 2020. A high price point, limited effectiveness, and a very competitive market will make Merck's aspiration of a return to sustainable growth a challenge, although admittedly, U.S. NRx trends have rebounded.

Keytruda Approved; Other Pipeline Prospects Have Less Potential

Keytruda (PD-1 pembrolizumab) became the first PD-1 agent approved in the U.S. with accelerated approval gained in early September for metastatic melanoma. Based on data in melanoma, Keytruda could be a best-in-class PD1 antibody; key data in 2014-15 will further characterize its profile. Merck has entered some partnerships to combine pembrolizumab with targeted agents. Pembrolizumab's filing timing in lung is key; Phase II/III completes in September 2015, but there may be an opportunity to file the Phase II portion earlier. Beyond pembrolizumab, pipeline prospects are less exciting. Among non-oncology agents, hepatitis C candidates offer a significant opportunity, but odanacatib (osteoporosis) safety issues create uncertainty. Bridion (neuromuscular blockade reversal agent) is expected to be re-filed in H2:14.

Clarity On Cholesterol Franchise In 2014

Clarity should be gained on the direction of the cholesterol franchise, now keyed to IMPROVE-IT (final data expected Q4:14). Our consultants predict a positive trend, but probably not statistically significant. Data from anacetrapib's 30,000 patient REVEAL trial is not due until January 2017, unless an interim look proves successful. The first interim look is in early 2015.

Oncology

Keytruda In Melanoma First U.S. Approved PD-1; MAA Under Review In E.U.

On September 4th, the FDA gave accelerated approved to Keytruda (pembrolizumab) for use in unresectable or metastatic melanoma in patients who have failed ipilimumab or a BRAF inhibitor (if BRAF V600m positive), at a dose of 2 mg/kg every 3 weeks. The indication is in line with expectations. The accelerated approval was based on tumor response rate and durability of response. Continued approval may require verification and description of clinical benefits in confirmatory trials; Phase II and III studies in melanoma are ongoing and should form the basis for regular approval; data is expected in Q1:15.

The wholesale acquisition cost (WAC) for the 50 mg vial of Keytruda is \$2,158. Most patients will be use 3-4 vials per infusion. The estimated cost for many patients will be approximately \$12,500 per month or \$150,000/year. This compares to \$125,000/yr for Yervoy regimen. We anticipate minimal off-label usage in other tumor types, due to reimbursement limitations. In Japan where Opdivo (nivolumab) is marketed by Ono, it is priced at \$145,000/year. In June, Merck announced that its MAA for advanced melanoma was accepted for review in the E.U.

Merck has 12+ monotherapy and combo therapy trials ongoing (4,000+ patients) in 30 tumor types, including head & neck, bladder, triple-negative breast, gastric, hematologic, and CRC. Merck either has started or expects to start registrational trials in head & neck, bladder, first-line NSCLC, and adjuvant melanoma in 2014. Merck recently initiated a Phase I “signal finding” study in 20 different PD-L1+ solid tumor types, and has established partnerships with several companies (Glaxo, Pfizer, Incyte, Amgen and Ablynx) to evaluate pembrolizumab combinations. We estimate pembrolizumab sales of \$15MM in 2014, \$250MM in 2015, \$500MM in 2016, \$1B in 2018, and \$2B in 2020.

Data In Melanoma Continues To Be Compelling

At ASCO 2014, Merck presented Phase 1B (KEYNOTE-001) data of pembrolizumab as monotherapy in 411 patients with advanced melanoma. OS at one year was 69%; 74% in patients not on prior ipilimumab and 65% following ipilimumab. At 18 months, the estimated OS was 62%. Overall ORR was 34%, 40% in ipi-naïve, 44% in treatment-naïve, and 28% in ipi-treated patients. The discussant noted that this was the largest trial in melanoma at this stage of development.

At ASCO 2013, Merck presented data from a Phase I trial of pembrolizumab in advanced melanoma. Patients were dosed with either 10mg/kg every two or three weeks or 2mg/kg every three weeks. Tumor responses were assessed every 12-weeks. The confirmed response rate across all doses tested was 38% (52% at 10mg/kg Q 2 weeks). A majority of responses were durable with 81% of patients remaining on therapy at the time of analysis. The median PFS among all 135 patients was >7-months. A data summary is below.

Pembrolizumab Efficacy In Melanoma

	RECIST	irRR
10mg/kg Q2-weeks		
No prior Ipi	21 (54%)	23 (56%)
Prior Ipi	8 (62%)	9 (56%)
Total	29 (56%)	32 (56%)
10mg/kg Q3-weeks		
No prior Ipi	7 (37%)	8 (33%)
Prior Ipi	9 (35%)	7 (22%)
Total	16 (36%)	15 (27%)
2mg/kg Q3-weeks		
Total	52 (44%)	50 (37%)

Source: ASCO 2013

In November 2013, Merck provided an update from an additional five months of data for this trial. The ORR (one year) for all doses was 41% (using RECIST 1.1), an improvement from the 38% presented at ASCO 2013. OS, reported for the first time, was an impressive 81%. Seven patients developed pneumonitis. Merck initiated combo trials with ipilimumab +Votrient at the end of 2013 and will initiate other combo trials in 2014 in melanoma and other cancers. This data and that from Bristol's nivolumab are depicted below:

Anti-PD-1 Data In Melanoma

	BMY*	MRK**
OS (1 year)	62%	81%
ORR	37% (all doses) 41% (3mg/kg)	41%
*RECIST 1.0 **RECIST 1.1		

Source: Company data

Data In NSCLC Also Promising

At ASCO 2014, MRK presented data of pembrolizumab monotherapy in untreated, PD-L1 positive NSCLC patients. The ORR was 47% by investigator-assessed, immune-related response criteria (n=21/45) and 26% by centrally evaluated RECIST v1.1 (Response Evaluation Criteria in Solid Tumors) (n=11/42). 80% of patients demonstrated tumor shrinkage as measured by centrally evaluated RECIST criteria (n=28/35). The median duration of response has not been reached, with some patients continuing on treatment for at least one year.

A Phase III study (KEYNOTE-024) comparing pembrolizumab to platinum-based doublet chemotherapy in treatment-naïve PD-L1 positive metastatic NSCLC patients is slated to begin in September 2014.

At the World Lung Conference in late October 2013, Merck presented interim data on its Phase 1b trial of pembrolizumab in previously treated patients with NSCLC and reported a 21% ORR based on RECIST 1.1 criteria (see table below). Acknowledging the limitations of comparing across studies, this is in line with data from Bristol's nivolumumab, which reported a 17% ORR at all doses and 24% at the 3mg/kg dose in trials for advanced NSCLC, and Roche which reported an ORR of 23% in metastatic

NSCLC, including an ORR of 46% in PDL1 IHC2/IHC3, and 83% in PDL1 IHC3 (IHC3 > 10% tumor cells positive for PDL1; IHC2/3 > 5%; IHC1/2/3 > 1%). The median OS was 51 weeks. Pembrolizumab appeared to be well tolerated.

Interim Efficacy Data For Pembrolizumab (10mg/kg Q3-Weeks)*

	RECIST 1.1 Independent Review		Median OS-Weeks (95% CI)
	N	ORR (%) (95% CI)	
Non squamous	26	16% (95% CI)	10.3
Squamous	6	33% (95% CI)	15.2
Total	33	21% (95% CI)	9.7

*In previously treated patients with advanced NSCLC

Source: Company data

Data on the relationship between PD-L1 expression and response rates was also looked at in this study. Tumors with high levels of PD-L1 expression (per assay criteria) were associated with an ORR of 57% per RECIST while zero/low level PD-L1 tumor expression were associated with a 9% ORR per RECIST. Sample size was too small for conclusions to be made and larger studies will be required.

Pembrolizumab is currently in Phase II/III studies (KEYNOTE 010) for lung cancer. Management indicated they are optimistic for this indication but need to see the data before next steps identified. They did state an accelerated filing (such as was done in melanoma) would be pursued if warranted.

PD-L1 Expression Data Suggest Usefulness In Lung Cancer

NSCLC: At ESMO 2014 in September, Merck presented data from a study evaluating correlation of PD-L1 expression with pembrolizumab effectiveness in NSCLC. Results showed antitumor activity in both treatment-naïve (ORR 26%) and previously treated (ORR 20%) NSCLC patients for all doses and schedules assessed. At 2mg/kg q3weeks, ORR was 20%. Strong PD-L1 tumor expression correlated with improved response (37%), PFS (HR=0.52), and OS (HR+0.59).

Another study also presented at ESMO 2014, evaluated PD-L1 expression and correlation with OS in NSCLC patients treated with chemotherapy. Results showed no statistically significant association between PD-L1 expression and OS since the start of first or second-line chemotherapy. OS from time of first-line chemotherapy was 1.31 for the PD-L1 strong-positive group and 1.04 for the PD-L1-weak-positive group when compared with the PD-L1-negative group. HR was 1.36 for the PD-L1-strong-positive group and 1.09 for the PD-L1-weak-positive group.

At AACR in April 2014, Merck presented early data from studies looking at PD-L1 expression and clinical outcomes with pembrolizumab monotherapy in patients with advanced melanoma and NSCLC. Higher PD-L1 expression was associated with higher overall response rates, although PD-L1 negative patients responded as well. In sum, PD-L1 expression in melanoma appears to be of little diagnostic usefulness, whereas in lung, there appears to be significant benefit to determining PD-L1 expression.

PD-L1 expression in 129 NSCLC patients in KEYNOTE-001 study were also presented. 45% of NSCLC patients had positive PD-L1 tumors at a cut-point of ≥1% of tumor cells stained, and 25% of patients on the ≥50% criteria. The ORR was 19% (n=129) as measured by RECIST. In the strong expresser population, responses were seen in 37%

of patients, and in 11% of patients with PD-L1 low or negative tumors. In the ≥1% cut-point group, responses were observed in 25% of patients with PD-L1 positive tumors and 7% of patients with PD-L1 negative tumors.

Melanoma: PD-L1 expression in 125 melanoma patients from the Phase 1B KEYNOTE-001 study were presented. Cut-points of ≥1% and ≥10% of tumor cells stained were evaluated. The ORR was 40% (n=113) as measured by RECIST 1.1. Based on the ≥1% cut-point, responses were observed in 49% of patients with positive PD-L1 tumors and 13% of patients with PD-L1 negative tumors. Based on the ≥10 percent cut-point, responses were observed in 52% of patients with PD-L1 positive tumors and 23% of patients with PD-L1 negative tumors.

Pembrolizumab Data In Head And Neck Promising

At ASCO 2014, Merck presented a Phase 1B study (KEYNOTE-012) evaluating pembrolizumab as monotherapy in patients with PD-L1 positive, advanced head and neck cancer. Data showed an ORR of 20% (n=11/56) with 29% of patients having stable disease via RECIST (n=16/56). Similar ORRs were observed in HPV-positive and negative patients. Tumor shrinkage was demonstrated in 51% of evaluable patients. A Phase III study in advanced head and neck cancer with pembrolizumab vs. standard of care is (KEYNOTE-040) is set to start in November 2014 with a primary completion date of March 2017.

At ESMO 2014, Merck presented updated Phase Ib data which showed that 51% of HNC cancer patients experienced no change or a decrease from baseline in the size of target lesions. ORR was 19.6%. ORR was similar in patients with HPV+ (20.0%) and HPV- (19.4%) HNC. 7 of 11 responders remain on therapy, and the median duration of response has not been reached (range, 8+ to 41+ weeks). ORR was 50.0% in the 12 patients with PD-L1 expression above the cutpoint and 11.4% in the 44 patients with PD-L1 expression below the cutpoint. 6-month OS rates were 64.8% for the overall population, 73.9% for the HPV+ cohort, and 58.1% for the HPV- cohort. Most common AE's were fatigue (n=11, 18.3%) and pruritis (n=6, 10.0%). Grade 3-4 treatment related AE's were observed in 10 (16.7%) patients.

Advanced Gastric Cancer Also Shows Promise

At ESMO 2014, Merck presented data from a Phase Ib study of pembrolizumab in advanced gastric cancer. Results showed an ORR of 30.8% overall, with 30% in non-Asian patients, and 31.6% in Asian patients with preliminary evidence of a relationship between ORR and PD-L1 status. 41% of patients had a decrease in tumor burden. Response duration was 9-20 weeks (median not reached) for non-Asian patients and 8-16 weeks for Asian patients (median also not reached).

Partnerships Evaluating Various Pembrolizumab Combos

Merck has numerous efforts under way in PD-1 combinations. In melanoma, there are ongoing studies with pembrolizumab + BRAF/MEK inhibitor, and pembrolizumab+Ipi+interferon; a study with AMGN's T-VEC is planned. In NSCLC, pembrolizumab is being studied with chemo, ipi, and TKI and studies are planned with abraxane and IDO1. In 2014, Merck expects to initiate 7 additional registrational trials of pembrolizumab in combination with other therapies in melanoma, NSCLC, RCC, and HER2+ breast cancer. Preclinical data of pembrolizumab plus anti-GITR (study to initiate in 2014) and pembrolizumab plus anti-LAG3 hold promise. Merck's partnerships in PD-1 include:

- **Pfizer** – Phase I/II studies of pembrolizumab + Pfizer's Inlyta (small molecule kinase inhibitor) in RCC; pembrolizumab + PF-05082566 (immunotherapy agent targeting the 4-1BB receptor) in multiple cancer types. Enrollment for both studies is expected to start in 2014. In August 2014, a collaboration was announced to evaluate pembrolizumab + Xalkori in a Phase Ib study in NSCLC; it is expected to begin in 2015 (Pfizer will conduct study).
- **Incyte** – Phase I/II studies of pembrolizumab + Incyte's INCB24360 (an indoleamine 2, 3-dioxygenase inhibitor) in previously treated metastatic/recurrent NSCLC and other advanced cancers.
- **Amgen** – Phase I/II studies of pembrolizumab + Amgen's oncolytic immunotherapy talimogene laherparepvec in untreated advanced melanoma.
- **Glaxo** – Evaluation of pembrolizumab + pazopanib in advanced RCC.
- **Ablynx** – Partnership to develop nanobodies to target immune checkpoint modulators.
- **Agenus** – Partnership to develop two of Merck's immune checkpoint agents using Agenus' Retrocyte Display platform.

More Pembrolizumab Data Upcoming In 2014-15

Pembrolizumab data are impressive and may make it the best-in-class PD-1, but more data is required to support this assertion. Merck does not believe pembrolizumab is differentiated from BMY's nivolumab on potency and that clinical data will distinguish the two molecules. Merck is excited about potential combination therapy with pembrolizumab and other immunomodulatory agents. There is also an ongoing Phase I study enrolling across all solid tumors, and Merck plans to begin Phase I studies in liquid tumors.

Data on several ongoing pembrolizumab trials will be presented over the next two years:

- Melanoma, ipi refractory, Phase II, monotherapy, 510 patients (KEYNOTE-002)
 - Data March 2015, PFS and OS endpoints
- Melanoma, vs. ipi, Phase III, 645 patients (KEYNOTE-006)
 - Data February 2015, PFS and OS endpoints
- NSCLC, Phase II/III, 920 patients (KEYNOTE-010)
 - Data September 2015, OS and PFS endpoints; interim analysis sooner

IP Litigation In PD-1 Area

In June 2014, the Opposition Division of the EPO found the claims in Ono's '878 patent covering use of anti-PD-1 antibody for the treatment of cancer valid. Merck received the Opposition Division's written opinion in late September, on which it will appeal. On April 30, 2014, Merck and three other companies opposed another European patent "336" owned by Bristol-Myers and Ono that it believes is invalid. The '336 patent, if valid, broadly claims anti-PD-1 antibodies that could include pembrolizumab. In May 2014, Merck filed a lawsuit in the UK seeking revocation of the UK versions of both

the '878 and '336 patents. Issues of validity and infringement of both patents likely will be heard at the same time by the UK court, which has scheduled trial to begin in July 2015. The USPTO recently granted US Patent Nos. 8,728,474 to Ono and 8,779,105 to Ono and Bristol. These patents, which Merck believes to be invalid, are equivalent to the '878 and '336 patents, respectively.

Temodar Sales In Decline Post Generics

Temodar, an oral alkylator chemotherapeutic agent, is indicated for the treatment of malignant glioma in relapse patients and for the first-line treatment of glioblastoma multiforme (GBM) when administered in combination with radiotherapy and as maintenance therapy. Temodar crosses the blood brain barrier, delivering more drug to the brain than comparative glioma therapies. Additionally, Temodar is an active metabolite, and thus does not need to be metabolized once inside the body to become effective. Teva (Barr) was first-to-file and launched its generic product during the six-month pediatric extension period, in August 2013. U.S. Temodar sales are approximately one-third of the franchise. We estimate Temodar sales of \$320MM (-55%) in 2014, \$230MM in 2015, \$150MM in 2016, \$50MM in 2018, and \$5MM in 2020.

Metabolic Disorders

Januvia Forecast To Decline Modestly Through 2020

Januvia (sitagliptin), a once-daily DPP-IV inhibitor, dominates a highly competitive market where there is little differentiation. Competitors include AstraZeneca's Onglyza, Lilly/BI's Tradjenta and Takeda's Nesina. In August 2014, Januvia had 5.5% share of the oral diabetes market; NRxs were up 9% Y/Y. At its May 2014 R&D day, management expressed optimism with recent Januvia (DPP4) trends, indicating that most recent rolling 4-week scrip data show volumes flat in the U.S. Januvia has 65% WW share and 75% in the U.S. Janumet, a twice-daily fixed-dose combination with metformin, was approved in the U.S. in 2007 and the E.U. in 2008. The once daily, fixed dose combination, Janumet XR, was approved in February 2012. Januvia's label has been expanded to include monotherapy and combination therapy with concomitant use with SUs. As a result of post-marketing reports of serious allergic and hypersensitivity reactions including Stevens-Johnson syndrome, these were added to the "warnings and precautions" section. In addition, hepatic enzyme elevations and pancreatitis were added to the Postmarketing Experience section. We forecast Januvia/Janumet sales of \$5.945B (+2%) in 2014, \$5.875B in 2015, \$5.8B in 2016, \$5.6B in 2018, and \$5.4B in 2020.

TECOS CV Outcomes Data Expected Early 2015

In a pooled analysis of more than 10,000 patients with greater than two-years of exposure to Januvia published in BMC Endocrine Disorders, patients exposed to Januvia had a similar relative risk 0.68 (NS; 95 CI: 0.41-1.12) to developing CV events as non-exposed patients. This relative risk is similar to that seen with other DPP-IV inhibitors. TECOS, a 14,000 patient outcome study in type 2 diabetes, will look at a combined CV endpoint. TECOS is being managed by Duke Clinical Research and the Oxford Diabetes Trial Unit and it began in December 2008. Enrollment will take two years and patients will be followed for between four and five years. Data is anticipated in early 2015 as the last patient visit is expected in December 2014. Our physician consultants assign only a 10-25% chance of DPP-IV inhibitors meeting their primary

endpoint in ongoing CV outcomes trials, and the failure of Onglyza in SAVOR to demonstrate a cardiovascular benefit is another concern.

A recent study (a retrospective analysis of insurance claims) published in JACC: Heart Failure indicated that sitagliptin use in patients with a history of heart failure was not associated with an increased risk of all-cause hospitalization or death (the primary endpoint in TECOS). However, the analysis did show that sitagliptin use was associated with an increased risk for heart failure hospitalizations (12.5% vs 9.0%). The authors cite a number of limitations surrounding the analysis including differences between sitagliptin users and non-users not identified/available in the database and small number of events. The authors, and Merck, believe that TECOS will be the first true gold standard in that it is a prospective, randomized trial with a specified heart failure endpoint; Merck also points out that TECOS is evaluated regularly by the DSMB (and with no changes in the study made to date).

Concerns Over GLP-1 Related Neoplasms May Be Overblown

A March 2013 publication by Butler, *et al.* in Diabetes speculated the DPP-IVs and GLP-1s may be associated with an increased incidence of pancreatic duct metaplasia in patients with T2DM. FDA and EMA have investigated these findings and, according to Merck, found the data to be inconclusive and have not changed their existing recommendation. They will evaluate further when additional outcome data is available.

The Butler, *et al.* study compared pancreatic tissue from organ donors with T2DM with or without incretin therapy (DPP-IV or GLP-1). Patients on incretin therapy demonstrated an increase in endocrine and exocrine cell hyperplasia with the potential for evolution into neuroendocrine tumors. The study was not sufficiently controlled to determine whether a causal relationship between GLP-1 and pancreatic ductal metaplasia exists.

Confounding variables from the study include:

1. The sample sizes are very small; only 8 patients treated with incretin and 12 diabetic controls.
2. Groups were not controlled for gender; 38% of patients on incretin therapy were female vs. 67% of diabetic controls.
3. The average age of incretin treated patients was 58 y/o (12 years on average with diabetes) vs. 40y/o for diabetic controls (8 years on average with diabetes). Age and duration of diabetes likely contribute to the development of pancreatic tumors.
4. Severity of diabetes and/or diabetes control was not controlled.

Diabetes And Hyperinsulinemia Are Independent Risk Factors For Developing Pancreatic Ductal Adenocarcinoma

Several studies have shown patients with T2DM to be at increased risk of developing pancreatic ductal adenocarcinoma (PDAC), as PDAC is closely associated with insulin signaling. PDAC is also associated with the use of exogenous insulin. Insulin receptors are expressed in the pancreas and are involved in the autocrine regulation of insulin secretion. However, hyperinsulinemia has been shown to activate PI3K and mTOR pathways, increase proliferation of cancer cells in PDAC, and increase replication of PDAC cells in culture. By not controlling for duration of diabetes, age, diabetes control, and inulin use, the findings of Butler *et al* are difficult to interpret.

Januvia is almost entirely excreted via the kidneys and therefore requires two downward dose-adjustments depending on the level of renal impairment: 50mg is recommended for patients with moderate renal insufficiency and 25mg with severe renal insufficiency or ESRD. The two-tier adjustment is a relative disadvantage versus Onglyza which only requires one downward adjustment. However, Januvia is not metabolized via the CYP450 system and therefore has limited drug-drug interactions.

Once-Weekly DPP-IV Omarigliptin To Be Filed In Japan In 2014

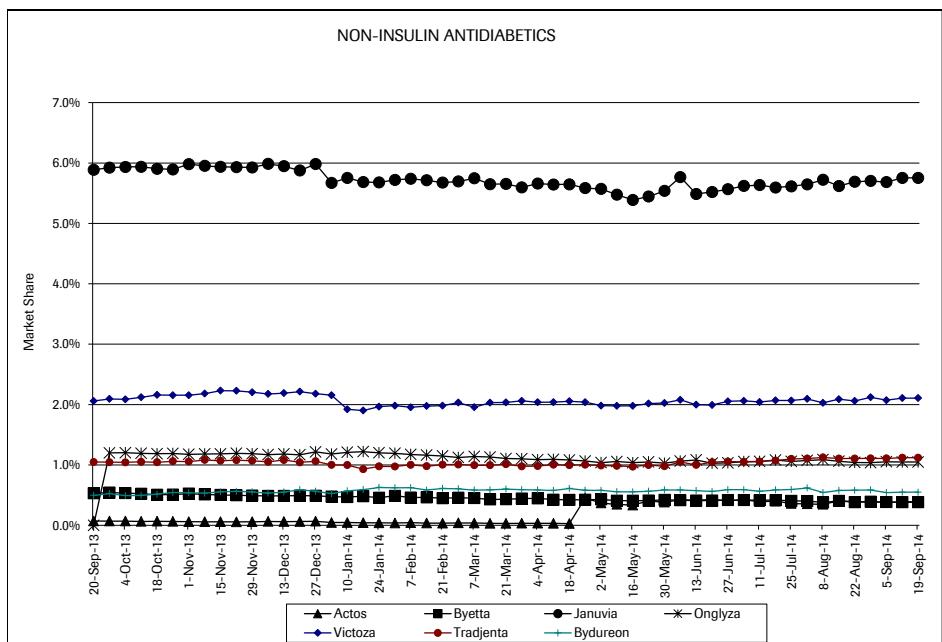
In November 2011, Merck announced the development of a once-weekly oral DPP-IV inhibitor, omarigliptin (MK-3102), as a convenient option for patients to achieve and maintain glycemic control. Merck presented data that showed >80% inhibition of DPP-IV up to 7-days post dosing. At its May 2014 R&D day, Merck showed data suggesting that curves for omarigliptin and Januvia are virtually superimposed. In September 2014, Merck presented its first Phase III data for omarigliptin. This pivotal study was in Japanese patients (n=414) and compared once weekly omarigliptin 25mg to once daily 50mg sitagliptin/Januvia (starting dose in Japan) and placebo. The primary endpoint of HbA1c reduction at 24 weeks was met. Omarigliptin significantly reduced HbA1c levels by -0.8% vs placebo and by -0.02% vs Januvia (non-inferior). There were no meaningful differences in incidence of side effects among the groups. The most common AE in the omarigliptin group was nasopharyngitis (12.7% vs 30.5% in placebo, and 11.0% with Januvia). Hypoglycemia was uncommon across all groups and omarigliptin was generally weight neutral.

The full Phase III program includes 10 trials with 8,000 T2DM patients. Merck intends to file omarigliptin in Japan by year end. We estimate omarigliptin sales of \$100MM in 2017, \$200MM in 2018, and \$400MM in 2020.

Phase II Data Positive

In October 2012 Merck announced that omarigliptin met its primary endpoint of HbA1c lowering vs. placebo in its Phase IIb trial. At 12-weeks, the placebo-adjusted reduction from baseline was 0.71 with the 25mg dose, 0.67mg with the 10mg dose, 0.49 with the 3mg dose, 0.50 with the 1mg dose, and 0.28 with the 0.25mg dose. A statistically significant (0.001) trend was observed across all doses for the secondary endpoints of 2-hour post-meal glucose and fasting blood glucose. Omarigliptin was generally well tolerated at all doses with a safety profile that was similar to placebo.

Non-Insulin Antidiabetics



Source: IMS America

Merck Stepping Up Efforts In Biosimilar Insulin

In February 2014, Merck announced that it had entered into an agreement with Samsung for the development, manufacture, and commercialization of MK-1293, Merck's insulin glargine candidate. Phase III trials are in progress. This initiative is an extension of an existing agreement between the two companies for the development of other biosimilar products.

Odanacatib Full Phase III Data Released; Filing Expected In 2015

Odanacatib is a selective and reversible inhibitor of cathepsin K, being evaluated in osteoporosis. Cathepsin K, a cysteine protease abundantly expressed in osteoclasts, is necessary for bone collagen degradation. Odanacatib decreases bone resorption similar to the bisphosphonates but decreases bone formation to a lesser extent. In addition, it can be dosed with or without food. Increases in cortical bone thickness have been demonstrated in preclinical studies. In May 2012, Merck announced odanacatib's Phase III trial was stopping early for efficacy, but noted a safety signal that required further observation. In September 2014, full data from the pivotal Phase III fracture outcomes study was released with primary endpoints met, although some safety concerns still persist. Odanacatib appears likely to have a niche role in osteoporosis. Merck sees odanacatib used as an adjunct in high-risk women. Tier 3 coverage is anticipated. Merck expects to file in the U.S. in 2015, representing a delay from the late 2014 expectation previously, given the need to adjudicate Phase III results. We estimate odanacatib sales of \$100MM in 2016, \$300MM in 2018, and \$500MM in 2020.

Full Phase III Data Supports Use In About 10% Of Osteoporosis Population

The Phase III program (LOFT) began in 2007 (n=16,713) with a three-year event-driven fracture study, a two-year blinded extension phase, and then an open-label

extension (five years total blinded data). Results showed once-weekly odanacatib led to a substantial reduction in the risk of osteoporotic fractures, including vertebral, non-vertebral, and hip. However, AE's were concerning and included <0.2% incidence of morphea, <0.01% incidence of atypical fractures, and numerical imbalances for afib and stroke, although MACE events balanced overall; no cases of osteonecrosis of the jaw were reported.

Full data released in September 2014 showed odanacatib significantly reduced the risk of three types of osteoporotic fractures compared to placebo (primary endpoints), and reduced the risk of clinical vertebral fractures (secondary endpoint):

- 54% relative risk reduction of new and worsening vertebral fractures
- 47% relative risk reduction of clinical hip fractures
- 23% relative risk reduction of clinical non-vertebral fractures
- 72% relative risk reduction of clinical vertebral fractures

Odanacatib also led to progressive increases over five years in BMD at the lumbar spine and total hip. Compared to placebo, the change in BMD from baseline at five years for lumbar spine was 11.2% and for total hip was 9.5%.

On safety, adjudicated morphea-like skin lesions occurred more frequently on odanacatib: in 12 patients in the odanacatib group (0.1% incidence) and 3 patients in the placebo group (<0.1% incidence). These skin lesions resolved or improved after discontinuation of the study drug. Adjudicated atypical femoral shaft fractures were reported for 5 patients in the odanacatib group (incidence of 0.1%) and not reported in patients in the placebo group. There were no adjudicated cases of osteonecrosis of the jaw.

Adjudicated atrial fibrillation was reported in 92 patients in the odanacatib group (incidence of 1.1%) and 80 patients in the placebo group (incidence of 1.0%). In the MACE analysis, events were reported for 215 patients in the odanacatib group and 194 patients in the placebo group (hazard ratio 1.12). There were 271 deaths reported in the odanacatib group and 242 deaths in the placebo group (hazard ratio 1.13); this numeric difference does not appear to be related to a particular cause of death.

There was a numeric imbalance in adjudicated strokes with more events occurring in the odanacatib group. Based on the adjudication committee assessment, 109 patients in the odanacatib group experienced stroke (incidence 1.4%) and 86 patients (incidence 1.1%) in the placebo group (hazard ratio 1.28). Investigator-reported cerebrovascular events occurred in 305 patients in the odanacatib group (incidence 3.8%) and 290 patients taking placebo (incidence 3.6%).

Merck is still collecting data from the extension study and is planning an additional analysis of the data including an independent re-adjudication of MACE, in support of planned filing in 2015.

Experts Believe Niche Role Is Appropriate

Cathepsin K is not expressed outside of the bone under normal conditions, but is expressed in a number of tissues during inflammation. However, the inhibition of Cathepsin K in the setting of inflammation only has favorable effects. Our scientific experts note that Cathepsin inhibitors are notoriously promiscuous and believe odanacatib likely also inhibits Cathepsin L, B, and S, although inhibition of Cathepsins

other than Cathepsin K have only been associated with beneficial effects. Our experts believe the toxicity associated with odanacatib is likely due to the molecule-specific inhibition of an unrelated enzyme.

Our osteoporosis physician expert noted that the 5 yr improvements seen with odanacatib in hip BMD are higher than that of other drugs, supporting animal data which suggests that odanacatib does not suppress cortical formation as much as cortical resorption and thus may have real-world application for patients at high risk for hip fracture. Patients with "allergy" issues are another primary target group; patients who think that they are allergic to bisphosphonates, or who are allergic to a lot of other drugs and think that they may be allergic to Zometa or dmab, or are reluctant to take long-acting parenteral drugs in case they are allergic. The "allergic" population represents a few percent of patients. After adding in patients with bad hip BMD (particularly those at high risk for hip fracture: nursing home patients, fallers, patients whose hip fracture risk by FRAX assessment is especially high), the target population could be a double digit percent of patients. On the negative side, the 5 yr increases in spine BMD are not quite as much improvement as with dmab. There is a lack of data suggesting that the better hip BMD data translated into better fracture efficacy that is seen with Fosamax or dmab. Unsubstantiated but concerning signals of morphea and stroke are also concerns.

Trial Stopping Early For Efficacy, Consistent With Our Expectations

Odanacatib was being studied in a 16,731 patient Phase III outcomes study in postmenopausal women with osteoporosis. Primary endpoints were number of patients who experience a morphometrically- assessed vertebral fracture, time from baseline to first hip-fracture, time from baseline to first clinical non-vertebral hip fracture, and volumetric bone mineral density at lumbar spine at 24-months. Interim analyses of hip fracture data were scheduled for 70% and 85% of events. The odanacatib trial was 90% powered to detect a risk reduction in hip fractures of 35%, began enrollment in July 2007, and completed enrollment in late 2009. We calculated that 234 events were required for the final analysis and that 164 events (70%) were required for the first interim analysis. Our previous statistical analysis assumed 29 months for accrual and a conservative placebo event rate of 2.5% (FIT trial hip fracture rate in women >65 years old). If the first-interim analysis was not triggered until July 2012, our statistical analysis assigned >90% chance that the trial would be stopped early for efficacy using standard O'Brien Flemming stopping criteria.

Odanacatib Phase III Trial Design

Drug	Odanacatib 50mg once weekly (plus 5600 IU Vitamin D3 per week)
Comparator	Placebo once weekly (5600 IU Vitamin D3 per week)
Enrollment	16,731 (enrollment began July 2007, completed YE:2009)
Estimated date of completion	November 2014
Primary outcome measures	Number of participants who experience a morphometrically assessed vertebral fracture (baseline to 5 years); time from baseline to first hip fracture; time from baseline to first clinical non-vertebral fracture; volumetric bone mineral density at the lumbar spine using quantitative CT (24 months)
Secondary Outcome measures	Time from baseline to first clinical osteoporotic vertebral fracture; change in height from baseline stature; % change in BMD (lumbar spine, hip, femoral neck, trochanter, distal forearm); change from baseline in serum c-telopeptides of type I collagen; cortical volumetric BMD of the hip using quantitative CT (24 months)
Inclusion criteria	Postmenopausal women (for at least 5 years who are at least 65 years old who have low bone mineral density; able to walk)
Exclusion criteria	Osteoporosis therapy or have metabolic bone disorder other than osteoporosis; has or has had a hip fracture; currently participating in another study

Source: clinicaltrials.gov

Fosamax In Decline Post Generic Launches

Multiple generics of Fosamax have been launched in the U.S. and Fosamax D lost exclusivity in April 2010. Our physician experts view Fosamax's long-term spine and hip fracture data as a hurdle to other bisphosphonates. The FACT study showed that Fosamax increased BMD versus Actonel with similar tolerability. Boniva is differentiated from Fosamax by once-monthly dosing, and intravenous Boniva and once-yearly Aclasta/Reclast have even less frequent dosing. However, managed care formularies have vigorously pursued generic Fosamax. We forecast Fosamax sales of \$475MM (-15%) in 2014, \$350MM in 2015, \$270MM in 2016, \$170MM in 2018, and \$70MM in 2020.

Some Settlements In Fosamax Product Liability Cases

Merck is a defendant in product liability lawsuits in the United States involving Fosamax (the "Fosamax Litigation"). As of June 30, 2014, 5,510 cases, which include approximately 5,720 plaintiffs, had been filed and were pending against Merck in either federal or state court, including one case which seeks class action certification, as well as damages and/or medical monitoring. In approximately 1,080 of these actions, plaintiffs allege, among other things, that they have suffered osteonecrosis of the jaw (ONJ), generally subsequent to invasive dental procedures, such as tooth extraction or dental implants and/or delayed healing, in association with the use of Fosamax. In addition, plaintiffs in approximately 4,430 of these actions generally allege that they sustained femur fractures and/or other bone injuries in association with the use of Fosamax.

In December 2013, Merck reached an agreement in principal with the Plaintiff's Steering Committee (PSC) in the ONJ cases to resolve any outstanding cases for an aggregate amount of \$27.7MM (recorded in Q4:13). Merck subsequently formalized the terms of this agreement in a Master Settlement that was executed in April 2014.

In March 2011, all federal cases involving alleged femur fractures were consolidated in the District of New Jersey (Fosamax Femur Fracture MDL) with 1,020 cases pending as of June 30, 2014. In March 2014, claims were dismissed for 650 plaintiffs; a majority are appealing the ruling. On a state basis, there are 2,880 claims outstanding in New Jersey and 515 in California; discovery is ongoing in both states.

Cardiovascular

Vytorin's IMPROVE-IT Continues, Final Data Expected In November 2014

Vytorin (simvastatin+ezetimibe fixed dose combination) prescriptions were down 24% Y/Y in August 2014 (NRx share 0.9%) stemming from a number of factors. Vytorin has demonstrated significant LDL lowering power but its outcomes study (IMPROVE-IT) will not report full data until Q4:14. The controversy surrounding Vytorin and Zetia reflects the fact that Zetia has performed poorly in IMT trials (ENHANCE, SEAS, and ARBITER-6) despite lowering LDL significantly. Skeptics believe that this is because Zetia's mechanism for lowering LDL levels is different from the statins. A turnaround in prescribing is unlikely until outcomes data from the IMPROVE-IT trial are available, and Glenmark may launch a generic in 12/16. Vytorin successfully navigated its 85% interim look in IMPROVE-IT in March 2013; the DSMB recommended trial continuation without modification post their analysis; no additional interim analyses are planned.

In April 2012, Merck announced that the U.S. District Court for the District of New Jersey ruled in Merck's favor in two jointly related patent infringement suits against Mylan. The patent in question was RE 42,461 which covers ezetimibe's composition of matter and expires in 2017. In its decision, the court upheld Merck's patent and ruled that the patent was valid and enforceable. The court also issued an injunction blocking the approval of Mylan's generic Zetia and Vytorin until 2017 when the '561 patent expires. We forecast Zetia sales of \$2.705B (+2%) in 2014, \$2.655B in 2015, \$2.55B in 2016, \$750MM in 2018, and \$250MM in 2020, post the 12/16 entry of generics; and Vytorin sales are forecast to be \$1.565B (-5%) in 2014, \$1.42B in 2015, \$1.215B in 2016, \$500MM in 2018, and \$100MM in 2020.

New Cholesterol Guidelines A Risk, But Apt To Take Time To Gain Traction

The new 2013 ACC/AHA blood cholesterol treatment guidelines, released in November, no longer target specific LDL levels. Rather, the new guidelines recommend categorizing patients by CV risk, then treating with an appropriate intensity of statin dose that has been shown to improve outcomes in a randomized clinical trial. The guidelines do not recommend the use of nonstatin drugs as adjuncts to statins in most patients, as these have not been shown to improve outcomes. Familial hypercholesterolemia is an exception and treatment remains targeted to LDL level goals.

Our consultants notes the guidelines emphasize moderate to high dose statin, either atorvastatin 40-80 or Crestor 20-40. Crestor has an advantage in that it raises HDL-C more. Zetia will still be used in patients who can't tolerate high dose daily statin (we note about one-third of Zetia use is monotherapy and 10-15% of Zetia scripts are estimated to be for statin-intolerant patients) but will likely be stopped if they do tolerate atorvastatin or Crestor and their LDL is close to 100. Niacin will not be used to raise HDL but solely to lower LDL more in patients who can't tolerate a potent statin or cannot get close to an LDL-C of 100. Our consultants still believe that there is an optimal level of LDL-C which is likely between 40-60. Our consultants predict PCSK9 inhibitors will work and the guidelines will be much different in four years.

IMPROVE-IT

The IMPROved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is a multicenter, randomized, double-blind, active-control trial designed to test the hypothesis that Vytorin will result in an increased clinical benefit on cardiovascular outcomes relative to simvastatin monotherapy in patients with ACS. IMPROVE-IT recruited 18,141 moderate- to high-risk patients stabilized after ACS. Patients are randomized in a 1:1 ratio to once-daily doses of either Vytorin 10/40 mg or simvastatin 40 mg. If a patient's LDL does not go below 79 mg/dL at follow-up visits, the simvastatin dose will be increased to 80 mg in a double-blind manner. The primary endpoint is the first occurrence of cardiovascular death, nonfatal myocardial infarction, re-hospitalization for unstable angina, coronary revascularization (occurring at least 30 days after randomization), or stroke. Patients will be followed for a minimum of 2.5 years and until at least 5,250 patients experience a primary endpoint.

IMPROVE-IT Statistical Design, Analysis, And Amendments

An initial sample size of 10,000 patients was selected for IMPROVE-IT to provide a 90% power to detect a 10% relative risk reduction in the primary endpoint at a p-value of 0.05. The trial originally was planned to continue until a minimum of 2,955 primary endpoint events had occurred and each patient completed a minimum 2.5 years of study exposure. The sample size was calculated using an anticipated event rate at 2 years of 23.5% in the control arm (simvastatin 40 mg). The investigators made several changes to the protocol based on changes to their original assumptions. Their original assumption (not known) about the relationship between LDL-C reduction and clinical benefit was changed to reflect a 1.6mg/dL LDL change translating into a 1% clinical benefit. The expected 15mg/dL difference in LDL between the two groups (based on previous Vytorin studies) would then translate into a 9.375% hazard reduction. 5,250 events were therefore required to have sufficient power to detect a significant reduction in risk. Accordingly, the sample size was increased to 12,500. Subsequent review of pooled and blinded data from IMPROVE-IT, as well as of rates in prior studies in patients who would meet IMPROVE-IT eligibility criteria, found that a rate of 0.43% per month was a reasonable estimate. The investigators felt that to complete the trial in a timely fashion, 18,000 patients were required; 18,141 patients were enrolled.

Vytorin Clinical Endpoint Trials

Trial	Target
Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE)	Study evaluated Zetia 10mg and Zocor 80mg together versus Zocor 80 mg therapy alone in reversing the atherosclerotic thickening of the carotid artery wall in familial hyperlipidemic patients with high cholesterol levels. Non-invasive ultrasound measurements of the carotid arteries were done at 6,12, 18 and 24 months. Results demonstrated no significant difference in the primary endpoint despite a significant reduction in cholesterol.
Simvastatin and Ezetimibe in Aortic Stenosis (SEAS)	Four-year study of Vytorin 10/40 versus placebo to examine the reduction of mortality and morbidity in 1,800 patients with aortic stenosis. Study missed primary endpoint, but demonstrated statistically significant benefit in secondary non-AS related end points. An increase rate of malignancies in the Vytorin arm was determined to be unrelated to Vytorin.
Study Of Heart and Renal Protection (SHARP)	Four-year, event-driven study to evaluate the effects of lowering LDL-C with Vytorin 10/20mg or placebo in 9,438 patients with chronic kidney disease (CKD) and normal LDL-C: 6,382 pre-dialysis patients with remainder on dialysis. Vytorin met primary composite endpoint by decreasing non-fatal MI; non-fatal ischemic stroke; and revascularization. Vytorin did not show a mortality benefit or delay time to dialysis in the non-dialysis cohort.
Improved Reduction of Outcomes: VYTORIN Efficacy International Trial (IMPROVE IT)	Secondary prevention ACS study, including unstable angina (UA), non-ST-segment elevation acute myocardial infarction (NSTEMI) and ST-segment elevation acute myocardial infarction (STEMI). Patients will be randomized to either Vytorin 10/40 mg or simvastatin 40 mg per day. Composite primary end point includes CV death, major coronary events, and non-fatal stroke. Trial size increased from 12,500 to 18,000 patients in 3/08 to speed up accrual of the planned 5,250 events. Patients are required to be followed for a minimum of 2.5 years. In 5/10 more than 17,000 patients were enrolled. Results expected 2014. Interim efficacy analysis conducted in Q1:12 (after 2,600 events) and Q1:12 (after 3,500 events) recommended study continuation. Final data are expected in November 2014.

Source: Company reports, clinicaltrials.gov

Anacetrapib Outlook Unclear As HDL Hypothesis Uncertain

Merck initiated a sequenced Phase III program (DEFINE) for anacetrapib (CETP inhibitor for HDL elevation) in April 2008 to obtain additional clinical experience and evaluate key safety parameters including blood pressure, and aldosterone and electrolyte levels before initiating a cardiovascular outcomes study. Merck initiated a pivotal CV outcomes study in 2011. The outcomes study, called REVEAL, enrolled 30,624 patients and seeks a primary endpoint of major coronary events, defined as coronary death, MI, or coronary revascularization procedures. The study is expected to conclude in January 2017, but various interim looks will be taken, the first expected in early 2015. While anacetrapib increased HDL by 138% and lowered LDL by 40% in DEFINE, the failure of HPS2-THRIVE (Merck's Cordaptive) and dal-OUTCOMES (Roche CETP) increases uncertainty around the HDL hypothesis. We estimate anacetrapib sales of \$300MM in 2017, \$600MM in 2018, and \$1.2B in 2020.

Comparison Between HDL Raising Agents

	Cordaptive*	Dalcetrapib**	Anacetrapib***	Evacetrapib****
HDL	+20%	+31%	+138%	+132%
LDL	-18%	0%	-40%	-36%
Triglycerides	-26%	-14%	-7%	-11%
LpPLA2	-20%	-17%	N.A.	N.A.

*2g Cordaptive for 24 weeks (n=800)

**600mg dalcetrapib for 36 weeks (n=211)

***100mg anacetrapib for 24 weeks (n=811)

****500mg evacetrapib (LLY) for 12 weeks (n=42)

Source: ESC 2007, ESC 2011, DEFINE trial, Phase II trial, NEJM

Role In Add-On Therapy May Shorten Time to Filing

Anacetrapib is also in a Phase III randomized, double-blind, study (REALIZE) in 306 patients to determine efficacy and safety as add-on to statin therapy for the treatment of heterozygous familial hypercholesterolemia. The primary outcome measure is percent change from baseline in LDL-C at 52-weeks. Secondary endpoints include changes in HDL-C, non-HDL-C, Apo B, Apo I and lipoprotein (a) at 52-weeks. The study completed in February 2014, with data read-out potentially late 2014 or 2015. If successful, this indication could provide a quicker path to market, although Merck denies this is the intention.

Anacetrapib Modifies HDL/LDL In Phase IIb

Merck presented data from an 8-week double-blind, randomized, parallel-group dose-ranging (10, 40, 150, and 300mg) study at DALM in October 2007. The study evaluated lipid level changes and the safety profile of anacetrapib, administered as monotherapy or co-administered with Lipitor 20 mg, in 589 patients with dyslipidemia (primary hypercholesterolemia or mixed hyperlipidemia). Both anacetrapib monotherapy and the combination with Lipitor 20mg produced statistically significant changes from placebo in the tested cholesterol parameters. When comparing these Phase IIb data with Torcetrapib and R1658, anacetrapib's higher doses appear more potent on both the LDL and HDL parameters. Anacetrapib was not associated with a mean increase in blood pressure in any treatment arm. The incidence rates of individual adverse events were similar across the placebo, Lipitor and active treatment groups (≤ 5.5 percent). There were non-dose related incidences of clinically important elevations in ALT, AST and CPK. There were no treatment-related serious adverse events or deaths. Treatment-related discontinuations were rare (≤ 5 percent) and no patients discontinued due to serious treatment-related adverse events. There were no reports of hepatitis, myopathy, or rhabdomyolysis observed in this study.

DEFINE Data Appears Solid

In the DEFINE trial, 1,623 patients with coronary heart disease or CHD risk equivalents, anacetrapib showed no significant differences from placebo in the primary safety measures. There were no significant differences in mean changes in blood pressure and no significant differences in serum electrolytes or aldosterone levels.

During the 76-week study, the pre-specified cardiovascular endpoint (defined as cardiovascular death, myocardial infarction, unstable angina or stroke) occurred in 16 anacetrapib-treated patients (2.0%) compared with 21 placebo-treated patients (2.6%) ($p=0.40$). At 24 weeks, anacetrapib decreased LDL-C by 40% using the Friedewald equation to estimate LDL-C (from 81 to 45 mg/dl vs. 82 to 77 mg/dl for placebo,

p<0.001) and increased HDL-C by 138% (from 40 to 101 mg/dl vs. 40 to 46 mg/dl for placebo, p<0.001).

The lipid and safety trends are impressive. While the study was small and the number of events low, the LDL-C decrease from 81 to 45 with anacetrapib (36pt reduction) alone should translate to a 22.5% reduction in events (from IMPROVE-IT, 1.6mg/dl LDL change assumed to result in 1% clinical benefit). Events decreased from 21 to 16 which is a 24% reduction in events--if this relationship is correct, then one may conclude that the benefit from changes in HDL-C was actually derived from LDL-C reduction. Thus, DEFINE answers key safety questions about anacetrapib but does not fully answer whether the HDL is active.

At its November 2011 R&D Day, Merck presented animal and cell data suggesting that anacetrapib enhances HDL-mediated cholesterol efflux from macrophages, increases reverse cholesterol transport, and preserves the anti-inflammatory properties of HDL. Ex-vivo studies showed anacetrapib increased cholesterol efflux with increased cholesterol efflux also observed in cells expressing ABCA1, ABCG1, or SR-B1. Anacetrapib treated hamsters showed elevated reverse cholesterol transport as measured by fecal excretion of radioactively-labeled cholesterol. Additionally, HDL from anacetrapib treated animals was shown to reduce the ex-vivo expression of anti-inflammatory markers of inflammation (TNF α , IL6, MIP1 α , and MIP-2) in macrophages.

Anacetrapib LDL-C Lowering Less Robust Than Previously Reported Post New Analysis; Likely Not Relevant To Outlook

Merck reported LDL-C measurements from anacetrapib's Phase II DEFINE trial using a new method, which they believe to be more accurate than previously utilized algorithms. In November 2011, Merck reported that 100mg of anacetrapib produced a 40% reduction in LDL-C based on the Friedewald method. Because the Friedewald method can be influenced by changes in the ratio of triglycerides to cholesterol, such as were observed in DEFINE, it does not provide an accurate quantification of LDL-C lowering by anacetrapib. The new method for measuring LDL-C (beta quantification) suggested that anacetrapib lowered LDL-C by 25-30% in DEFINE. Our physician consultant believes that the changes in reported LDL-C concentrations are not meaningful given that the beta quantification method does not reflect any potential benefit from the depletion of VLDL and cholesterol remnants and believes that the event reduction will more accurately reflect the 40% reduction number.

In May 2012, Roche announced the termination of dalcetrapib's dal-OUTCOMES study due to a lack of clinically meaningful efficacy at the 70% interim look. As a result, Roche terminated all six dalcetrapib studies in the dal-HEART program. The termination of dalcetrapib clearly demonstrates that raising HDL by ~30% is not sufficient to prevent secondary CV events in patients with a recent ACS event.

Also in May 2012, the Lancet published a study entitled "Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomization study." The investigators evaluated the impact of several gene variants known to specifically modulate HDL and LDL cholesterol levels on cardiovascular (CV) risk. Single nucleotide polymorphisms (SNPs) that increased LDL were consistently associated with an increased risk of myocardial infarction while a SNP that significantly elevates HDL cholesterol showed no association with the risk of MI. Such observations challenge the hypothesis that HDL elevation reduces the risk of adverse CV events and suggest that LDL may be the biomarker most closely associated with cardiovascular risk. Together these data explain why agents that solely impact HDL, such as dalcetrapib, were not successful

in reducing CV events and suggest that HDL raising agents that also impact LDL and/or triglycerides are most likely to achieve their CV endpoints.

Cozaar/Hyzaar In Decline Post Generic Entry

In the U.S., Cozaar/Hyzaar patents expired in April 2010 — this included pediatric extension. In E.U., Merck received pediatric extension in many markets for Cozaar, extending the date to March 2010. In E.U., Hyzaar expired in February 2010. Hyzaar did not garner pediatric exclusivity because it is not available for combination products. We peg Cozaar/Hyzaar sales of \$760MM (-24%) in 2014, \$560MM in 2015, \$465MM in 2016, \$360MM in 2018, and \$255MM in 2020.

Zonivity Approved In U.S.

Zonivity (vorapaxar), a PAR-1 antagonist, was approved in May 2014 for use, in addition to aspirin and/or clopidogrel, in post-MI or PAD patients without a history of stroke or TIA. The label includes a black box warning regarding bleeding risk. MRK anticipates that a lot of education and market development will be necessary to make Zonivity a success. We estimate Zonivity sales of \$25MM in 2014, \$90MM in 2015, \$110MM in 2016, \$150MM in 2018, and \$190MM in 2020.

Merck Establishing CV Collaboration With Bayer

In addition to the sale of its Consumer business, Merck will also be entering into a development/marketing collaboration with Bayer in the cardiovascular area. This will include Bayer's portfolio of soluble guanylate cyclase (sGC) modulators including Adempas (riociguat), which is approved in U.S and E.U. for PAH and CTEPH, and in Japan for CTEPH. The collaboration also will include Bayer's vericiguat (BAT102), which is in Phase II for heart failure. Merck's early stage compounds in this area also will be part of the venture. Merck will make a \$1B upfront payment to Bayer as well as future milestone payments.

Immunology

Remicade: Modest Decline In Sales Expected Through 2020

Remicade (infliximab) is a chimeric anti-TNF monoclonal antibody approved for the treatment of RA (signs and symptoms, inhibition of disease and radiographic progression), ankylosing spondylitis, psoriasis and psoriatic arthritis, Crohn's disease (acute and maintenance use; fistula closure or prevention), and ulcerative colitis. Merck markets Remicade in some ex-U.S. markets. Remicade sales in Europe have increased substantially, driven by new indications and broader marketing. However, AbbVie's Humira and Pfizer's Enbrel are formidable competitors in Europe. Humira's main advantage relative to Remicade is more convenient dosing — a bi-weekly injection versus every-8-week infusions — and a cleaner adverse event profile. Near term, we expect Humira and Enbrel to compete with Remicade in RA, psoriatic arthritis, ankylosing spondylitis, and psoriasis. Bristol's Orencia, Roche's Actemra and Pfizer's Xeljanz are more likely to be used after TNF-failures limiting their impact on Remicade. In September 2011, FDA updated the boxed warning for all TNF's to include the risk of infection from Legionella and Listeria. In mid-2013, Celtrion received approval for a biosimilar of infliximab for all six indications. Celtrion has launched its product in several small E.U. markets so far; there are 18 E.U. countries where Remicade currently has no composition of matter patent, primarily Eastern and

Central Europe and Nordic countries. Remicade has good patent protection in major markets through early 2015. Our Remicade sales forecasts (ex U.S.) are \$2.51B (+11%) in 2014, \$2.41B in 2015, \$2.3B in 2016, \$2.1B in 2018, and \$1.9B in 2020.

In April 2011, Merck and Johnson & Johnson revised the agreement on the distribution rights to Remicade and Simponi, concluding the arbitration proceeding initiated by JNJ in May 2009. Under the terms of the amended distribution agreement, Merck relinquished exclusive marketing rights for Remicade and Simponi to Johnson & Johnson in Canada, Central and South America, the Middle East, Africa and Asia Pacific, effective as of July 1, 2011. Merck retains exclusive marketing rights throughout Europe, Russia and Turkey. The retained territories represent approximately 70% of Merck's 2010 revenue of \$2.8B from Remicade and Simponi. All profit derived from Merck's exclusive distribution of the two products in the retained territories have been equally divided between Merck and Johnson & Johnson, as of July 1, 2011 (versus 2014 in the previous agreement) through October 1, 2024. Under the prior terms of the distribution agreement, the profit split was 58% Merck/42% JNJ. JNJ received a one-time payment of \$500MM from Merck during Q2:11.

Simponi Marketed In The E.U. For RA, PsA, And AS

In October 2009, the E.U. approved Simponi for the treatment of adult RA, psoriatic arthritis, and ankylosing spondylitis. Schering launched Simponi in the same month. Simponi's subcutaneous dosing utilizes the SmartJect Auto-Injector which places it on a level field with Humira and Enbrel. Once-monthly dosing also may be an advantage but there is competition with longer acting agents, especially for psoriasis, including JNJ's Stelara (ustekinumab) (IL-12, IL-23; approved in Europe for moderate severe plaque psoriasis 01/09) which is dosed every three months. Simponi's efficacy and safety appear robust. In May 2013, FDA approved Simponi for the treatment of moderately to severely active ulcerative colitis that have had an inadequate response to conventional therapy. In September 2013, Simponi received E.U. approval for ulcerative colitis. We forecast Simponi sales (ex-U.S.) of \$670MM (+34%) in 2014, \$770MM in 2015, \$875MM in 2016, \$1.075B in 2018, and \$1.275B in 2020.

Infectious Disease

Isentress Facing Increasingly Competitive HIV Landscape

Isentress (raltegravir), an oral integrase inhibitor, was approved in October 2007 for use in combination with other antiretroviral agents for the treatment of HIV-1 infections in treatment-experienced adult patients with multi-drug resistance at a dose of 400mg bid. Integrase is a key enzyme that enables HIV integration into the host genome, and is a vital element in the HIV-1 replication life cycle

In 2009, Isentress was approved in the U.S. and E.U. for treatment-naïve HIV patients. In January 2014, the FDA approved Isentress pediatric oral suspension, which expands its use to patients four weeks and older (in combination with other agents). A once-daily formulation is in Phase III (ONCEMRK) after a failed attempt many years ago. The reformulated version is a 600mg tablet, with two tablets given together once daily with tenofovir/emtricitabine in the trial. Viral suppression is the primary endpoint; data is expected in H1:2016. In June 2014, Merck filed an NDA for a fixed-dose combination of 300mg Isentress + 150mg lamivudine to be used in combination with other antiretroviral agents. The application was accepted in June. We forecast Isentress sales of \$1.765B (+7%) in 2014, \$1.71B in 2015, and \$1.65B in 2016, \$1.5B in 2018, and \$1.35B in 2020.

Isentress Efficacy On Par With Protease Inhibitors

At CROI 2014, data was presented from an AIDS Clinical Trials Group (ACTG) study that compared twice-daily Isentress to once-daily, ritonavir-boosted, protease inhibitors atazanavir (Reyataz) and darunavir (Prezista) in a large (1,809 treatment-naïve patients) 96-week open-label trial. Results showed high and equivalent efficacy, as measured by time to virologic failure (co-primary endpoint), for all three regimens. The percentage of patients maintaining ≤ 50 copies/mL at week 96 was 94% for Isentress, 88% for Reyataz, and 89% for Prezista, based on ITT analysis. On the other co-primary endpoint of tolerability failure, Isentress and Prezista regimens were superior to Reyataz. The percentage of patients who discontinued treatment for toxicity reasons was 1% for Isentress, 16% for Reyataz, and 5% for Prezista.

SWITCHMRK Failed, But REALMRK Demonstrated Combo Efficacy

Treatment-naïve data and switch data were presented at CROI 2009. The 24-week treatment-naïve data were positive but the SWITCHMRK study failed and was stopped early. In July 2009, results presented at the 5th International AIDS Society's Conference on HIV Pathogenesis, Treatment & Prevention showed that Isentress was as effective as efavirenz at maintaining viral load suppression to undetectable levels (less than 50 copies/mL) and at improving CD4 counts in treatment-naïve patients through 144 weeks in a Phase II study. Both medicines were administered in combination with two other anti-HIV medicines, tenofovir and lamivudine.

Our consultants believe that SWITCHMRK data indicate that Isentress has a lower genetic barrier and will prompt greater caution in its use as a first-line agent and in combinations that are potentially fragile. A Phase III trial compared once daily Isentress (800mg) to the current FDA approved dosing regimen (400mg BID) in treatment naïve adults infected with HIV-1. The once-daily dosing regimen failed to meet the pre-specified non-inferiority endpoint, with 5.7% more patients achieving undetectable viral loads after 48 weeks in the BID treatment group compared to those dosed once-daily. The difference in effect was driven primarily by patients with high viral loads (>100,000 copies/mL of HIV-RNA) with 84.2% of patients achieving suppression with twice-daily dosing compared to 74.3% of patients receiving Isentress once a day. These data prompted Merck to end the study. In September 2011, Merck announced results from the REALMRK clinical study showing that after 48 weeks of treatment in an open-label, single-arm, observational study, Isentress tablets in combination therapy demonstrated efficacy and tolerability, regardless of gender or race, in a diverse population of adult patients with HIV-1 infection similar to results from other Phase III studies.

Gilead's Stribild and GSK/ViiV's Tivicay Solid Competition

Despite competition from GSK's Tivicay and Gilead's Stribild, Isentress continues to maintain the leading share in new patient starts in this class, although it is steadily losing share to Tivicay in the integrase class. Stribild (Quad) was approved May 2012 based on two successful Phase III trials and demonstrated a trend toward superiority when compared to ritonavir-boosted atazanavir plus Truvada. Glaxo's unboosted integrase inhibitor, dolutegravir (Tivicay), was approved in August 2013, for both treatment-naïve and treatment-experienced patients. Isentress claimed 72% share of the U.S. integrase inhibitor market in August 2014, representing Y/Y decline of 1%. Tivicay claimed the other 28% share. Tivicay's label relative to Isentress indicates fewer severe side effects. Dolutegravir's successful Phase III trial may indicate a superior tolerability and resistance profile compared to Isentress.

Doravirine Could Bolster Isentress Franchise

A next-gen NNRTI (non-nucleoside reverse transcriptase inhibitor) agent, doravirine (MK-1439), will be advancing to Phase III studies in combo with antiretroviral therapy in H2:14. It is highly suited to QD fixed dose regimens and has the same potency as Efavirenz but without the CNS side effects. We estimate doravirine sales of \$25MM in 2017, \$50MM in 2018, and \$100MM in 2020.

Intron In Decline; Interferon-Free Regimens To Accelerate Erosion

The hepatitis C treatment market underwent substantial change in 2011, following the approval of both Telaprevir (VRTX) and Bocepravir (MRK) in May. The emergence of interferon-free regimens in 2014 is further pressuring Intron franchise sales in developed markets.

We forecast Pegintron sales of \$380MM (-23%) in 2014, \$335MM in 2015, \$280MM in 2016, \$155MM in 2018, and \$55MM in 2020. Intron franchise sales are forecast at \$580MM (-21%) in 2014, \$495MM in 2015, \$400MM in 2016, \$215MM in 2018, and \$70MM in 2020.

Victrelis Success Short-Lived

In May 2011, Victrelis (boceprevir), a first-generation protease inhibitor, was approved for patients with residual liver function who either have not been previously treated with drug therapy or who have failed such treatment. The label specifies that Victrelis has not been studied in historical null responders (<2-log₁₀ decline in HCV-RNA by treatment week 12) during prior therapy with peginterferon alpha and ribavirin, although does note that the registration trials included subjects who were poorly interferon responsive (<0.5-log₁₀ decline in HCV-RNA) after 4 weeks of lead-in therapy and that this patient group is predicted to have a null response to peginterferon alpha and ribavirin therapy. Victrelis is priced at \$1,100 per week of therapy. We assume a majority of patients receive 32 or 44 weeks of therapy at an average cost of \$40,000 per patient. Our physician consultants note that real-world efficacy appears to be in-line to worse compared to clinical trial data; they have observed an increase in the frequency of anemia. However, the onset of Boceprevir-related anemia is much slower than what has been observed for telaprevir and is easily treated with Procrit. We forecast Victrelis sales of \$190MM (-56%) in 2014, \$145MM in 2015, \$95MM in 2016, \$50MM in 2018, and \$15MM in 2020.

Response Guided Therapy Recommended For Most Patients; Extended Therapy Recommended In Cirrhosis

Response guided therapy is recommended for previously untreated patients or previous partial responders or relapsers without cirrhosis. Patients are to receive lead-in therapy with PEG-Riba for 4 weeks at which time Victrelis 800mg TID is to be added to PEG-Riba. Treatment paradigms are dependent on patient population and HCV-RNA response at treatment week 8 and 24 and are as follows:

Victrelis Response Guided Therapy Label Recommendations

	HCV-RNA Results		Recommendation
	Week 8	Week 24	
Previously Untreated Patients	Undetectable	Undetectable	Complete three-medicine regimen at TW28
	Detectable	Undetectable	Continue all three medicines and finish through TW36; and then administer PEG+Riba and finish through TW48
Previous Partial Responders/Relapsers	Undetectable	Undetectable	Complete three-medicine regimen at TW36
	Detectable	Undetectable	Continue all three medicines and finish through TW36; and then administer PEG+Riba and finish through TW48

Treatment Futility: if patient has HCV-RNA results greater than or equal to 100IU/mL at TW12, then discontinue three-medicine regimen.

If patient has confirmed detectable HCV-RNA at TW24, then discontinue three-medicine regimen

Source: Company data

Patients with compensated cirrhosis should receive four weeks of PEG-Riba followed by 44 weeks of Victrelis 800mg TID in combination with PEG-Riba.

MK-5172/MK-8742 Combo Promising; Shorter Duration Therapy A Key Strategy

Merck's Hep C oral combo of MK-5172 (second-gen protease inhibitor) and MK-8742 (NS5A inhibitor) appears well suited to capture a piece of the evolving hep C market with demonstrated success in a wide range of patients. The combo has demonstrated 90%+ SVRs across a wide range of patients regardless of comorbid conditions. Merck is working on a shorter duration therapy that includes MK-5172/MK-8742 plus sofosuvir (C-SWIFT) in four, six, and eight week regimens, with some data from these trials expected at AASLD in November 2014. Merck indicated that 450,000 U.S. patients may get coverage in 2014-2020. We estimate MK-5172 sales of \$50MM in 2016, \$250MM in 2017, \$500MM in 2018, and \$500MM in 2020 and MK-8742 sales of \$50MM in 2016, \$250MM in 2017, \$500MM in 2018, and \$500MM in 2020

C-WORTHY EASL 2014 Phase II Data Impressive; Phase III Initiated

At EASL 2014 (April), data presented from the Phase II C-WORTHY trial of MK-5172+MK-8742 all-oral 12-week regimen in treatment-naïve patients showed impressive SVRs of 97-100% for gt-1 treatment-naïve, non-cirrhotic patients. 8-week data in this group +RBV showed an SVR of 83%. Most common SEs were fatigue, headache, and nausea. No early discontinuations occurred. Based on these positive results, Merck has initiated Phase III studies for the combination (C-EDGE).

A further analysis of hard-to-treat patients also showed very solid results:

Cirrhotic patients: the combo achieved SVRs at 12 weeks of 90% (28/31) with RBV and 97% (30/31) without RBV; at 18 weeks, the SVR was an impressive 97% (28/29 and 29/30) with and without RBV.

Null responders: the combo achieved an SVR of 94% (30/32) with RBV and 91% (30/33) without RBV; at 18 weeks the SVR was 100% (32/32) with RBV and 97% (29/30) without RBV.

Co-Infected w/HIV: the combo achieved an SVR of 97% (28/29) with RBV and 90% (26/29) without RBV at 12 weeks.

Results From MK-5172/MK-8742 Combo Phase II Trial Encouraging

In November 2013, Merck presented data from its Phase II C-WORTHY study evaluating MK-5172 and MK-8742 in combination with and without ribavirin in treatment-naïve HCV patients (n=65). The results from this small trial showed 100% SVR12 in two of the three arms. Most frequent side effects were fatigue, headache, nausea, diarrhea, dizziness, and rash. Anemia was also seen in the ribavirin arms. There were no grade 3 or 4 lab abnormalities. The MK-5172/MK-8742 oral combination received Breakthrough Therapy designation in October 2013.

The C-WORTHY trial was expanded to evaluate safety/efficacy of the Merck combination with and without ribavirin in an approximately 400 genotype1 patient trial as shown below.

Expanded C-WORTHY Trial - Phase II

Treatment Duration	Treatment Regimen	Population
8 weeks	MK-5172/MK-8742 + RBV	Treatment naïve non-cirrhotic patients
12 weeks	MK-5172/MK-8742 without RBV	Treatment naïve non-cirrhotic patients
12 weeks	MK-5172/MK-8742 with or without RBV	HIV co-infected patients
12 or 18 weeks	MK-5172/MK-8742 with or without RBV	Patients w/cirrhosis
12 or 18 weeks	MK-5172/MK-8742 with or without RBV	Patients who had failed to respond to prior peginterferon and RBV therapy ("null responders")

Source: Cowen and Company

MK-5172 Phase II Data Highlighted Benefits As Part Of Combo Regimen

In November 2011, Merck announced it had in development a QD pan-genotypic protease inhibitor, MK-5172. Merck observed profound viral suppression in patients infected with genotype 1 and 3, but pre-clinical data also supports activity against genotypes 2, 4, 5, and 6. In November 2012, Merck presented Phase II data assessing the safety and efficacy of MK-5172 in combination therapy in treatment naïve GT1 patients at AASLD. The primary endpoint of the study was to evaluate the cEVR of four regimens of MK-5172 in combination with interferon and ribavirin compared to the control arm in which patients received a 4-week lead-in of PEG/Riba followed by the addition of Victrelis. MK-5172 regimens had rates of cEVR ranging from 82.8-93% vs. 74.2% for controls. In the initial 136 patient cohort, 96% of patients who received a regimen containing 100mg QD of MK-5172 in combination therapy achieved SVR12 compared to 54% of patients in the control arm. Merck aims to position MK-5172 as the protease inhibitor of choice for combination regimens.

Vaniprevir (MK-7009) Under Priority Review In Japan

Vaniprevir (MK-7009) is a 2nd generation protease inhibitor (PI). A Phase III study in Japanese patients with genotype 1 completed in March 2013. Vaniprevir, in combo with peg interferon and ribavirin, is currently under priority review in Japan. We estimate Vaniprevir sales of \$15MM in 2015, \$50MM in 2016, \$100MM in 2018, and \$150MM in 2020.

Data from a Phase II trial of MK-7009 were presented at EASL 2009. The trial was a randomized, double-blind placebo-controlled study of MK-7009 in combination with PEG-IFN and ribavirin in 94 patients with genotype 1 HCV. MK-7009 was administered for 28 days in 1 of 5 regimens: placebo, 300mg BID, 600mg BID, 600mg QD, or 800mg QD. All patients then continued PEG-IFN and ribavirin for an additional 44 weeks. The

primary endpoint was the percent of subjects with undetectable HCV RNA (< 10 IU/mL) at day 28 (otherwise known as an RVR).

The efficacy data are in the following table, and were impressive. More than 80% of the subjects treated with MK-7009 had HCV RNA below the lower limit of detection on day 28.

MK-7009 Phase II 28-Day Data

MK-7009 Dose Group	Pts. w RVR/Pts Treated	% RVR	P-Value	% <10IU/mL Day 42
300mg BID	12/16	75.0	<0.0001	87.5
600mg BID	15/19	78.9	<0.0001	89.5
600mg QD	11/16	68.8	<0.0001	76.5
800mg QD	14/17	82.4	<0.0001	94.1
Placebo	1/18	5.6	n/a	11.8

Source: Cowen and Company

Although there were no serious adverse events or discontinuations due to adverse events in the trial, MK-7009 was associated with high rates of nausea and vomiting. Nausea rates were 30-40% for the MK-7009 dose groups, compared to 26% in the placebo group. Vomiting rates were 15-40% in the MK-7009 dose groups, compared to 5% in the placebo group. Therefore, while MK-7009 would appear to be potent, managing its nausea and vomiting would seem to be important for its success.

Merck Acquired IDIX For \$24.50/Share Cash

In June 2014, Merck announced that it would acquire Idenix Pharmaceuticals for \$3.85B, a seemingly lofty price but likely reflecting the urgency of companies to get a step-up in the rapidly evolving Hep C market. Merck completed a tender offer in early August and acquired the remaining shares thorough a second-step merger.

IDIX Agents Expected to Accelerate Nex Gen Development

Merck believes the acquisition will accelerate its goal of achieving all oral, riba free, short duration treatment. Idenix has 3 hep C drugs and some preclinical candidates in its pipeline: two nucleotide prodrugs (IDX21437, IDX21459) and an NS5A inhibitor (samatasvir). In April 2014, IDIX reported that IDX21437, in a Phase I/II 7-day POC clinical trial in healthy volunteers and Hep C-infected patients, showed a 4 log drop in genotypes 1-3 at the highest dose of 300mg and was well tolerated. A Phase II study of IDX21437 + samatasvir is under evaluation.

Other nucs have produced similar Phase I data, and then failed to progress. Thus, with only a couple of nucs left in the clinic, and sofosbuvir likely to generate \$15B annually, it is easy to see how this is the valuation that the market would bear.

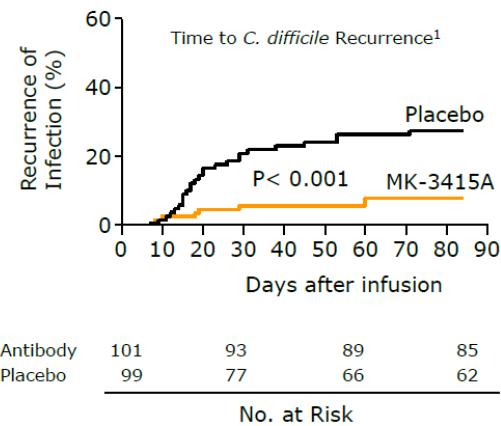
Idenix is in Phase II studies in collaboration with Janssen (JNJ) with a combo of samatasvir + simeprevir + TMC647055/r; SVR4 data is expected in H2:14. In April 2014, Idenix initiated enrollment for a Phase I trial of IDX21459, a follow-on nucleotide prodrug in Europe.

Merck has its own nuc in Phase I so the Idenix agents may speed up this process.

MK-3415A, A Novel Approach To Targeting CDAD

In April 2009, Merck gained worldwide rights from Medarex (now Bristol) to develop and commercialize actoxumab/bezlotoxumab (MK-3415A), an antibody against *C. difficile*. Top-line results from a Phase II multicenter, randomized, double-blind, placebo-controlled trial evaluating MK-3415A provided evidence of a statistically significant reduction in the rate of recurrence of CDI compared with placebo. In this study, 200 patients from 30 clinical sites received either MK-3415A (101 patients) or placebo (99 patients) in addition to standard of care antibiotics. Treatment with MK-3415A resulted in a 70% reduction in recurrence rate in a complete intent to treat analysis. Of those who received MK-3415A treatment for the initial episode of *C. difficile*, 29.7% experienced severe diarrhea compared to 43.4% of those in the placebo group. Duration of initial hospitalization for patients was unaffected by MK-3415A (9.5 vs. 9.4 days), however exploratory analysis found that the affected proportion of patients who were subsequently hospitalized after infusion was significantly reduced (8.9% vs. 20%). All adverse events that reached significance were experienced by patients on the placebo arm, such as dehydration (0% vs. 5%) and low blood pressure (0% vs. 7%). MK-3415A demonstrated a 72% decrease in recurrence in a Phase IIb study and is currently in two pivotal Phase III studies (MODIFY I) with an anticipated filing in 2015. We estimate actoxumab/bezlotoxumab sales of \$100MM in 2016, \$200MM in 2018, and \$300MM in 2020.

MK-3415A Phase II Efficacy Data



Source: Company data

Relebactam (MK-7655) Gets QIDP And Fast Track Designation For Use In Resistant Bacterial Infections

In September 2014, Merck's beta-lactamase inhibitor, Relebactam (MK-7655) was designated a Qualified Infectious Disease Product (QIDP) by the FDA along with Fast Track Status for its potential use in the treatment of complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), and hospital-acquired bacterial pneumonia/ventilator-associated pneumonia. In preclinical studies, relebactam demonstrated activity against a broad spectrum of Gram-negative and beta-lactam-resistant pathogens.

QDIP status allows (among other incentives) for a 5-year extension on data exclusivity under Hatch-Waxman and priority review upon filing. Phase II trials are ongoing (in

combo with imipenem/cilastatin) in cUTI and CIAI. and Phase III studies are expected to be started in 2015. We estimate rebactam sales of \$25MM in 2017, \$50MM in 2018, and \$100MM in 2020.

Vaccines

V503 On Track To Become The Next-Gen Gardasil

Merck has developed a nine-valent HPV vaccine (V503) to provide broader coverage against HPV. V503 is designed to provide immunity against 87% of cervical cancers compared to 70% with Gardasil. V503 uses alum as the adjuvant. The addition of 5 new HPV antigens: HPV types 31, 33, 45, 52, and 58 is in addition to the four already covered by Gardasil: HPV types 6, 11, 16, and 18. Four Phase III safety/immunogenicity studies, enrolling over 6,000 patients, have completed and met all primary and secondary endpoints. The V503 vaccine has been shown to provide sufficient immunogenicity in adolescents, safe concomitant use with vaccines Adacel and Menacra, and solid immunogenicity in patients who were previously vaccinated with Gardasil.

Results from a 14,000+ patient (16-26 yo females who received all three vaccine doses in one year) event-driven Phase III efficacy study with Gardasil as an active comparator were released in November 2013. The data showed that for the 5 additional HPV Types (31,33,45,52, and 58) V503 demonstrated: a 96.7% reduction in the incidence of high grade cervical, vaginal, and vulvar disease, a 97.1% reduction in any grade cervical, vaginal, and vulvar disease, and 96% efficacy against 6-month persistent HPV infection. As a second primary endpoint, V503 also demonstrated non-inferior immune responses to the 4 HPV types covered by Gardasil (6, 11, 16, and 18). Frequency of adverse events was comparable between V503 and Gardasil, however, more injection-site AEs were seen with V503 than Gardasil (90.8% vs. 85.1%). These events (swelling, pain, erythema) were characterized as mild to moderate. The most common systemic side effects (headache, pyrexia, nausea, dizziness, and fatigue) occurred at rates that were similar/modestly higher for V503.

Our consultants believe an incremental improvement over existing vaccines is likely sufficient to drive adoption of V503. In February 2014, the FDA announced it had accepted Merck's BLA for V503. V503 has also been filed in the E.U. Approval is expected in late 2014. Once approved, the replacement of Gardasil will be a process, not an event, implying that the two products will co-exist on the market for some time. Superior health economics data for V503 vs. Gardasil imply that it will price V503 at a premium. Emerging markets are viewed as a significant opportunity.

We forecast V503 sales of \$750MM in 2015, \$1,600MM in 2016, \$2,000MM in 2018, and \$2,200MM in 2020.

Gardasil Sales To Trend Down As V-503 Gains Traction

Gardasil's (quadrivalent 11,16,18,24, 3-dose HPV vaccine) initial success in the U.S. was dampened by the rapid saturation of the 13-18 year-old age group and Merck's ongoing struggle to penetrate the 19-26 age cohorts. In September 2008, FDA approved the vulvar and vaginal cancer prevention claim. However, Gardasil's U.S. label also was revised at that time to note that current information does not support cross protection. Merck had sought a cross-protection indication (coverage beyond the 4 serotype). Merck has received two complete response letters for its sBLA for women 27-45 years of age and filed a response in January 2010. In April 2011, the FDA refused to grant the indication for adult woman and instead the "Limitations of

Use and Effectiveness" portion of the label was updated to state that Gardasil has not been shown to prevent HPV-related CIN2/3 or worse in women older than 26 years of age. Gardasil is approved for use in boys and men 9 through 26 years of age for the prevention of genital warts caused by human papillomavirus (HPV) types 6 and 11. These new indications are critical for Gardasil's growth, although universal reimbursement for the male indication was not granted. GSK's Cervarix was approved in the U.S. in October 2009 and was recommended by the ACIP in the same month. Cervarix appears more potent than Gardasil although the clinical relevance of this potency is unknown but may be advantageous in engendering longer-term immunity and greater cross-protection than Gardasil. However, Cervarix does not protect against genital warts.

In May 2013, Merck was awarded a significant portion of the UNICEF human papillomavirus vaccine tender, and will provide a sustained supply of Gardasil to GAVI-eligible countries. This agreement followed the FAVI Alliance's earlier announcement that HPV vaccines would be included in its portfolio for the first time. GAVI is expected to support the introduction of HPV vaccination in 28 countries by the end of 2017.

In June 2013, the Japanese government withdrew its recommendation for use of HPV vaccine (both Gardasil and GSK's Cervarix) in girls, citing concerns from the public about potential adverse effects. The vaccine will still be available, but its use will not be promoted while studies are done to evaluate alleged adverse effects (including pain, joint pain, convulsions, other). Merck will work with the government to obtain/verify necessary safety data. Japanese sales of Gardasil in 2012 were \$120MM. This decision was announced at roughly the same time the CDC reported that HPV vaccines were underutilized in the U.S., and efforts are now being made to encourage immunization, especially in girls age 13-17. Also in July 2013, the government of Brazil announced that it would be including HPV vaccine in its health program effective January 2014. In April 2014, the EC approved a two-dose schedule for Gardasil (at 0 and 6 months) for children age 9-13 years old.

In Europe Gardasil is developed and commercialized by the Sanofi Pasteur MSD JV. We forecast Gardasil sales of \$1,965MM (+7%) in 2014, \$1,400MM in 2015, \$550MM in 2016, \$250MM in 2018, and \$150MM in 2020 as V503 replaces Gardasil in most areas.

Gardasil Approvals And Filings

Claim	FDA Action
9- to 15-year old girls	Approved
9- to 26-year old boys*	Approved
16- to 26-year old girls	Approved
27- to 45-year old women	Complete response letter (06/08 and 1/09)
Vulvo-vaginal cancer	Approved
Cross-protection	Complete response letter (06/08); MRK no longer pursuing
Anal cancer and AIN prevention in 9 to 26-year old boys and girls	Approved

*Recommendation is gender neutral in some markets, such as the U.K.

Source: Company data

Gardasil Anal Cancer Claim Approved

Up to 90% of anal cancer and anal intraepithelial neoplasia (AIN) are caused by HPV 16 and 18. Studies in women and men who have sex with men aged 9 to 26 support the use of Gardasil in prevention of anal cancer and AIN. The FDA approved Gardasil for primary prevention of anal cancer and AIN in December 2010. Health Canada approved Gardasil for the prevention of anal cancer in both men and women in May 2011.

Zostavax Seeking Inroads in 50+ Age Group

Zostavax, a single high-dose varicella vaccine (FDA approved 2006), has had a constrained rollout for prevention of shingles and shingles-related pain for adults 60+ due to supply issues. Merck had slowed active promotion of Zostavax and delayed the global launch of the refrigerated version, which requires higher potency. In July 2010, Merck indicated that customers would experience back orders throughout 2010-11. In February 2012, Merck announced they had resolved Zostavax production issues, filled all remaining backorders, and had begun to build inventory. Merck anticipates Zostavax uptake to be similar to that of flu vaccine in the 60+ age group. Merck states that it is being reimbursed by plans covering 94% of managed care lives. Zostavax is priced at \$145-155 per dose. Zostavax has been recommended for inclusion in the elderly vaccination schedule, boosting managed care reimbursement.

In March 2011, the FDA approved Zostavax for the prevention of shingles in 50-59 year olds, although to date, the CDC recommendation is for vaccination of those 60 years and older. The inclusion of the 50 to 59-year-old cohort is a significant business opportunity, because there are 37MM Americans alone in the cohort, and these people account for more than 40% of the eligible population and 20% of the disease burden. The 87MM adults age 50 or older who account for 60% of shingles in the U.S. qualify for Zostavax immunization. We estimate Zostavax sales of \$805MM (+6%) in 2014, \$875MM in 2015, \$955MM in 2016, \$1,095MM in 2018, and \$1,235MM in 2020.

V212 is an inactivated Herpes Zoster Vaccine for use in immunocompromised patients who are at a higher risk for developing herpes. Zostavax is contraindicated in this population due to an increased risk of vaccine-related adverse events. The antigens in V212 are the same as in Zostavax, although they have been inactivated by proprietary technologies. A NEJM paper highlighted V212 use in autologous hematopoietic stem cell transplant recipients. The incidence of herpes within the first twelve months was 33% in the non-vaccinated group compared to 13% in V212 patients ($p=0.01$). Phase III studies are ongoing in stem cell transplant patients (completion in 2015-16). We estimate V212 sales of \$100MM in 2016, \$300MM in 2018, and \$500MM in 2020.

RotaTeq A Good Success, Despite Competition From GSK's Rotarix

RotaTeq, an oral, liquid, pentavalent bovine reassortant vaccine (G1, G2, G3, G4, G9P1A) is marketed for the prevention of rotavirus (a disease that prompts severe diarrhea in infants). ACIP recommends RotaTeq for routine immunization of infants starting at 6 to 12 weeks of age. All doses are administered by 32 weeks, with a 4 to 10 week interval between the doses. RotaTeq is included in the Vaccines for Children (VFC) program. In its safety trials (70,300 patients), RotaTeq demonstrated 98% efficacy against severe rotavirus gastroenteritis (RGE) and 74% efficacy against RGE of any severity.

In the European subset of the large clinical study REST (Rotavirus Efficacy and Safety Trial), RotaTeq demonstrated 100% clinical efficacy against severe rotavirus disease

for the first rotavirus season after vaccination. The efficacy remained high through two rotavirus seasons of follow up, preventing 98% of severe rotavirus cases. In this REST sub-analysis, RotaTeq reduced the number of hospitalizations and emergency department visits due to serotypes G1 to G4 by 95% and the number of GP surgery visits by 87% up to two years post vaccination in Europe. Intussusception, a type of bowel blockage, is a potential side effect of the rotavirus vaccines. At their June 2013 meeting, ACIP (Advisory Committee on Immunization Practices) reviewed new data showing an increased risk of intussusception after receiving GSK's Rotarix, and to a lesser degree, Rotateq. The incidence range was 0.7 to 5.4 extra cases per 100,000 children who receive the vaccine. However, the data also showed a marked decrease in hospitalizations and deaths due to rotavirus, which ACIP believes far outweighs the intussusception risk.

In 12/07, RotaTeq's label was updated to include data demonstrating the reduction in hospitalizations and emergency visits caused by the G9P1A rotavirus serotype. In September 2008, RotaTeq's label was updated to include pertussis immune response data from REST to support concomitant use of DTaP with RotaTeq. RotaTeq's first-mover advantage, with penetration into 60% of the U.S. birth cohort, positioned it well for competition from GlaxoSmithKline's Rotarix, which was approved by FDA in April 2008 and recommended by the ACIP in June 2008. However Rotarix, a humanized monovalent vaccine, is potentially more potent and requires only two vaccinations versus RotaTeq's three. Our vaccine consultants highlight that since the introduction of RotaTeq, rotavirus infections in the U.S. have dropped by 90% despite most infants only receiving one dose of RotaTeq; the implication of this is unclear given that there are no scientific data supporting the efficacy of a single dose of RotaTeq. We forecast RotaTeq sales of \$660MM (+4%) in 2014, \$690MM in 2015, \$720MM in 2016, \$780MM in 2018, and \$840MM in 2020.

Comparison Of Merck's Rotateq And Glaxo's Rotarix

	Rotateq	Rotarix
Company	Merck/SanofiAventis	GlaxoSmithKline
Valencies	G1, G2, G3, G4, G9P1A	G1P
Dose	3 x 2mL	2 x 1mL
Schedule	1st dose: 6-12 weeks 2nd dose: 4-10 week interval 3rd dose: 4-10 week interval; no later than 32 weeks	1st dose: 6 weeks 2nd dose after 4 weeks prior to 24 weeks
Indications where approved	Prevention of rotavirus gastroenteritis caused by G1, G2, G3, and G4 serotypes	Prevention of rotavirus gastroenteritis caused by G1, G3, G4, and G9 serotypes
Price per course (WAC)	\$225.60	\$213.15

Source: www.fda.gov, product labels, www.emea.europa.eu, PriceRx

CNS

Bridion Launched In Europe; Response To CRL Expected In 2014

Bridion (sugammadex) is a first-in-class novel modified gamma-cyclodextran, selective non-depolarizing neuromuscular blocker reversal agent. In July 2008, the European Commission approved Bridion for routine reversal of rocuronium and vecuronium, immediate reversal of rocuronium in adults, and routing reversal of rocuronium in children ages 2 to 17 years. Bridion has been launched in 47 countries including Japan. In August 2008, FDA issued a "not-approvable" letter for Bridion, citing issues primarily relating to hypersensitivity reactions. In May 2010, Merck stated

that Bridion results in a 20% increase in the aPTT. In addition to FDA's hypersensitivity concern, this has raised questions about the effects of the drug on blood coagulation.

Hypersensitivity is being assessed in a 450 patient Phase I study evaluating the potential for hypersensitivity symptoms at the time of initial exposure to sugammadex and upon repeat exposure. The study was initiated in February 2009, but subsequently had to be re-run; the data has not yet been made publicly available. The study evaluated 4mg/kg and 16mg/kg doses given at Days 8, 36, and 78. While this may address FDA's hypersensitivity concerns, it will not address the coagulation issue. If Merck is able to address FDA concerns, then the biggest barrier to Bridion's commercial success will be the availability of broadly adopted inferior generic reversal agents. These are likely to create a ceiling for Bridion's price, or alternatively limit its use. A CRL was issued on September 23, 2013, citing concerns about the operational aspect of the hypersensitivity study that was requested in 2008. Updated hypersensitivity data has been submitted, and the NDA is expected to be re-filed in H2:14. We forecast Bridion sales of \$330MM (+15%) in 2014, \$390MM in 2015, \$450MM in 2016, \$500MM in 2018, and \$550MM in 2020.

Belsomra (Suvorexant) Receives FDA Approval And Scheduling

In August 2014, Belsomra (suvorexant/MK-4305), an orexin receptor antagonist, was FDA approved for difficulty in falling and staying asleep. It was approved in four dosages: 5, 10, 15, and 20mg. The starting dose is 10mg with an increase to 15mg (elderly) and 20mg (non-elderly) in whom the 10mg dose is not effective. The 5mg dose is indicated for patients on CYP34A inhibitors. Belsomra was then reviewed by the DEA as it is a controlled substance (Schedule IV) and can be abused or lead to dependence and scheduled. In late August the DEA issued its final scheduling for Belsomra as a Class IV drug, which becomes effective 30 days after publication in the Federal Register. This will delay availability until late 2014/early 2015. Pricing will be announced upon launch. Suvorexant was filed in Japan; the E.U. filing strategy is under evaluation. The U.S. and Japan account for 70% of sleep agent usage. Belsomra sales are forecast at \$65MM in 2015, \$200MM in 2016, \$400MM in 2018, and \$600MM in 2020.

Orexin antagonists are proposed to offer similar efficacy to approved insomnia agents, but without many of the liabilities. Belsomra has a shorter half-life than GSK's Almorexant, which was discontinued in January 2011 likely due to its 18-hour half-life. GlaxoSmithKline has another orexin receptor antagonist (649868) in collaboration with HGSI, for sleep disorders in Phase II.

In May 2013, a FDA AdCom recommended approval of the 15mg (elderly) and 20mg (non-elderly) doses of suvorexant for the treatment of insomnia characterized by difficulties with sleep onset or maintenance. While higher doses (30mg and 40mg) were deemed effective, the AdCom voted against their safety profile. The panel recognized a need for new mechanisms for the treatment of insomnia, but expressed concerns around next day impairment

In July 2013, Merck received a CRL indicating that while effectiveness of suvorexant at doses of 10-40mg was established, the starting dose should be 10mg and the 10mg formulation must be available before approval may be granted; 15mg and 20mg doses would be appropriate for patients in whom the 10mg dose is not effective. For patients on CYP34A inhibitors, a 5mg dose is needed. Merck has formulated 5mg and 10mg doses and submitted data to the FDA in February 2014.

Higher Doses More Effective, But Also Less Safe

FDA questioned the efficacy of lower doses of suvorexant (10-20mg) and expressed concerns with the safety of higher doses (30-40mg). The committee ultimately voted in favor of the safety and efficacy of the proposed starting doses of 15-20mg, while voting against the safety of the 30-40mg doses.

AdCom Voting Summary

	Yes	No	Abstain
Efficacy for sleep onset	12	4	1
Efficacy for sleep maintenance	16	0	1
Safety 15-20mg	13	3	1
Safety 30-40mg	7	8	2

Source: 5/22/13 FDA AdCom

In June 2010, Merck presented data at the SLEEP 2010 APSS meeting from its randomized, double-blind, placebo-controlled Phase IIb study of MK-4305 that evaluated 10mg, 20mg, 40mg, and 80mg doses of MK-4305 compared to placebo in 503 patients with primary insomnia (10mg: n=62; 20mg: n=61; 40mg: n=59; 80mg: n=61; placebo: n=249). The study demonstrated that all four doses of MK-4305 achieved statistically significant increases from baseline in sleep efficiency of 6.2%, 6.6%, 11.6%, and 12.2% at one night and 4.7%, 10.4%, 7.9%, and 7.7% at 4-weeks for the 10mg, 20mg, 40mg, and 80mg doses of MK-4305, respectively, compared to placebo ($p<0.005$). The study also achieved its secondary endpoints of improvement in wake after sleep onset (WASO) and delay in time to persistent sleep (LPS) compared to placebo at night one and at four weeks of treatment. Patients receiving MK-4305 showed statistically significant reductions in baseline adjusted WASO compared to placebo across all four doses on night one with an LS mean difference of -26.9 minutes, -22.9 minutes, -33.2 minutes, and -37.9 minutes and after four weeks with an LS mean difference of -23.0 minutes, -26.9 minutes, -32.3 minutes, and -28.4 minutes for doses 10mg, 20mg, 40mg, and 80mg, respectively, compared to placebo ($p<0.0005$). Patients treated with MK-4305 also showed a statistically significant improvement from baseline in LPS vs. placebo at night one with an LS mean difference of -21.3 minutes and at four weeks with an LS mean difference of -10.7 minutes at the 80mg dose compared to placebo ($p<0.05$). Patients treated with MK-4305 also demonstrated an improvement in sleep onset at the 20mg dose at four weeks with an LS mean difference of -24.0 minutes and at the 40mg dose at night one with an LS mean difference of -21.6 minutes compared to placebo ($p<0.05$).

The study also showed that the compound was well tolerated with the most common treatment-related AEs (defined as $\geq 3\%$ incidence rate across multiple doses) in the study being upper respiratory tract infection, urinary tract infection, increased levels of alanine aminotransferase, increased levels of creatinine phosphokinase, dizziness, drowsiness upon awakening, headache, sedation, somnolence and vivid dreams. No serious AEs were observed in the study. In November 2011, Merck presented data where suvorexant demonstrated improvements in time to sleep onset and sleep maintenance with little next-day residual effect. The lack of a next-day effect was validated by a next-day driving study in elderly where both 15 and 30mg doses of suvorexant performed similarly to placebo and significantly better than zopiclone. At ACNP 2011, Merck presented a study comparing four doses (10, 20, 40, and 80mg) of suvorexant to other hypnotics on EEG power spectral profile. Merck reported that suvorexant had no effect on sleep EEG spectra relative to placebo. In contrast, three hypnotics (trazodone, zolpidem and the failed experimental drug gaboxadol) did

change EEG spectral profiles during sleep. Merck believes these data differentiate suvorexant from existing agents.

In April 2012, Merck presented several additional abstracts at SLEEP 2012 to support previously presented data. The abstracts supported the profile of suvorexant as an effective sleep enhancer that is devoid of ECG abnormalities and next-day impairment. Suvorexant improved several sleep parameters and demonstrated tolerability that was similar to that of placebo in a 12-month placebo-controlled safety and efficacy study. In an ECG study, patients were randomized to suvorexant or several hypnotic sleep medications. ECGs were taken during non-REM and REM sleep at day 1 and week 4. Suvorexant had limited effects on ECG profiles, which was in contrast to hypnotics. In the third study, elderly subjects were randomized to zopiclone or suvorexant for eight consecutive nights and several measures of driving performance were measured the next morning. Suvorexant did not produce any clinically meaningful changes relative to placebo, while zopiclone significantly impaired patients' next-day driving performance.

In February 2012, Merck announced completion of the Phase III program for suvorexant. Twelve-month Phase III data was presented at ESRS in September 2012. While the study was designed as a safety study without a primary efficacy endpoint, suvorexant improved time to sleep and significantly reduced time awake compared to placebo ($p<0.001$). Adverse events were evenly distributed amongst the treatment groups.

Our physician experts characterized the Phase III safety and efficacy data for suvorexant as robust. Suvorexant is expected to capture 16-20% of the insomnia market 12-months post launch given its superior mechanistic specificity compared to drugs that target the GABA system. Share gains will be driven by strong promotional efforts from Merck. Our physician experts believe that Suvorexant will take share from both Lunesta and Ambien/CR, but that the greatest opportunity will be in taking share from Lunesta.

BACE Inhibitor Advances To Phase III Trial In Alzheimer's Disease

Merck's BACE inhibitor, MK-8931 is currently in a Phase III trial in mild-to-moderate Alzheimer's disease (AD). Merck initially enrolled 200 patients in a Phase II trial to evaluate the safety of MK-8931 before transitioning to a 1,960 patient, 78-week Phase III trial (EPOCH). The primary endpoints for the EPOCH trial are ADAS-Cog (cognitive) and ADCS-ADL (functional). In December 2013, Merck announced that the Data Monitoring Committee (DMC) for the EPOCH study recommended that the trial continue to recruit patients, with no changes to the protocol. The DMC recommendation was post an interim safety look that included a safety cohort of 200 patients treated with MK-8931 for at least 3 months. Merck also announced that it will start a new Phase III study (APECS study) in prodromal Alzheimer's disease. The advancing development was not certain given that at least two other molecules targeting BACE have been dropped by other companies because of toxicity.

While MK-8931 has demonstrated >90% reduction in CSF β -Amyloid in healthy volunteers, our physician consultants believe BACE inhibitors will take longer to demonstrate efficacy compared to β -Amyloid antibodies such as solanezumab (LLY) as antibodies bind to monomers and oligomers and BACE inhibitors only prevent monomer formation. Given the modest efficacy of solanezumab in the 80-week EXPEDITION studies, the 78-week duration of EPOCH is a risk. Given that our physician consultants believe BACE inhibitors are most likely to be effective in patients

with prodromal-to-mild AD, the inclusion of moderate AD patients is also a risk. No efficacy data will be generated until Phase III is complete, implying sometime in 2016. We estimate MK-8931 sales of \$100MM in 2018 and \$300MM in 2020.

MK-8931 Unique Structure May Have Cleared The Toxicity Bar For Now

While it is difficult to draw conclusions from structural comparisons of the Lilly and Merck compounds targeting BACE, it is clear that the Merck compound (MK-8931) offers some very unique structural features not present in Lilly's LY2886721, which include:

1. a 6-membered cyclic N-methyl guanidine,
2. a central thiophene core ring that does not contain amide functional groups, and
3. a pyridine ring system that bears a methylacetylene substituent.

BACE Inhibition May Be Associated With Impaired Axonal Guidance

BACE1^{-/-} mice have been associated with a complex neuronal phenotype that remains poorly understood. The Journal of Biological Chemistry recently highlighted a paper by Hitt, *et al.* (*JBC*, Vol. 287, No. 46, pp. 38408–38425) that defines the role of BACE in hippocampal axonal guidance. BACE1^{-/-} mice exhibit impaired neuronal outgrowth in brain regions associated with memory formation, prompting the authors to raise the question of whether pharmacological BACE inhibition could be associated with deficits in adult neurogenesis and/or regenerating neural systems. While CNS deficits in BACE1^{-/-} mice are mild and BACE inhibitors have been shown to be relatively safe in humans, the potential for BACE inhibitors to limit neuronal outgrowth in Alzheimer's patients is a risk.

Loss Of BACE Results In Impaired Axonal Outgrowth In Memory-Associated Areas Of The Brain, But...

Investigators observed that mossy fibers had significantly reduced intrapyramidal bundle (IPB) length in BACE1^{-/-} mice. Dentate gyrus granule cells undergo adult neurogenesis and require ongoing axonal guidance throughout adulthood and mossy fiber axon projections from the dentate gyrus granule cells to CA3 pyramidal neurons is a plastic process that is critical for memory formation. Additionally, longer IPB bundles have been associated with improved memory performance. While highly speculative, these data may suggest that impaired BACE activity could negatively impact memory in adults.

...Adverse BACE^{-/-} Phenotype Is Mild And May Be Acceptable Given The Unmet Medical Need

The authors note that these data add a note of caution to the development of BACE inhibitors for the treatment of Alzheimer's disease, but also present several arguments that suggest that BACE inhibitors may have an acceptable risk-benefit profile:

- The BACE1^{-/-} phenotype in mice is very mild and only present in BACE1^{-/-} homozygotes (equivalent to 100% BACE1 inhibition) while only 50% BACE inhibition is hypothesized to delay or prevent amyloid deposition;
- BACE phenotypes may be primarily related to developmental impact and may not be relevant to BACE inhibition in adult humans;
- BACE inhibitors have been shown to be relatively safe in humans thus far; and

- Given the devastating impact of AD on patients and society, a “modicum of side effect risk” may be acceptable if BACE inhibitors provide a sufficient benefit.

Respiratory

Allergy Immunotherapy Tablet (AIT) A Niche Opportunity

Schering-Plough acquired the U.S. license to develop a sub-lingual tablet-based immunotherapy for grass and ragweed allergy from Alk Abello. Alk Abello markets the tablet as Grazax in select European countries. Merck notes that ~30MM individuals in North America are affected by seasonal allergies of which the most common are grass/ragweed pollen and dust mites.

Grastek And Ragwitek Approved In U.S.

In April 2014, The FDA approved both Grastek (the U.S. name for the Timothy grass pollen allergen extract) for use in patients age 5-65 years, and Ragwitek (ragweed extract) for use in patients 18-65 years. The committee also recommended that adrenaline auto-injectors should be available for the patients at home.

Merck and Alk Abello are also working on a house dust mite product, MK-8237, which recently reported positive Phase II data and has started a Phase III study. We estimate Ragwitek sales of \$10MM in 2014, \$40MM in 2015, \$80MM in 2016, \$160MM in 2018, and \$240MM in 2020 and Grastek sales of \$10MM in 2014, \$40MM in 2015, \$80MM in 2016, \$160MM in 2018, and \$240MM in 2020.

Grazax sublingual tablets contain a standardized extract of grass pollen allergen from Timothy grass (*Phleum pratense*). It is not fully understood how Grazax works. However, the grass pollen extract is thought to stimulate the body's immune system to produce antibodies against grass pollen. These antibodies can then bind to any grass pollen that one might encounter during the grass pollen season and prevent it from causing allergic symptoms. The allergy must be diagnosed with a positive skin prick test and/or specific IgE test to grass pollen. The therapy will only work in people with this specific allergy. To have the greatest effect, the tablets should be started four months before the grass pollen season starts. However, some effect will still be seen if they are started at least two to three months before the season begins. The tablets are taken once a day and should be continued all year round for three years. The most common allergic responses are itching in the mouth and ears, throat irritation, sneezing and swelling in the mouth. Sublingual immunotherapy is not recommended in patients with active autoimmune or malignant conditions. There is no hard evidence that these conditions can be made worse by immunotherapy.

AIT is currently approved in the E.U. for children and adults (ages 5-65) with grass pollen allergy. In August 2011, Merck announced that two pivotal clinical Phase III studies with AIT met the combined primary efficacy endpoint of reducing allergy symptoms and use of concomitant symptom relieving medication. The studies also showed that the treatment was well tolerated, with adverse events experienced by subjects receiving the drug similar to previous studies in adults, with no new or unexpected findings. European Phase III studies showed sustained efficacy with disease modifying effects for up to 2 years. In Phase III, AIT significantly reduced the total combined score that measured nasal and eye symptoms, and use of rescue allergy medicines in ragweed-allergic adults with or without asthma; the study was conducted during the peak of ragweed pollen season.

Singulair Decline Annualized In U.S. And E.U.

Singulair (montelukast) was the #2 asthma controller globally. In asthma, Singulair's benefits include oral administration, reduced daytime symptoms, nighttime awakenings, reduced asthma attacks, and improved quality of life with a safe side-effect profile. Singulair is also marketed for the treatment of the symptoms of seasonal allergic rhinitis (SAR; also known as hay fever), perennial allergic rhinitis (or indoor allergies) in adults and children 6 months of age or older, and for exercise-induced bronchoconstriction. Our physician experts view Singulair as only modestly effective in SAR. In June 2009, FDA required that the manufacturers include a precaution in the drug labeling, and patients and healthcare professionals be made aware of the potential for neuropsychiatric events (suicidality) with these medications. Merck had previously updated Singulair's label to reflect these findings. Singulair's patent expired in 8/12 in the U.S. and 2/13 in the E.U. The patent in Japan expires in 10/16. In May 2014, an FDA panel rejected the proposed OTC use of Singulair for the treatment of allergic rhinitis in adults 18yrs and older. The panel expressed concerns for potential off-label use in pediatric and asthma patients as well as neuropsychiatric side effects; the panel did not believe these issues/risks could be adequately addressed in labeling. Despite sale of the OTC business to Bayer, Merck retains rights to Singulair OTC. We forecast Singulair sales of \$1,040MM (-13%) in 2014, \$940MM in 2015, \$835MM in 2016, \$630MM in 2018, and \$430MM in 2020.

Dulera Marketed For Asthma In U.S.; E.U. Development For COPD Only

Dulera, the foradil/mometasone combination, is approved in the U.S. for the treatment of asthma in children over 12 years of age. The marketing application for Dulera (under the brand name Zenhale) has been withdrawn in the E.U. as a result of Merck's inability to address the CHMP's request to provide data within the timeframe allowed. The Phase III pivotal studies met the primary endpoints in mild and severe asthma. Dulera is available in a MDI with a dose counter. Dulera is dosed twice-daily, which is identical to Advair (GSK) and Symbicort (AZN). Merck presented results from two 26-week investigational Phase III clinical studies evaluating the efficacy and safety of two dose strengths of Dulera in adults 40 years and older with moderate to very severe COPD at CHEST 2011. The two dose strengths evaluated in the studies were Dulera 100 mcg/5 mcg and Dulera 200 mcg/5 mcg, both administered as two inhalations twice daily (i.e. 200 mcg/10 mcg and 400 mcg/10 mcg, twice daily). In both studies, Dulera 200 mcg/10 mcg and Dulera 400 mcg/10 mcg significantly improved lung function as measured by forced expiratory volume in one second (FEV1) area under the curve over 0-12 hours (AUC0-12hr) at Week 13 (one of the co-primary endpoints) compared to treatment with mometasone furoate 400 mcg (administered as two inhalations of mometasone furoate 200 mcg twice daily), the primary treatment comparison for this endpoint, or placebo alone.

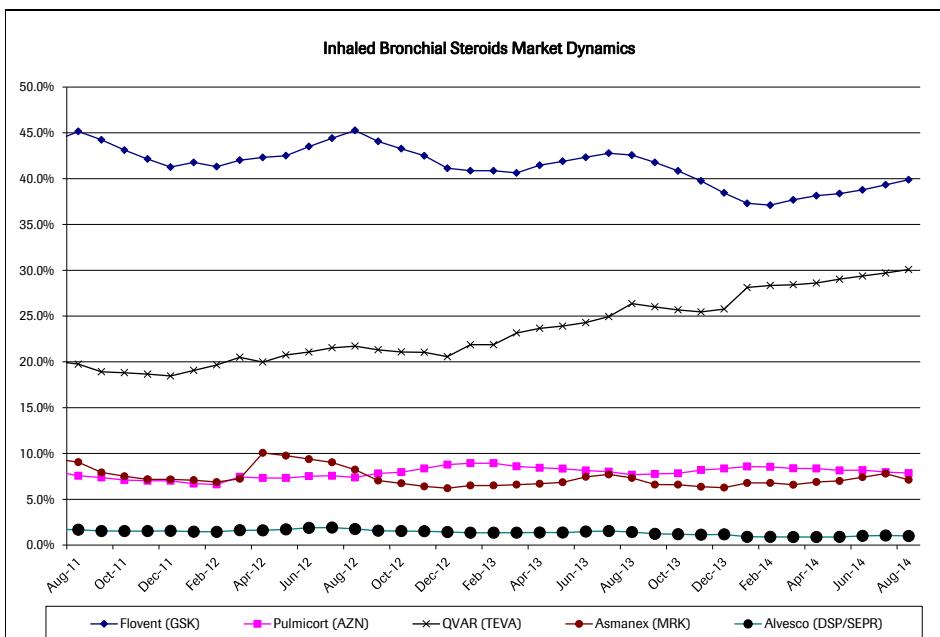
In February 2012, Merck received a CRL for Dulera's COPD indication and has discontinued trials for this indication. We estimate Dulera sales of \$435MM (+34%) in 2014, \$525MM in 2015, \$595MM in 2016, \$715MM in 2018, and \$835MM in 2020.

Asmanex A Niche Product In Asthma

Asmanex, a once-daily inhaled ICS, has benefited from concerns over long acting beta-agonists (LABAs). The Asmanex device is viewed as effective and easy to use, although not particularly intuitive. In May 2009, Schering and Novartis announced a restructuring of their respiratory collaboration. Schering assumed exclusive rights to develop and commercialize the twice-daily fixed-combination of mometasone plus

formoterol (MFF) using a pMDI device. Novartis assumed development responsibility for the once-daily indacaterol/mometasone combination. The agreement provides for a royalty sharing arrangement based on sales. Asmanex is protected by device and use patents that expire in 2017 and 2014, respectively. In 2008, FDA approved Asmanex Twisthaler 110 mcg for the maintenance treatment of asthma as a preventive therapy in patients 4 to 11 years of age, broadening the label. Our Asmanex sales forecasts are \$195MM (+6%) in 2014, \$175MM in 2015, \$160MM in 2016, \$140MM in 2018, and \$120MM in 2020.

Inhaled Bronchial Steroids Market Dynamics



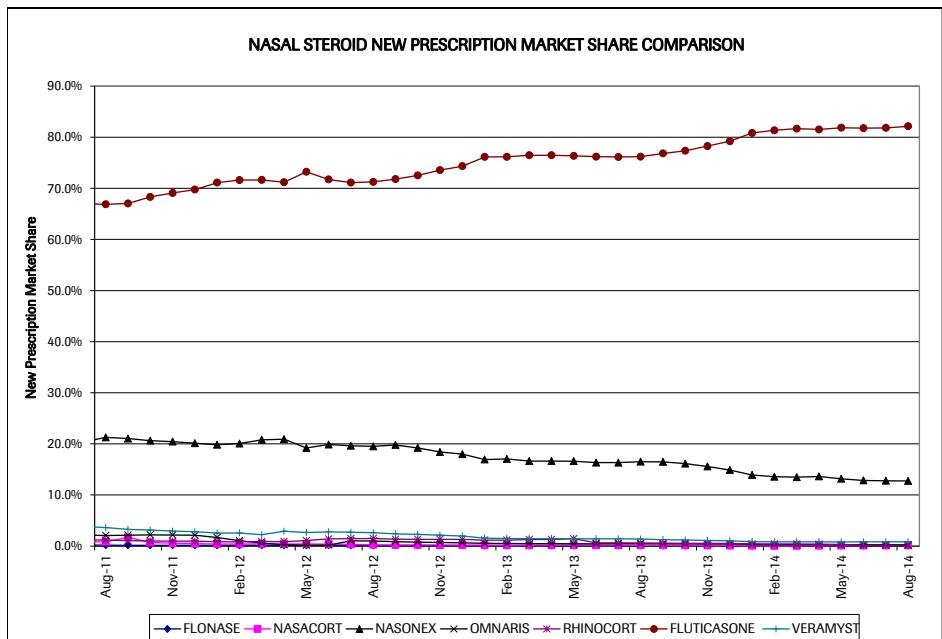
Source: IMS America

Nasonex At Risk To Generic Competition At Any Time

Nasonex growth has slowed due to the availability of multiple Flonase (GlaxoSmithKline) generics and once-daily Veramyst (GlaxoSmithKline). Veramyst has a marginally broader indication than Nasonex with data supporting relief of ocular symptoms in seasonal allergic rhinitis. However, fluticasone generics are a greater source of competition. Nasonex's patent expired in April 2014 in the E.U. and April 2018 (formulation patent) in the U.S. There are three patents in the Orange Book. Two expired in July 2014 (including pedi) and they are both methods patents (5837699 and 6723713). The third (6127353) expires in April 2018 (including pedi) and includes compound claims to the monohydrate salt; claim to composition; claim to excipients; and claim to the x-ray crystallography form. These claims cite improved stability, although there are no details on what is improved. In June 2012, in litigation with Apotex, a U.S. District Court judge ruled that Merck "failed to present credible evidence of infringement," but also denied Apotex's claim that the patent was invalid. In October 2012, Merck appealed the decision and in June 2013 the Court of Appeals affirmed the district court's decision; Merck has now exhausted all of its appeal options. However, to date, Apotex does not have final approval. In July 2014, Merck filed a patent infringement suit against Teva which automatically stays FDA approval until November 2016 or an adverse court decision. Nasonex sales are forecast to be

\$1,095MM (-18%) in 2014, \$950MM in 2015, \$850MM in 2016, \$650MM in 2018, and \$450MM in 2020.

Nasal Steroid New Prescription Market Share Comparison



Source: IMS America

Claritin Sold To Bayer As Part Of Consumer Business

Claritin's (seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria) market share in the U.S. has declined to nearly zero. The Claritin composition-of-matter patent expired in October 2007, but it had market exclusivity until December 2009. Claritin generics launched in July 2012. Claritin was sold to Bayer as part of the OTC sale, for \$14.2B. The deal is expected to close in H2:14. We forecast Claritin/Claritin sales of \$370MM (-16%) in 2014 with no sales thereafter.

Women's Health

NuvaRing A Winner, But Liability Cases Continue To Build

NuvaRing is an intra-vaginal contraceptive. NuvaRing is inserted for 21 days and a new ring is inserted after a 7-day break. If insertion of the ring is not an issue, NuvaRing's excellent bleeding profile, favorable side-effect profile, and convenience have made it the contraceptive of choice for both patients and physicians. One "side-effect" is an increased vaginal discharge, but this has been associated with a decrease in bacterial vaginosis, a vaginal infection. Recent reports suggest a thromboembolic side-effect profile in line with low dose OCPs. NuvaRing is also being used off-label for up to 5 weeks. Our Obgyn consultant estimates that NuvaRing is used by about 10% of eligible females in the age group 18 to 35 years. Once a patient starts NuvaRing, the continuation rate is about 90%, suggesting high satisfaction. We estimate NuvaRing sales of \$725MM (+6%) in 2014, \$775MM in 2015, \$850MM in 2016, \$250MM in 2018, and \$50MM in 2020 (4/18 patent expiry).

Watson's Vaginal Ring Poses A Threat To NuvaRing

Our Obgyn consultant believes that Watson/Population Council's vaginal ring could gain significant share of the vaginal ring contraception market given that it is more convenient (fewer trips to the pharmacy) and potentially better priced. The ring, which contains two hormonal products—ethinyl Estradiol and Nestorone, a synthetic progestin—is currently in Phase III clinical development. Our consultant noted that the ring simultaneously releases Nestorone along with a low dose of ethinyl estradiol for up to 13 cycles (one full year). Nestorone also provides a theoretical advantage over the steroids used in NuvaRing. Nestorone is not absorbed orally and therefore would be safe in mothers who use the ring while breast-feeding since their babies will not absorb the Nestorone. Our consultant also noted that hygiene was a concern (because the Watson/Population Council ring has to be cleaned and reinserted each month), but the required maintenance is manageable. Therefore, our consultant predicts that there will be a fairly receptive audience to the product.

NuvaRing Settlement Pending

Beginning in May 2007, complaints were filed in various jurisdictions asserting that Organon/Schering failed to adequately warn patients against the increased VTE risk associated with NuvaRing. As of June 30, 2014, there were approximately 1,940 NuvaRing cases. Of these cases, approximately 1,720 are pending in the NuvaRing MDL in the U.S. District Court for the Eastern District of Missouri before Judge Rodney Sippel, and 210 are pending in consolidated discovery proceedings in the Bergen County Superior Court of New Jersey before Judge Brian R. Martinotti. Several additional cases are pending in various other state courts.

Merck recently reached a settlement agreement to resolve 95% of all cases filed and all cases unfiled but under retainer as of February 7, 2014 for a lump sum of \$100MM. The vast majority of plaintiffs opted into the settlement. The agreement became effective on June 4, 2014. Merck has an unspecified amount of insurance coverage being utilized for legal fees and funding of settlement.

Merck A Leader In Animal Health

Merck Animal Health is the second-largest player in animal health with \$3.36B (-1%) in sales in 2013. The portfolio is well diversified with a balanced mix of companion animal and food animal segments and a robust pipeline. In May, Merck received FDA approval for Bravecto (fluralaner), a chewable flea and tick tablet for use in dogs. Our animal health expert believes Merck Animal Health is well positioned to grow organically and that the failure to combine with Merial refocused attention on growing operating margins (currently low 20% range). Merck has said it is evaluating strategic options for this business; however, with Lilly's pending acquisition of Novartis Animal Health, and Merck's strong market position, we think it increasingly likely that Merck retains and perhaps even expands this segment. We forecast Animal Health sales of \$3.42B (+2%) in 2014, \$3.575B (+5%) in 2015, \$3.73B in 2016, \$4.04B in 2018, and \$4.35B in 2020. This implies 4% compound growth during 2014-20.

Consumer Business Sold To Bayer

In May 2014, Merck announced that it will be selling its Consumer products business (2014E revenue \$1.91B) to Bayer for \$14.2B in cash. The transaction is expected to close in H2:14. Management stated that while it was a good business, it did not have global scale necessary to compete effectively.

AZN Exercised JV Option; JV Ended On June 30

In June 2012, Merck and Astra (AZN) announced they have amended the option related to AZLP. As part of the agreement, Astra did not exercise the option to acquire Merck's partnership in the joint venture in 2012. Merck granted Astra a new second option exercisable in 2014 for \$327MM based on forecasts for sales of Nexium and Prilosec in the U.S. and a payment equal to 10x the average of Merck's 1% annual profit allocation from 2011-13 (estimated at \$80MM). As a result of the amendment, Merck will continue to record supply sales and equity income from AZLP through mid-2014. Astra has exercised its option and the JV closed on June 30, 2014. Therefore, there is no contribution for the JV in our models post Q2:14.

EPS Flat In 2014-15, Recover In 2016, Decline 2017, Before Rebound In 2018-20

EPS Estimated To Be Flat In 2014

Even with the Singulair U.S. patent expiration annualized, Merck still faces top line pressures from competitive dynamics involving Januvia, Isentress, and Victrelis, as well as continued erosion in other products. But driven by Merck's restructuring initiatives, EPS should stay flat despite a 4% decline in sales. We forecast operating expenses of \$17.465B in 2014, which is \$2.9B below the 2012 level. This consists of SG&A of \$10.615B (\$1.8B below 2012) and R&D of \$6.845B (\$1.1B below 2012). We estimate a 0.3pp decline in gross PM to 74.0%, reduced non-operating expenses of \$200MM vs. \$455MM in 2013 (despite termination of the AZLP JV as of mid year), and a lower share count (2,951MM vs. 2,996MM in 2013). We do factor in a higher tax rate (24.5% vs. 21.8% in 2013). All told, we forecast EPS at \$3.50 (flat) on sales of \$42.4B (-4%).

Merck Guidance Versus Our Estimates

	Merck 2014 Guidance	Our 2014 Forecasts
Total Revenues #	\$42.4 - 43.2B @ CER	\$42.4B (-4%)
Gross P.M.	Slightly lower than 74.3% (in H1 ~73%; in H2 ~ improve)	74.0%
SG&A	Below 2013	\$10.615B (-9%)
R&D	Below 2013 but H2:14 somewhat higher than H2:13	\$6.845B (-4%)
Tax Rate *	24-26%	24.5%
EPS	\$3.43-3.53	\$3.50
Share Count	FY share count slightly lower than 2.95B	2.95B

* Does not include R&D Tax Credit; # Reflects sale of Consumer

Source: Cowen and Company

On October 1, 2013, Merck announced a restructuring of its operations to reduce its cost base (including workforce reductions, facility closings) and better target its R&D efforts on products with the greatest commercial potential. The company expects net annual cost savings of \$2.5B by the end of 2015 (\$1B by the end of 2014) using 2012 as the base year. Our 2014 operating expense forecast is \$2.9B below 2012, substantially more aggressive than management guidance. Pre-tax cost of the restructuring is estimated at \$2.5-3B.

Merck 2013-15 P&L Buildup (\$MM)

	2013			2014E			2015E		
	Sales	Op. Pft.	P.M.	Sales	Op. Pft.	P.M.	Sales	Op. Pft.	P.M.
Total Merck Sales	\$44,030	\$13,902	31.6%	\$42,400	\$13,941	32.9%	\$38,630	\$13,390	34.7%
Interest Income		264			240			520	
Interest Expense		(801)			(745)			(690)	
Exchange		(290)			(54)			0	
Minority Int.		(5)			0			0	
Pretax Equity Income		132			78			0	
After Tax Equity Income		52			58			65	
Pretax Priority Return		220			110			0	
Equity Income - Affiliates		404			246			65	
Other		(27)			113			105	
Total Non-Op.		-\$455			-\$200			\$0	
Pretax Income		\$13,447	30.5%		\$13,741	32.4%		\$13,390	34.7%
As Reported Tax Rate		21.8%			24.5%			23.9%	
Net Income		\$10,442			\$10,317			\$10,192	
EPS BASIC		\$3.53			\$3.54			\$3.55	
Shares (MM) - BASIC		2,962			2,912			2,870	
EPS DILUTED		\$3.49			\$3.50			\$3.50	
Shares (MM) - DILUTED		2,996			2,951			2,915	

Source: Company reports, Cowen and Company

EPS Flat Again In 2015, But Rebound In 2016

We project EPS to remain flat in 2015, before ramping up in 2016 off the depressed base. This assumes a 9% top-line decline in 2015 due to sale of Consumer business (expected to close late 2014) and a 1% decline in revenue in 2016, a 2.3pp improvement in gross profit margin in 2015 reflecting absence of lower-margin Consumer business and a 0.5pp improvement in 2016, declining operating expenses, improvement in non-operating income despite termination of AZLP, a tax rate of 23.9%, and a declining share count (by roughly 1% per year). All told, we peg EPS at \$3.50 (flat) in 2015 and \$3.80 (+9%) in 2016.

Post A Down Year In 2017, Good Growth Should Be On Tap Through 2020

EPS is estimated to be down 1% in 2017 reflecting a 1% decline in sales due to patent expirations on Zetia and Vytorin. Thereafter, we look for 7-8% EPS growth on 2-4% revenue growth. Gross profit margin should rise during this time, with even greater increases in operating margin. We forecast a flat tax rate and declining share count (by 50MM shares per year) through 2020. EPS are pegged at \$3.75 (-1%) in 2017, \$4.05 (+8%) in 2018, and \$4.70 in 2020. All told, Merck's 2014-20 EPS CAGR is 5%, just below the average for the sector.

Speculation On 2013-20 EPS Outcomes

2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2013-16		2013-20		2014-20	
								CGR	CGR	CGR	Comments		
Newer Drugs/Vaccines	\$0.11	\$0.16	\$0.32	\$0.56	\$0.87	\$1.22	\$1.57	\$1.95	72%	51%	52%	- V503, MK-3475, Simponi, Bridion, Dulera, Suvorexant, Odanacatib, anacetrapib most critical	
Remicade/Simponi	0.27	0.32	0.33	0.34	0.35	0.36	0.37	0.39	8%	5%	3%	- Crohn's, UC, RA, AS, PA, early RA, psoriasis; patent expires in 2/15; biosimilar exposure in 20% of MRK's markets	
Singular	0.12	0.10	0.10	0.09	0.08	0.07	0.06	0.05	-9%	-11%	-11%	- Asthma/allergy	
Vytorin/Zetia	0.42	0.43	0.42	0.40	0.19	0.14	0.09	0.04	-1%	-28%	-32%	- Ezetimibe generic 12/16; IMPROVE-IT data in 9/14	
AZLP Revenues	0.18	0.09	0.00	0.00	0.00	0.00	0.00	0.00	NM	NM	NM	- Assumes AZN exercises option in June 2014, 90% GPM, 35% tax rate	
Other Pharma	1.99	2.00	2.14	2.19	2.02	2.00	1.98	1.96	3%	0%	0%	- Moderate growth thru 2016	
Total Pharma	3.08	3.10	3.30	3.58	3.52	3.80	4.07	4.40	5%	5%	6%	- In line with MRK overall	
Joint Ventures - Equity	0.11	0.07	0.02	0.02	0.02	0.02	0.03	0.03	-44%	-17%	-14%	- Sanofi-Pasteur JV post Q3:11	
Animal Health	0.15	0.16	0.18	0.19	0.21	0.23	0.25	0.28	9%	9%	9%	- SGP Animal Health; Merial included in Equity Income in 2011 but deleted thereafter	
Consumer	0.15	0.16	0.00	0.00	0.00	0.00	0.00	0.00	NM	NM	NM	- Sold to Bayer AG for \$14.2B or \$8.9B after tax; deal to close in H2:14	
EPS - DILUTED	\$3.49	\$3.60	\$3.50	\$3.80	\$3.75	\$4.05	\$4.35	\$4.70	3%	4%	5%	- Versus +4%, +6% and +8% industry averages	
% Change	-9%	0%	0%	9%	-1%	8%	7%	8%					
EPS - BASIC	3.53	3.64	3.55	3.88	3.82	4.14	4.48	4.83	3%	5%	5%		
% Change	-9%	0%	0%	9%	-1%	8%	8%	8%					

Source: Cowen and Company

Merck Key Upcoming Events

Time Frame	Event Type	Product	Event
2014	Clinical	Vytorin	IMPROVE-IT data at AHA
		Pembrolizumab	Data at San Antonio Breast Cancer Symposium (Dec. 9-13)
		MK-5172/MK-8742	Interim data on Phase II and short-duration triplet trial at AASLD (Nov. 7-11)
	Regulatory	Bridion	Re-file NDA in H2:14
		V503	Approval; 9 valent HPV vaccine
		V419	E.U. and U.S. filings 2014; pedi hexavalent vaccine
		Vaniprevir	Japan approval chronic HCV
Corporate	Consumer		Sale to Bayer AG for \$14.2B (\$8-9B after tax); H2:14 close; will update financial guidance then

Source: Company data

Merck 2013-20 P&L Buildup (\$MM)

	Total Sales	% Chg	Gross P.M.	SG&A \$MM	%SIs	R&D \$MM	%SIs	Oper. P.M.	Non-Op	Pretax P.M.	Tax Rate	Net Income	EPS	Y/Y % Chg	Shares (MM)
Q1	\$10,671	-9%	74.4%	\$2,947	27.6%	\$1,862	17.4%	29.3%	(\$149)	27.9%	12.5%	\$2,585	\$0.85	-14%	3,053
Q2	11,010	-11%	75.7%	3,105	28.2%	1,853	16.8%	30.7%	(98)	29.8%	21.9%	2,530	0.84	-20%	3,010
Q3	11,032	-4%	74.0%	2,752	24.9%	1,651	15.0%	34.1%	(70)	33.4%	25.3%	2,728	0.92	-3%	2,960
Q4	<u>11,319</u>	-4%	73.0%	<u>2,869</u>	25.3%	<u>1,758</u>	15.5%	32.1%	<u>(138)</u>	30.9%	25.8%	<u>2,599</u>	<u>0.88</u>	5%	2,959
2013	\$44,030	-7%	74.3%	\$11,673	26.5%	\$7,124	16.2%	31.6%	(\$455)	30.5%	21.8%	\$10,442	\$3.49	-9%	2,996
Q1	\$10,264	-4%	74.1%	\$2,692	26.2%	\$1,523	14.8%	33.0%	\$163	34.6%	26.0%	\$2,603	\$0.88	3%	2,971
Q2	10,934	-1%	72.6%	2,897	26.5%	1,621	14.8%	31.3%	(91)	30.4%	24.2%	2,493	0.85	1%	2,949
Q3E	10,450	-5%	74.5%	2,445	23.4%	1,800	17.2%	33.9%	(135)	32.6%	23.9%	2,592	0.88	-5%	2,945
Q4E	<u>10,760</u>	-5%	75.0%	<u>2,581</u>	24.0%	<u>1,901</u>	17.7%	33.4%	<u>(137)</u>	32.1%	23.9%	<u>2,628</u>	<u>0.89</u>	2%	2,940
2014E	\$42,400	-4%	74.0%	\$10,615	25.0%	\$6,845	16.1%	32.9%	(\$200)	32.4%	24.5%	\$10,317	\$3.50	0%	2,951
Q1E	\$9,185	NM	75.8%	\$2,430	26.5%	\$1,450	15.8%	33.5%	(\$10)	33.4%	23.9%	\$2,335	\$0.80	-9%	2,930
Q2E	9,765	NM	75.8%	2,630	26.9%	1,550	15.9%	33.0%	(5)	32.9%	23.9%	2,447	0.84	-1%	2,920
Q3E	9,560	NM	76.8%	2,170	22.7%	1,725	18.0%	36.1%	0	36.1%	23.9%	2,623	0.90	2%	2,910
Q4E	<u>10,115</u>	NM	76.8%	<u>2,300</u>	22.7%	<u>1,825</u>	18.0%	36.0%	<u>15</u>	36.2%	23.9%	<u>2,787</u>	<u>0.96</u>	7%	2,900
2015E	\$38,630	NM	76.3%	\$9,530	24.7%	\$6,550	17.0%	34.7%	\$0	34.7%	23.9%	\$10,192	\$3.50	0%	2,915
2016P	\$38,435	-1%	76.8%	\$8,660	22.5%	\$6,600	17.2%	37.1%	\$77	37.3%	23.9%	\$10,918	\$3.80	9%	2,875
2017P	\$37,940	-1%	76.3%	\$8,800	23.2%	\$6,400	16.9%	36.3%	\$149	36.7%	23.9%	\$10,592	\$3.75	-1%	2,825
2018P	\$38,765	2%	76.9%	\$8,750	22.6%	\$6,500	16.8%	37.5%	\$222	38.1%	23.9%	\$11,244	\$4.05	8%	2,775
2019P	\$39,940	3%	77.1%	\$8,900	22.3%	\$6,600	16.5%	38.3%	\$295	39.0%	23.9%	\$11,866	\$4.35	7%	2,725
2020P	\$41,660	4%	77.3%	\$9,250	22.2%	\$6,800	16.3%	38.8%	\$368	39.7%	23.9%	\$12,584	\$4.70	8%	2,675

Source: Company data, Cowen and Company estimates

Merck Product Line Quarterly Sales Buildup (\$MM)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
CARDIOVASCULAR															
Anacetrapib															
Zetia - U.S.	334	351	369	400	1,454	323	408	370	400	1,500	320	400	360	395	1,475
Zetia - Int'l	295	299	293	317	1,204	288	309	290	315	1,200	285	300	285	310	1,180
Zetia - Global	629	650	662	717	2,658	611	717	660	715	2,705	605	700	645	705	2,655
Cozaar/Hyzaar - U.S.	11	5	11	9	36	6	8	5	5	25	5	5	5	5	20
Cozaar/Hyzaar - Int'l	256	250	227	237	970	199	206	170	160	735	150	140	130	120	540
Cozaar/Hyzaar - Global	267	255	238	246	1,006	205	214	175	165	760	155	145	135	125	560
Vytorin - U.S.	156	170	165	182	673	120	158	145	160	585	100	140	115	130	485
Vytorin - Int'l	238	247	232	253	970	241	259	230	250	980	230	245	220	240	935
Vytorin - Global	394	417	397	435	1,643	361	417	375	410	1,565	330	385	335	370	1,420
Integriulin - U.S.	43	44	41	42	170	32	36	35	35	140	30	30	30	30	120
Integriulin - Int'l	4	4	4	4	16	5	4	5	0	15	5	5	5	0	15
Integriulin - Global	47	48	45	46	186	37	40	40	35	150	35	35	35	30	135
Zocor - U.S.	6	6	6	7	25	5	5	5	5	20	5	5	5	0	15
Zocor - Int'l	76	68	59	73	276	59	63	55	55	230	50	50	45	45	190
Zocor - Global	82	74	65	80	301	64	68	60	60	250	55	55	50	45	205
Adempas								10	15	25	20	20	30	30	100
Vericiguat															
Zontivity								10	15	25	20	20	25	25	90
Vasotec	42	42	42	40	166	35	36	30	30	130	25	25	25	25	100
Adalat	1	1	2	1	5	1	1	2	1	1	1	1	2	1	5
Nitro-Dur	1	1	2	1	5	1	1	2	1	5	1	1	2	1	5
Mevacor	2	2	4	2	10	1	1	2	1	5	1	1	2	1	5
Other	10	10	5	5	30	10	5	4	7	25	7	7	4	7	25
TOTAL CARDIOVASCULAR	\$1,475	\$1,500	\$1,462	\$1,573	\$6,010	\$1,326	\$1,500	\$1,370	\$1,455	\$5,650	\$1,255	\$1,395	\$1,290	\$1,365	\$5,305
% Chg	-7%	-10%	0%	-6%	-8%	-6%	-5%	-7%	-6%	-6%	-5%	-7%	-6%	-6%	-6%
CNS															
Belsomra											\$5	\$10	\$20	\$30	\$65
Bridion	63	69	75	82	288	73	82	85	90	330	90	95	100	105	390
MK-8931															
MK-7622															
Remeron - U.S.	1	1	1	3	6	1	1	2	1	5	1	1	2	1	5
Remeron - Int'l	51	52	43	54	200	49	39	40	40	170	45	35	35	35	150
Remeron - Global	52	53	44	57	206	50	40	42	41	175	46	36	37	36	155
Maxalt/Maxalt MLT - U.S.	9	14	14	1	38	5	1	5	5	15	5	5	0	0	10
Maxalt/Maxalt MLT - Int'l	32	29	27	24	111	15	22	15	15	65	10	10	10	10	40
Maxalt/Maxalt MLT - Global	41	43	41	25	149	20	23	20	20	85	15	15	10	10	50
Zemuron	30	30	29	28	117	28	25	20	20	95	20	20	15	15	70
Sinemet	1	1	2	1	5	1	1	2	1	5	1	1	2	1	5
Taloxa	1	1	2	1	5	1	1	2	1	5	1	1	2	1	5
Saphris	40	40	39	39	158	25	23		50						
TOTAL CNS	\$227	\$236	\$232	\$233	\$928	\$198	\$195	\$171	\$173	\$745	\$178	\$178	\$186	\$198	\$740
% Chg	-35%	-13%	-17%	-26%	-26%	-20%	-10%	-9%	-9%	-10%	-9%	-9%	-14%	-14%	-1%

Source: Company data, Cowen and Company estimates

Merck Product Line Quarterly Sales Buildup (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
ANTI-INFECTIVES															
Isentress - U.S.	\$187	\$217	\$227	\$250	\$881	\$190	\$228	\$235	\$255	\$910	\$190	\$225	\$230	\$250	\$895
Isentress - Int'l	175	195	199	192	761	200	225	220	210	855	190	215	210	200	815
Isentress - Global	362	412	427	442	\$1,643	390	453	455	465	1,765	380	440	440	450	1,710
Noxafil - U.S.	18	22	23	43	106	20	35	30	45	130	25	40	35	50	150
Noxafil - Int'l	47	49	52	55	203	54	63	60	65	240	60	65	65	70	260
Noxafil - Global	65	71	75	98	309	74	98	90	110	370	85	105	100	120	410
MK-5172															
MK-8742															
IDX21437															
Actoxumab/bezlotoxumab															
Vaniprevir															
MK-7655															
Doravirine															
Letermovir															
PEG-Intron A - U.S.	9	13	9	11	42	4	8	5	5	20	5	5	5	0	15
PEG-Intron A - Int'l	117	129	95	113	454	108	95	75	80	360	100	85	65	70	320
PEG-Intron A - Global	126	142	104	124	496	112	103	80	85	380	105	90	70	70	335
Intron A	40	40	41	41	162	30	36	35	35	135	25	30	30	30	115
Ribavirin/Rebetol	19	19	18	18	74	13	19	15	15	60	10	15	10	10	45
Intron Franchise	185	201	163	183	732	155	158	130	135	580	140	135	110	110	495
Victrelis - U.S.	37	52	45	25	159	5	1	0	0	5	0	5	0	0	5
Victrelis - Int'l	73	64	75	57	269	54	46	45	40	185	40	35	35	30	140
Victrelis - Global	110	116	120	82	428	59	47	45	40	190	40	40	35	30	145
Cancidas - U.S.	7	8	7	9	31	7	4	5	5	20	5	5	5	0	15
Cancidas - Int'l	156	155	144	175	629	159	152	140	170	620	140	140	100	80	460
Cancidas - Global	163	163	151	184	660	166	156	145	175	640	145	145	105	80	475
Invanz - U.S.	54	61	70	66	251	60	64	70	70	265	70	70	70	75	285
Invanz - Int'l	57	59	59	62	237	54	71	65	60	250	70	70	70	70	280
Invanz - Global	111	120	129	128	488	114	135	135	130	515	140	140	140	145	565
Primaxin - U.S.	4	4	8	3	19	3	0	5	5	15	5	5	5	5	20
Primaxin - Int'l	80	81	80	76	316	68	81	70	65	285	60	70	60	50	240
Primaxin - Global	84	85	88	79	335	71	81	75	70	295	65	75	65	55	260
Crixivan/Stocrin	39	39	39	38	155	24	37	30	30	120	20	30	25	25	100
Avelox - U.S.	33	27	34	35	130	20	2	0	0	20					
Avelox - Int'l	2	2	3	2	10	5	0	0	0	5					
Avelox - Global	36	29	38	37	140	25	2	0	0	25					
Garamycin	5	5	5	5	20	5	5	0	5	15	5	0	5	0	10
Cipro Line	1	1	2	1	5	1	1	2	1	5	1	1	2	1	5
Netromycin	1	1	2	1	5	1	1	2	1	5	1	1	2	1	5
Isepacin	1	1	1	1	4	1	1	1	1	5	1	1	1	1	4
Other	14	14	14	14	56	14	15	15	12	55	12	12	15	12	51
TOTAL ANTI-INFECTIVES	\$1,176	\$1,257	\$1,254	\$1,293	\$4,980	\$1,100	\$1,190	\$1,125	\$1,175	\$4,585	\$1,035	\$1,125	\$1,050	\$1,040	\$4,250
% Chg					-4%	-6%	-5%	-10%	-9%	-8%	-6%	-5%	-7%	-11%	-7%

Source: Company data, Cowen and Company estimates

Merck Product Line Quarterly Sales Buildup (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E	
ANTI-INFLAMMATORY																
Remicade (ex-U.S.)	\$549	\$527	\$574	\$620	\$2,271	\$604	\$607	\$625	\$675	\$2,510	\$580	\$580	\$600	\$650	\$2,410	
Simponi (ex-U.S.)	108	120	126	146	500	157	174	165	175	670	180	200	190	200	770	
Arcoxia (ex-U.S.)	121	121	112	131	484	128	141	120	140	530	140	150	130	150	570	
TOTAL ANTI-INFLAMMATORY	\$778	\$768	\$812	\$897	\$3,255	\$889	\$922	\$910	\$990	\$3,710	\$900	\$930	\$920	\$1,000	\$3,750	
% Chg					14%	14%	20%	12%	10%	14%	1%	1%	1%	1%	1%	
ONCOLOGY																
Pembrolizumab MK-2206											\$15	\$15	\$25	\$50	\$75	\$100
Zolinza	7	7	7	6	27	7	8	10	10	35	10	10	15	15	50	
Emend - U.S.	66	74	73	80	293	70	78	75	85	310	75	35	30	30	170	
Emend - Int'l	50	61	49	54	214	52	66	55	55	230	55	30	30	30	145	
Emend - Global	116	135	122	134	507	122	144	130	140	535	130	65	60	60	315	
Temodar - U.S.	108	108	71	17	304	0	5	0	0	5	0	0	0	0	0	
Temodar - Int'l	108	111	91	95	405	83	88	75	70	315	65	60	55	50	230	
Temodar - Global	216	219	162	111	708	83	93	75	70	320	65	60	55	50	230	
Ethyol	2	3	2	3	10	2	2	2	3	10	2	3	2	3	10	
Leucomax	2	3	2	3	10	2	2	2	3	10	2	3	2	3	10	
Fulexin	1	1	2	1	5	1	1	2	1	5	1	1	2	1	5	
TOTAL ONCOLOGY	\$344	\$368	\$297	\$258	\$1,267	\$217	\$250	\$221	\$242	\$930	\$235	\$192	\$211	\$232	\$870	
% Chg					-13%	-37%	-32%	-26%	-6%	-27%	8%	-23%	-5%	-4%	-6%	
RESPIRATORY																
Nasonex - U.S.	\$150	\$177	\$179	\$174	\$681	\$133	\$141	\$150	\$150	\$575	\$120	\$130	\$130	\$130	\$510	
Nasonex - Int'l	235	148	118	153	654	179	117	100	125	520	150	100	90	100	440	
Nasonex - Global	385	325	297	327	1,335	312	258	250	275	1,095	270	230	220	230	950	
Dulera - U.S.	66	75	78	91	309	97	98	105	110	410	115	120	125	130	490	
Dulera - Int'l	3	4	4	5	15	5	5	5	10	25	5	10	10	10	35	
Dulera - Global	68	79	82	95	324	102	103	110	120	435	120	130	135	140	525	
Singulair - U.S.	1	15	29	16	61	5	8	5	5	25	5	5	5	0	15	
Singulair - Int'l	336	266	252	282	1,136	266	275	225	250	1,015	240	250	205	230	925	
Singulair - Global	337	281	280	298	1,196	271	283	230	255	1,040	245	255	210	230	940	
Ragwitek						1	5	5	10	5	20	10	5	5	40	
Grastek						1	5	5	10	20	10	5	5	5	40	
MK-8237																
MK-1029																
Asmanex - U.S.	34	44	39	45	162	35	48	40	45	170	30	45	35	45	155	
Asmanex - Int'l	6	5	4	6	22	5	5	10	5	25	5	5	5	5	20	
Asmanex - Global	40	49	43	51	184	40	53	50	50	195	35	50	40	50	175	
Proventil	41	41	41	41	164	30	34	40	35	140	30	35	35	30	130	

Source: Company data, Cowen and Company estimates

Merck Product Line Quarterly Sales Buildup (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
RESPIRATORY - continued															
Clarinex - U.S.	6	2	6	5	19	6	5	5	0	15					
Clarinex - Int'l	55	63	48	50	216	56	64	45	45	210					
Clarinex - Global	61	65	54	55	235	62	69	50	45	225					
Claritin (ex-U.S.)	61	33	31	44	169	35	37	25	20	115					
Claritin D	15	5	6	9	35	15	5	5	5	30					
Total Claritin and Claritin D	76	38	37	53	204	50	42	30	25	145					
Total Claritin/Clarinex Franchise	137	103	91	108	439	112	111	80	70	370					
Foradil	13	13	14	13	53	10	10	10	20	50	10	10	10	15	45
Unidur/Theo-Dur	1	1	2	1	5	1	1	2	1	5	1	1	2	1	5
Other	18	18	17	17	70	15	15	13	14	55	14	14	8	9	45
TOTAL RESPIRATORY	\$1,041	\$911	\$867	\$951	\$3,770	\$893	\$870	\$795	\$850	\$3,405	\$750	\$755	\$675	\$715	\$2,895
% Chg					-42%	-14%	-4%	-8%	-11%	-10%	-16%	-13%	-15%	-16%	-15%
DIABETES/METABOLIC															
Januvia/Janumet - U.S.	\$659	\$806	\$701	\$780	\$2,946	\$687	\$801	\$730	\$810	\$3,030	\$685	\$795	\$695	\$795	\$2,970
Januvia/Janumet - Int'l	634	740	668	844	2,886	642	776	685	810	2,920	645	775	680	805	2,905
Januvia/Janumet - Global	1,293	1,546	1,369	1,624	5,832	1,334	1,577	1,415	1,620	5,945	1,330	1,570	1,375	1,600	5,875
Odanacatib															
Omarigliptin															
Ertugliflozin															
MK-1293															
TOTAL DIABETES/METABOLIC	\$1,293	\$1,546	\$1,369	\$1,624	\$5,832	\$1,334	\$1,577	\$1,415	\$1,620	\$5,945	\$1,330	\$1,570	\$1,375	\$1,600	\$5,875
% Chg					2%	3%	2%	3%	0%	2%	0%	0%	-3%	-1%	-1%
VACCINES															
Zostavax - U.S.	\$152	\$122	\$169	\$210	\$653	\$129	\$116	\$170	\$250	\$665	\$135	\$130	\$175	\$275	\$715
Zostavax - Int'l	16	19	16	54	105	13	40	20	65	140	15	45	25	75	160
Zostavax - Global	168	141	185	264	758	142	156	190	315	805	150	175	200	350	875
V-503															
ProQuad, MMR II, Varivax - U.S.	246	301	386	238	1,172	240	276	390	260	1,165	245	280	395	280	1,200
ProQuad, MMR II, Varivax - Int'l	26	38	35	35	134	40	50	45	45	180	45	55	50	50	200
ProQuad, MMR II, Varivax - Global	272	339	421	273	1,306	280	326	435	305	1,345	290	335	445	330	1,400
RotaTeq - U.S.	130	98	154	88	470	130	101	155	95	480	135	105	155	95	490
RotaTeq - Int'l	32	46	47	41	166	39	46	50	45	180	45	50	55	50	200
RotaTeq - Global	162	144	201	129	636	169	147	205	140	660	180	155	210	145	690
Gardasil - U.S.	247	252	548	248	1,295	271	294	600	275	1,440	250	250	250	250	1,000
Gardasil - Int'l	142	131	117	146	536	112	115	150	150	525	100	100	100	100	400
Gardasil - Global	390	383	665	394	1,831	383	409	750	425	1,965	350	350	350	350	1,400
V-419															
V-212															
V-114															
Pneumovax - U.S.	86	80	149	176	491	83	85	150	175	495	85	85	175	175	520
Pneumovax - Int'l	25	28	44	65	162	18	17	45	70	150	20	20	50	75	165
Pneumovax - Global	111	108	193	241	853	101	102	195	245	645	105	105	225	250	685
TOTAL VACCINES	\$1,103	\$1,115	\$1,665	\$1,301	\$5,184	\$1,075	\$1,140	\$1,775	\$1,430	\$5,420	\$1,260	\$1,305	\$1,620	\$1,615	\$5,800
% Chg					9%	-3%	2%	7%	10%	5%	17%	14%	-9%	13%	7%

Source: Company data, Cowen and Company estimates

Merck Product Line Quarterly Sales Buildup (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
OPHTHALMOLOGY															
Trusopt/Cosopt - U.S.	\$4	\$5	\$5	\$3	\$17	\$1	\$0			\$0					
Trusopt/Cosopt - Int'l	102	98	100	100	400	98	99			195					
Trusopt/Cosopt - Global	105	103	105	103	\$416	99	99			\$195					
Zioptan	13	12	12	11	48	11	11			20					
Restasis	9	9	9	8	35	10	10			20					
Timoptic/Timoptic XE	20	10	10	10	50	17	10			25					
AzaSite	4	4	3	3	14					0					
TOTAL OPHTHALMOLOGY	\$151	\$138	\$139	\$135	\$563	\$137	\$130			\$260					
% Chg					-7%	-9%	-6%								
DERMATOLOGY															
Elocon	\$33	\$33	\$33	\$33	\$132	\$32	\$30	\$30	\$30	\$120	\$30	\$30	\$25	\$25	\$110
Diprolene	30	30	30	30	120	32	36	30	30	130	30	30	25	25	115
Valisone	10	10	5	5	30	10	10	5	5	30	10	10	5	5	30
Diprosone	1	1	2	1	5	0	0	5	0	5	0	0	5	0	5
Lotrisone	1	1	2	1	5	0	0	5	0	5	0	0	5	0	5
Other	10	10	10	15	45	10	10	10	10	40	10	10	10	5	35
TOTAL DERMATOLOGY	\$85	\$85	\$82	\$85	\$337	\$84	\$86	\$85	\$75	\$330	\$80	\$80	\$80	\$60	\$300
% Chg					-6%	-1%	1%	4%	-12%	-2%	-5%	-7%	-6%	-20%	-9%
CONTRACEPTION/WOMEN'S HEALTH															
Implanon - U.S.	\$42	\$51	\$50	\$62	\$205	\$60	\$67	\$65	\$75	\$265	\$65	\$75	\$70	\$80	\$290
Implanon - Int'l	42	51	46	59	198	42	52	45	60	200	45	55	50	65	215
Implanon - Global	84	102	96	121	\$403	102	119	110	135	465	110	130	120	145	505
NOMAC/E2	2	2	3	3	10	7	8	10	10	35	10	10	15	15	50
MK-8342B															
MK-8342															
MK-8175A															
Elonva	5	5	5	5	20	7	7	10	10	35	10	10	10	15	45
NuvaRing - U.S.	89	107	106	123	425	103	112	115	120	450	110	115	120	130	475
NuvaRing - Int'l	62	64	64	70	261	65	66	70	75	275	70	75	75	80	300
NuvaRing - Global	151	171	170	193	686	168	178	185	195	725	180	190	195	210	775
Mercilon	25	25	25	25	100	20	23	25	25	95	20	20	20	25	85
Follistim AQ - U.S.	41	62	55	23	181	34	30	30	20	115	20	20	20	20	80
Follistim AQ - Int'l	81	73	69	78	301	76	72	65	75	290	65	65	30	30	190
Follistim AQ - Global	122	134	124	101	481	110	102	95	95	400	85	85	50	50	270
Cerazette - U.S.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cerazette - Int'l	61	48	51	50	208	40	45	35	35	155	25	25	25	25	100
Cerazette - Global	61	48	51	50	208	40	45	35	35	155	25	25	25	25	100
Marvelon	29	29	28	27	113	20	25	25	25	95	20	20	20	20	80
Lival	29	29	28	28	114	27	25	25	25	105	25	20	20	20	85
TOTAL CONTRACEPTION/WOMEN'S HEALTH	\$508	\$545	\$530	\$553	\$2,135	\$501	\$534	\$520	\$555	\$2,110	\$485	\$510	\$475	\$525	\$1,995
% Chg					4%	-1%	-2%	-2%	0%	-1%	-3%	-4%	-9%	-5%	-5%

Source: Company data, Cowen and Company estimates

Merck Product Line Quarterly Sales Buildup (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
OTHER															
Proscar - U.S.	\$1	\$1	\$1	\$1	\$4	\$1	\$1	\$2	\$1	\$5	\$1	\$1	\$2	\$1	\$5
Proscar - Int'l	38	58	37	47	180	34	42	30	40	145	30	35	25	35	125
Proscar - Global	39	58	38	48	183	35	43	32	41	150	31	36	27	36	130
Fosamax - U.S.	5	4	7	4	20	4	6	5	5	20	5	5	5	5	20
Fosamax - Int'l	132	140	133	135	540	119	116	110	110	455	90	80	80	80	330
Fosamax - Global	137	144	140	139	560	123	122	115	115	475	95	85	85	85	350
Propecia - U.S.	6	5	7	6	24	5	5	0	5	15	5	0	0	5	10
Propecia - Int'l	62	62	64	70	258	69	53	50	50	220	50	50	40	40	180
Propecia - Global	68	67	71	77	283	74	58	50	55	235	55	50	40	45	190
Pepcid	1	1	2	1	5	1	1	2	1	5	1	1	2	1	5
Astra Merck (U.S.)	262	245	220	193	920	147	316			465					
Pharmaceutical Ingredients/diversified brands	93	93	92	92	370										
Other MRK and SGP Products	480	591	517	604	2192	771	545	565	665	2545	650	650	650	650	2600
TOTAL OTHER	\$1,080	\$1,199	\$1,080	\$1,154	\$4,513	\$1,151	\$1,085	\$764	\$877	\$3,875	\$832	\$822	\$804	\$817	\$3,275
% Chg					-1%	7%	-10%	-29%	-24%	-14%	-28%	-24%	5%	-7%	-15%
ANIMAL HEALTH															
Animal Health - U.S.	\$231	\$219	\$207	\$198	\$855	\$177	\$185	\$180	\$180	\$720	\$195	\$205	\$200	\$200	\$800
Animal Health - Int'l	609	632	593	673	2,507	636	687	650	725	2,700	650	700	675	750	2,775
Animal Health - Global	840	851	800	871	3,362	813	872	830	905	3,420	845	905	875	950	3,575
% Chg						-3%	2%	4%	4%	2%	4%	4%	5%	5%	5%
CONSUMER CARE															
Claritin OTC - U.S.	\$146	\$108	\$90	\$66	\$410	\$139	\$110	\$105	\$75	\$430					
Claritin OTC - Int'l	31	(29)	33	26	61	31	44	35	25	135					
Claritin OTC - Global	177	78	123	92	471	170	154	140	100	565					
Other Consumer Care - U.S.	\$254	\$282	\$192	\$188	916	\$251	\$296	\$205	\$200	950					
Other Consumer Care - Int'l	140	128	127	111	507	125	133	125	115	500					
Other Consumer Care - Global	394	412	320	300	1,423	376	429	330	315	1,450					
TOTAL CONSUMER CARE	\$571	\$490	\$443	\$392	\$1,894	\$546	\$583	\$470	\$415	\$2,015					
% Chg					-3%	-4%	19%	6%	6%	6%					
TOTAL SALES	\$10,671	\$11,010	\$11,032	\$11,319	\$44,030	\$10,264	\$10,934	\$10,450	\$10,760	\$42,400	\$9,185	\$9,765	\$9,560	\$10,115	\$38,630
% Chg					-7%	-4%	-1%	-5%	-5%	-4%	NM	NM	NM	NM	

Source: Company data, Cowen and Company estimates

Merck Product Line Annual Sales Buildup (\$MM)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
CARDIOVASCULAR											
Anacetrapib				\$300	\$600	\$900	\$1,200	NM	NM - CETP-inhib; excellent HDL elevation, LDL reduction; 30,000 patient REVEAL Phase III concludes 1/17, multiple interim looks, 1st in 2015		
Zetia - U.S.	1,454	1,500	1,475	1,400	550	400	275	135	-2.4%	share 6/14; patent expires 4/17 but Glenmark to enter in 12/16	
Zetia - Int'l	1,204	1,200	1,180	1,150	450	350	225	115	-33%	-29%	- Ezetimibe
Zetia - Global	2,658	2,705	2,655	2,550	1,000	750	500	250	-	-	
Cozaar/Hyzaar - U.S.	36	25	20	15	15	10	10	5			
Cozaar/Hyzaar - Int'l	920	735	540	450	400	350	300	250			
Cozaar/Hyzaar - Global	1,006	760	560	465	415	360	310	255	-17%	-18%	- ARB; hypertension; generic competition
Vytorin - U.S.	673	585	485	400	300	200	100	50		-0.9%	share 6/14
Vytorin - Int'l	920	980	935	815	450	300	150	50			
Vytorin - Global	1,643	1,565	1,420	1,215	750	500	250	100	-37%	-33%	- Ezetimibe/simvastatin; IMPROVE-IT data available end 2014/early 2015; SHARP a boost; Eze/atorva approved
Integriulin - U.S.	170	140	120	100	80	60	40	20			
Integriulin - Int'l	16	15	15	15	10	10	5	5			
Integriulin - Global	186	150	135	115	90	70	45	25	-26%	-25%	- U.S. revenue repurchased from Millenium
Zocor - U.S.	25	20	15	10	5	5	5	5			
Zocor - Int'l	276	230	190	150	100	50	25	5			
Zocor - Global	301	250	205	160	105	55	30	15	-37%	-35%	- Cholesterol reduction; patents expired in most developed markets
Adempas											
Vericiguat											
Zontivity											
Vasotec	166	130	100	75	50	25	10	5	-42%	-39%	- U.S. patent expired 8/00; little erosion in Japan despite patent lapse
Adalat	5	5	5	5	5	5	5	5	0%	0%	- Antihypertensive; generic competition
Nitro-Dur	5	5	5	5	5	5	5	5	0%	0%	- No AB-rated generic competition yet; patent exp. 2/10
Mevacor	10	5	5	5	5	5	5	5	0%	-9%	- Generics launched 12/01
Other	30	25	25	25	20	20	15	10	3%	0%	
TOTAL CARDIOVASCULAR	\$6,010	\$5,650	\$5,305	\$4,855	\$3,025	\$2,770	\$2,545	\$2,510	-13%	-12%	
% Chg	-7%	-6%	-6%	-8%	-38%	-8%	-8%	-1%			
CNS											
Belsomra											
Bridion	288	330	390	450	475	500	525	550	NM	NM - Suvorexant; insomnia; orexin neuropeptide; approved; likely tier 3 coverage; filed in Japan; not yet filed in EU	
MK-8931										10%	- Sugammadex (MK-8616); anesthesia reversal agent; approved in EU; pending in Japan; U.S. NDA refiled, hypersensitivity data filing in 2014
MK-7622										NM	- BACE inhibitor; Alzheimer's disease; Phase III
Zemuron										NM	- Adjunctive treatment of symptomatic therapy of Alzheimer's; Phase II
Remeron - U.S.	6	5	5	5	5	5	5	5			
Remeron - Int'l	200	170	150	130	110	90	70	50		-17%	- Antidepressant; patent expired January 2010 but majority of sales ex-U.S.
Remeron - Global	206	175	155	135	115	95	75	55	-18%		
Maxalt/Maxalt MLT - U.S.	38	15	10	5	5	5	5	5			- Patents expired 12/12 U.S.
Maxalt/Maxalt MLT - Int'l	111	65	40	30	20	10	5	5			- Patents expired 2/13 EU
Maxalt/Maxalt MLT - Global	149	85	50	35	25	15	10	10	-30%	-32%	- 5HT1 agonist for migraine
Zinemet	5	5	5	5	5	5	5	5	0%	0%	- Parkinson's Disease; foreign sales; U.S. bulk sales to Dupont
Taloxa	5	5	5	5	5	5	5	5	0%	0%	- Usage only in refractory patients
Saphris	158	50							NM	NM - Antipsychotic; U.S. rights divested to Forest for \$240MM; closed 1/17/14	
TOTAL CNS	\$928	\$745	\$740	\$880	\$955	\$1,130	\$1,375	\$1,630	14%	8%	
% Chg	-35%	-20%	-1%	19%	9%	18%	22%	19%			

Source: Company data, Cowen and Company estimates

Merck Product Line Annual Sales Buildup (\$MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
ANTI-INFECTIVES											
Isentress - U.S.	\$881	\$910	\$895	\$875	\$850	\$825	\$800	\$775			- 74.9% share 6/14; qD in Phase III
Isentress - Int'l	761	855	815	775	725	675	625	575			
Isentress - Global	\$1,643	1,765	1,710	1,650	1,575	1,500	1,425	1,350	-4%	-3%	- HIV integrase inhibitor; treatment resistant and naive approved; Gilead QUAD and GSK Tivicay pose competition
Noxafil - U.S.	106	130	150	170	190	210	230	250			
Noxafil - Int'l	203	240	260	280	300	320	340	360			
Noxafil - Global	309	370	410	450	490	530	570	610	9%	10%	- Posaconazole; oral antifungal; approved for prophylaxis and oral candidiasis
MK-5172				50	250	500	500	500	NM	NM	- Protease inhibitor (NS3) for hepatitis C; solid data across pt types in combo with MK-8742; short course tx explored; PIII in Q2:14
MK-8742				50	250	500	500	500	NM	NM	- NS5a for hepatitis C; solid data across pt types in combo with MK-5172; short course tx explored; Phase III in Q2:14
IDX21437					150	300	500	500	NM	NM	- Nuc for hep C; via \$3.85B Idenix acquisition; Phase I/II 7 day POC data shows 4 log drop in genotypes 1-3
Actoxumab/bezlotoxumab				100	150	200	250	300	NM	NM	- MK-3415A; combination tx for C. difficile associated diarrhea (CDAD); Phase III; NDA 2015; with Medarex/MA Biologic Labs
Vaniprevir			15	50	75	100	125	150	NM	NM	- MK-7009; hepatitis C protease inhibitor; under review in Japan
MK-7655					25	50	75	100	NM	NM	- Bacterial infections; Phase II
Doravirine					25	50	75	100	NM	NM	- MK-1439; NNRTI for HIV; will be advancing to Phase III; dosed qD with good safety
Letermovir					25	50	75	100	NM	NM	- MK-8228; CMV prophylaxis in transplant patients; Phase III
PEG-Intron A - U.S.	42	20	15	10	5	5	5	5			
PEG-Intron A - Int'l	454	360	320	270	200	150	100	50			
PEG-Intron A - Global	496	380	335	280	205	155	105	55	-28%	-27%	- Roche's Pegasys/Copegus pressures; new drugs clip duration of therapy
Intron A	162	135	115	90	70	50	30	10	-35%	-33%	- Supported by use in oncology applications
Ribavirin/Rebetol	74	60	45	30	20	10	5	5	-34%	-32%	- Pressured by generic competition
Intron Franchise	732	580	495	400	295	215	140	70	-30%	-28%	
Victrelis - U.S.	159	5	5	0	0	0	0	0			
Victrelis - Int'l	269	185	140	95	65	50	35	15			
Victrelis - Global	428	190	145	95	65	50	35	15	-35%	-38%	- Boceprevir; hepatitis C NS3 protease inhibitor; oral; pressure from all-oral, riba-free regimens
Cancidas - U.S.	31	20	15	10	5	5	5	5			- U.S. patent expires 7/26/15
Cancidas - Int'l	629	620	460	250	150	50	25	5			
Cancidas - Global	660	640	475	260	155	55	30	10	-50%	-45%	- Antifungal; qD, IV; new indications but price and share erosion due to competition
Invanz - U.S.	251	265	285	130	75	25	15	5			- U.S. patent expires November 2015
Invanz - Int'l	237	250	280	120	75	25	10	5			
Invanz - Global	488	515	565	250	190	50	25	10	-48%	-43%	- Broad spectrum carbapenem; oral, IM, IV, qD
Primaxin - U.S.	19	15	20	10	10	5	5	5			
Primaxin - Int'l	316	285	240	200	160	120	80	50			
Primaxin - Global	335	295	260	210	170	125	85	55	-24%	-23%	- Bolstered sales effort blunts erosion; patent expires 9/09
Crixivan/Stocrin	155	120	100	75	50	25	15	5	-41%	-39%	- Protease inhibitor for AIDS; Stocrin in certain fgn mkts; patent exp.: 5/12
Avelox - U.S.	130	20									
Avelox - Int'l	10	5									
Avelox - Global	140	25									- Quinolone antibiotic; respiratory tract infections; via Bayer; Patent exp.: 3/14
Garamycin	20	15	10	5	5	5	5	5	-17%	-18%	- Older aminoglycoside antibiotic
Cipro Line	5	5	5	5	5	5	5	5	0%	0%	- Quinolone antibiotic; UTI; XL patent expired in 2006; IR off patent; via Bayer strategic alliance
Netromycin	5	5	5	5	5	5	5	5	0%	0%	- Aminoglycoside antibiotic
Isepacin	4	5	4	4	4	4	4	4	-4%	0%	- Older aminoglycoside antibiotic
Other	56	55	51	56	56	56	56	56	0%	0%	- Older antibiotics
TOTAL ANTI-INFECTIVES	\$4,980	\$4,585	\$4,250	\$3,715	\$3,825	\$4,225	\$4,300	\$4,450	0%	-2%	
% Chg	-4%	-8%	-7%	-13%	3%	10%	2%	3%			

Source: Company data, Cowen and Company estimates

Merck Product Line Annual Sales Buildup (\$MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
ANTI-INFLAMMATORY											
Remicade (ex-U.S.)	\$2,271	\$2,510	\$2,410	\$2,300	\$2,200	\$2,100	\$2,000	\$1,900	-5%	-3%	- Crohn's, UC, RA, AS, PA, early RA, psoriasis; patent expires in 2/15; biosimilar exposure in 20% of MRK's markets
Simponi (ex-U.S.)	500	670	770	875	975	1,075	1,175	1,275	11%	14%	- Golimumab; RA, AS, PA, UC; with JNJ; approved in EU and Canada
Arcxia (ex-U.S.)	484	530	570	610	650	690	730	770	6%	7%	- Not approvable in the U.S.; marketed in 63 countries
TOTAL ANTI-INFLAMMATORY	\$3,255	\$3,710	\$3,750	\$3,785	\$3,825	\$3,865	\$3,905	\$3,945	1%	3%	
% Chg	14%	14%	1%	1%	1%	1%	1%	1%			
ONCOLOGY											
Pembrolizumab		\$15	\$250	\$500	\$750	\$1,000	\$1,500	\$2,000	NM	NM - PD-1 antibody; melanoma PDUFA 10/28/14, EU filing by YE, work continues in Japan; many other tumor types in development	
MK-2206					50	100	150	200	NM	NM - Cancer; ALK inhibitor; Phase II	
Zolinza	27	35	50	60	70	80	90	100	19%	21% - SAHA; cutaneous T-cell lymphoma rollout underway; 60 clinical trials underway	
Emend - U.S.	293	310	170	150	155	160	50	30			
Emend - Int'l	214	230	145	120	125	130	50	20			
Emend - Global	507	535	315	270	280	290	100	50	-33%	-28% - Aprepitant; substance P antagonist; emesis; patent expires April 2015 (oral) and March 2019 (IV); franchise 50/50 oral/IV	
Temodar - U.S.	304	5	0	0	0	0	0	0			
Temodar - Int'l	405	315	230	150	100	50	25	5			
Temodar - Global	708	320	230	150	100	50	25	5	-50%	-51% - Chemotherapeutic; AA, GBM	
Ethyol	10	10	10	10	10	10	10	10	0%	0% - Cytoprotective for reducing kidney toxicity post chemotherapy; Int. only	
Leucotamax	10	10	10	10	10	10	10	10	0%	0% - Launched in all major markets (except U.S. and Japan)	
Eulexin	5	5	5	5	5	5	5	5	0%	0% - Competition in the U.S., patent expirations overseas clip	
TOTAL ONCOLOGY	\$1,267	\$930	\$870	\$1,005	\$1,275	\$1,545	\$1,890	\$2,380	17%	9%	
% Chg	-13%	-27%	-6%	16%	27%	21%	22%	26%			
RESPIRATORY											
Nasonex - U.S.	\$681	\$575	\$510	\$450	\$400	\$350	\$300	\$250			
Nasonex - Int'l	654	520	440	400	350	300	250	200			
Nasonex - Global	1,335	1,095	950	850	750	650	550	450	-14%	-14% - Allergic rhinitis	
Dulera - U.S.	309	410	490	550	600	650	700	750			
Dulera - Int'l	15	25	35	45	55	65	75	85			
Dulera - Global	324	435	525	595	655	715	775	835	11%	14% - Mometasone/formoterol	
Singulair - U.S.	61	25	15	10	5	5	5	5			
Singulair - Int'l	1,136	1,015	925	825	725	625	525	425			
Singulair - Global	1,196	1,040	940	835	730	630	530	430	-14%	-14% - Asthma/allergy	
Ragwitek		10	40	80	120	160	200	240	70%	NM - Ragweed allergies; targets June pollen season; SL approved; North American rights from ALKO Abello	
Grastek		10	40	80	120	160	200	240	70%	NM - Grass pollen allergies; targets March grass pollen season; SL approved; North American rights from ALKO Abello	
MK-8237					25	50	75	100	125	NM - Allergy, house dust mite; Phase III	
MK-1029							50	75	100	NM - Asthma; Phase II	
Asmanex - U.S.	162	170	155	145	135	125	115	105			
Asmanex - Int'l	22	25	20	15	15	15	15	15			
Asmanex - Global	184	195	175	160	150	140	130	120	-8%	-6% - Asthma; dry powder, QD, inhaled corticosteroid	
Proventil	164	140	130	115	100	85	70	55	-14%	-14% - Beta agonist; asthma; CFC to HFA complete	

Source: Company data, Cowen and Company estimates

Merck Product Line Annual Sales Buildup (\$MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
RESPIRATORY - continued											
Clarinex - U.S.	19	15									
Clarinex - Int'l	216	210									
Clarinex - Global	235	225									
Claritin (ex-U.S.)	169	115									
Claritin D	35	30									
Total Claritin and Claritin D	204	145									
Total Claritin/Clarinex Franchise	439	370									
Foradil	53	50	45	40	35	30	25	20	-14%	-13%	- Sold to Bayer AG for \$14.2B, or \$8-9B after tax, as part of Consumer transaction; deal to close in H2:14
Unidur/Theo-Dur	5	5	5	5	5	5	5	5	0%	0%	- Asthma; SGP books sales and pays royalty to Novartis from COGS line; SGP relaunched in U.S.
Other	70	55	45	40	35	30	25	20	-16%	-16%	- Older products in Europe
TOTAL RESPIRATORY	\$3,770	\$3,405	\$2,895	\$2,825	\$2,750	\$2,730	\$2,685	\$2,640	-4%	-5%	
% Chg	-42%	-10%	-15%	-2%	-3%	-1%	-2%	-2%			
DIABETES/METABOLIC											
Januvia/Janumet - U.S.	\$2,946	\$3,030	\$2,970	\$2,950	\$2,900	\$2,850	\$2,800	\$2,750			- NRx sh 5.4% 6/14; competition undifferentiated; Janumet XR approved 2/12; MK0431D approved 10/11
Januvia/Janumet - Int'l	2,886	2,920	2,905	2,850	2,800	2,750	2,700	2,650			
Januvia/Janumet - Global	5,832	5,945	5,875	5,800	5,700	5,600	5,500	5,400	-2%	-1%	- QD antidiabetic; TECOS data anticipated by YE or early 2015
Odanacatib					100	200	300	400	NM	NM	MK-0822; osteoporosis; arthritis; cathepsin K inhibitor; compelling efficacy, concerning safety; NDA filing in 2015
Omarigliptin						100	200	300	NM	NM	Diabetes; qweek DPP4 inhibitor; Phase III; filing in Japan by YE
Ertugliflozin						100	200	300	NM	NM	MK-8835; diabetes; SGLT2 inhibitor; Phase III; with PFE
MK-1293							50	75	NM	NM	Diabetes mellitus; Phase III
TOTAL DIABETES/METABOLIC	\$5,832	\$5,945	\$5,875	\$5,900	\$6,100	\$6,350	\$6,575	\$6,800	2%	2%	
% Chg	2%	2%	-1%	0%	3%	4%	4%	3%			
VACCINES											
Zostavax - U.S.	\$653	\$665	\$715	\$775	\$825	\$875	\$925	\$975			- U.S. backorders resolved
Zostavax - Int'l	105	140	160	180	200	220	240	260			- International launches in 2013
Zostavax - Global	758	805	875	955	1,025	1,095	1,165	1,235	7%	7%	- Herpes zoster vaccine; adults 60+ years
V-503					750	1600	1900	2000	2100	2,200	NM
ProQuad, MMR II, Varivax - U.S.	1,172	1,165	1,200	1,250	1,300	1,350	1,400	1,450			
ProQuad, MMR II, Varivax - Int'l	134	180	200	220	240	260	280	300			
ProQuad, MMR II, Varivax - Global	1,306	1,345	1,400	1,470	1,500	1,550	1,600	1,650	3%	3%	- Could be supported by health initiatives
RotaTeq - U.S.	470	480	490	500	510	520	530	540			
RotaTeq - Int'l	166	180	200	220	240	260	280	300			
RotaTeq - Global	636	660	690	720	750	780	810	840	4%	4%	- Rotavirus vaccine; oral, liquid; good safety profile; marketed WW but competition from GSK
Gardasil - U.S.	1,295	1,440	1,000	200	0	0	0	0			- Approved for 9-26 year old females and males; recommended by CDC
Gardasil - Int'l	536	525	400	350	300	250	200	150			- Global ex 19 countries recorded in equity income by SPMSPD JV
Gardasil - Global	1,831	1,965	1,400	550	300	250	200	150	-35%	-30%	- HPV vaccine
V-419					100	200	300	400	500	NM	NM - Hexavalent combination pediatric vaccine; Phase III; NDA 2014
V-212					100	200	300	400	500	NM	NM - Inactivated herpes zoster vaccine; Phase III; NDA 2014
V-114					50	100	150	200	200	NM	NM - Pneumoconjugate vaccine; Phase II
Pneumovax - U.S.	491	495	520	550	580	610	640	670			- PFE's Prevnar 13 a competitive threat if ACIP recommended in adults (filed 12/10)
Pneumovax - Int'l	162	150	165	180	195	210	225	240			
Pneumovax - Global	653	645	685	730	775	820	865	910	6%	5%	- Pneumococcal vaccine for adults
TOTAL VACCINES	\$5,184	\$5,420	\$5,800	\$6,225	\$6,700	\$7,195	\$7,690	\$8,185	7%	7%	
% Chg	9%	5%	7%	7%	8%	7%	7%	6%			

Source: Company data, Cowen and Company estimates

Merck Product Line Annual Sales Buildup (\$MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
OPHTHALMOLOGY											
Trusopt/Cosopt - U.S.	\$17	\$0									- Rights sold to Akorn for \$52.8MM; deal closed 11/15/13
Trusopt/Cosopt - Int'l	400	195									- Rights in Japan, EU and Asia Pacific sold to Santen for \$600MM; deal closed 7/1/14
Trusopt/Cosopt - Global	\$416	\$195									
Zioptan	48	20									- Aspen purchased as of 4/1/14
Restasis	35	20									
Timoptic/Timoptic XE	50	25									
AzaSite	14	0									- Akorn purchased as of 11/15/13
TOTAL OPHTHALMOLOGY	\$563	\$260									
% Chg	-7%										
DERMATOLOGY											
Elocon	\$132	\$120	\$110	\$100	\$90	\$80	\$70	\$60	-11%	-11%	- Moderate potency steroid; patent exp. 9/01 (compound), cream (10/06), lotion (5/07)
Diprolene	120	130	115	100	85	70	55	40	-18%	-15%	- Moderate growth
Valisone	30	30	30	30	30	30	30	30	0%	0%	- Steroid cream
Diprosone	5	5	5	5	5	5	5	5	0%	0%	- Psoriasis lotion
Lotrisone	5	5	5	5	5	5	5	5	0%	0%	- Steroid; cream patent expired, lotion form launched; generics to cream
Other	45	40	35	30	25	20	15	10	-21%	-19%	
TOTAL DERMATOLOGY	\$337	\$330	\$300	\$270	\$240	\$210	\$180	\$150	-21%	-12%	-11%
% Chg	-6%	-2%	-9%	-10%	-11%	-13%	-14%	-17%			
CONTRACEPTION/WOMEN'S HEALTH											
Implanon - U.S.	\$205	\$265	\$290	\$315	\$340	\$365	\$390	\$415			
Implanon - Int'l	198	200	215	235	255	275	295	315			
Implanon - Global	\$403	465	505	550	595	640	685	730	8%	9%	- Implantable contraceptive; patent expired July 2009
NOMAC/E2	10	35	50	75	100	125	150	175	31%	NM	- Progesteron/estrogen; approved in EU; no longer pursued in the U.S.
MK-8342B					50	75	100	125		NM	- IUS next generation device; contraception; Phase II
MK-8342					50	75	100	125		NM	- Medicated IUS; contraception; Phase II
MK-8175A					50	75	100	125		NM	- Next generation ring; contraception; Phase II
Elonva	20	35	45	55	65	75	85	95	18%	25%	- MK-8962; Corifollitropin alpha; infertility; marketed in EU; U.S. filing 2012 but CRL 7/14
NuvaRing - U.S.	425	450	475	510	540	100	50	25			
NuvaRing - Int'l	261	275	300	340	370	150	50	25			
NuvaRing - Global	686	725	775	850	910	250	100	50	-36%	-31%	- Contraceptive vaginal ring; patent expires April 2018
Mercilon	100	95	85	75	65	55	45	35	-15%	-14%	- Contraceptive; patent expired September 2012
Follistim AQ - U.S.	181	115	80	60	40	20	10	5			
Follistim AQ - Int'l	301	290	190	150	100	50	25	10			
Follistim AQ - Global	481	400	270	210	140	70	35	15	-42%	-39%	- Follitropin beta injection; patent expires June 2015
Cerazette - U.S.	0	0	0	0	0	0	0	0			- Oral contraceptive; patent expired December 2012
Cerazette - Int'l	208	155	100	75	50	25	10	5			
Cerazette - Global	208	155	100	75	50	25	10	5	-44%	-41%	
Marvelon	113	95	80	70	60	50	40	30	-17%	-17%	- Contraceptive; patent expires September 2012
Livial	114	105	85	70	55	40	25	5	-40%	-36%	- Oral contraceptive; patent expired March 2010
TOTAL CONTRACEPTION/WOMEN'S HEALTH	\$2,135	\$2,110	\$1,995	\$2,030	\$2,190	\$1,555	\$1,475	\$1,515	-5%	-5%	-5%
% Chg	4%	-1%	-5%	2%	8%	-29%	-5%	3%			

Source: Company data, Cowen and Company estimates

Merck Product Line Annual Sales Buildup (\$MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
OTHER											
Proscar - U.S.	\$4	\$5	\$5	\$5	\$5	\$5	\$5	\$5			
Proscar - Int'l	180	145	125	105	85	65	45	25			
Proscar - Global	183	150	130	110	90	70	50	30	-24%	-23%	- BPH; generic competition in the U.S.
Fosamax - U.S.	20	20	20	20	20	20	20	20			
Fosamax - Int'l	540	455	330	250	200	150	100	50			
Fosamax - Global	560	475	350	270	220	170	120	70	-27%	-26%	- Osteoporosis; generics launched 2/08
Propecia - U.S.	24	15	10	5	5	5	0	0	NM	NM	Baldness; dominates small market; patent expired 10/13
Propecia - Int'l	258	220	180	150	100	75	50	25			
Propecia - Global	283	235	190	155	105	80	50	25	-31%	-29%	
Pepcid	5	5	5	5	5	5	5	5	0%	0%	- Generic competition prompts decline
Astra Merck (U.S.)	920	465							NM	NM	
Pharmaceutical Ingredients/diversified brands	370								NM	NM	- Merck/other supply sales plus royalty
Other MRK and SGP Products	2192	2545	2600	2675	2750	2825	2900	2975	3%	4%	- API (\$200MM in rev) and products with diversified brands (\$230MM in rev) divested to Aspen
TOTAL OTHER	\$4,513	\$3,875	\$3,275	\$3,215	\$3,170	\$3,150	\$3,125	\$3,105	-4%	-5%	- Crop protection to NVS \$70MM/yr; Ivomec to Merial; Levitra alliance revenue
% Chg	-1%	-14%	-15%	-2%	-1%	-1%	-1%	-1%			
ANIMAL HEALTH											
Animal Health - U.S.	\$855	\$720	\$800	\$880	\$960	\$1,040	\$1,120	\$1,200	9%	5%	- Zilmax (beta agonist) sales suspended in U.S. and Canada - \$160MM in 2012
Animal Health - Int'l	2,507	2,700	2,775	2,850	2,925	3,000	3,075	3,150	3%	3%	
Animal Health - Global	3,362	3,420	3,575	3,730	3,885	4,040	4,195	4,350	4%	4%	Mainly international feed animals
% Chg		2%	5%	4%	4%	4%	4%	4%			
CONSUMER CARE											
Claritin OTC - U.S.	\$410	\$430									
Claritin OTC - Int'l	61	135									
Claritin OTC - Global	471	565							NM	NM	
Other Consumer Care - U.S.	916	950									
Other Consumer Care - Int'l	507	500									
Other Consumer Care - Global	1,423	1,450									
TOTAL CONSUMER CARE	\$1,894	\$2,015							NM	NM	- Sold to Bayer AG for \$14.2B or \$8-9B after tax; deal to close in H2:14
% Chg	-3%	6%									
TOTAL SALES	\$44,030	\$42,400	\$38,630	\$38,435	\$37,940	\$38,765	\$39,940	\$41,660	0%	-1%	
% Chg	-7%	-4%	NM	-1%	-1%	2%	3%	4%			

Source: Company data, Cowen and Company estimates

Merck Estimated 2013-20 Summary Balance Sheet (\$MM)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Assets:								
Cash & Equivalents	\$15,621	\$13,247	\$14,746	\$16,885	\$17,964	\$19,428	\$21,196	\$23,242
Short-Term Investments	1,865	2,500	2,500	2,500	2,500	2,500	2,500	2,500
Receivables	7,184	7,000	6,350	6,300	6,250	6,350	6,550	6,850
Inventories	6,226	6,100	5,050	4,900	4,950	5,100	5,200	5,400
Other Current	<u>4,789</u>	<u>4,240</u>	<u>3,865</u>	<u>3,920</u>	<u>3,870</u>	<u>3,800</u>	<u>3,875</u>	<u>3,960</u>
Total Current Assets	\$35,685	\$33,087	\$32,511	\$34,505	\$35,534	\$37,178	\$39,321	\$41,952
Property, Plant & Equip.	\$14,973	\$14,000	\$13,150	\$13,050	\$12,900	\$13,200	\$13,600	\$14,150
Intangibles/Goodwill	36,102	32,000	32,000	32,000	32,000	32,000	32,000	32,000
Other Long-Term Assets	<u>18,885</u>	<u>19,000</u>	<u>19,000</u>	<u>19,000</u>	<u>19,000</u>	<u>19,000</u>	<u>19,000</u>	<u>19,000</u>
Total Long-Term Assets	69,960	65,000	64,150	64,050	63,900	64,200	64,600	65,150
Total Assets	\$105,645	\$98,087	\$96,661	\$98,555	\$99,434	\$101,378	\$103,921	\$107,102
Liabilities:								
Short-Term Debt	\$4,521	\$4,500	\$4,000	\$3,500	\$3,000	\$2,500	\$2,000	\$1,500
Accounts Payable	2,274	2,300	1,900	1,850	1,900	1,900	1,900	2,000
Other Current Liabilities	<u>11,073</u>	<u>10,900</u>	<u>9,100</u>	<u>8,850</u>	<u>8,850</u>	<u>8,900</u>	<u>9,150</u>	<u>9,500</u>
Total Current Liabilities	\$17,868	\$17,700	\$15,000	\$14,200	\$13,750	\$13,300	\$13,050	\$13,000
Long-Term Debt	\$20,539	\$18,500	\$18,000	\$17,500	\$17,000	\$16,500	\$16,000	\$15,500
Other Long-Term Liabilities	<u>14,912</u>	<u>14,500</u>	<u>14,500</u>	<u>14,500</u>	<u>14,500</u>	<u>14,500</u>	<u>14,500</u>	<u>14,500</u>
Total Liabilities	\$53,319	\$50,700	\$47,500	\$46,200	\$45,250	\$44,300	\$43,550	\$43,000
Net Equity	\$52,326	\$47,387	\$49,161	\$52,355	\$54,184	\$57,078	\$60,371	\$64,102

Source: Company data, Cowen and Company estimates

Merck Estimated 2013-20 Working Capital Analysis (\$MM)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Inventories	\$6,226	\$6,100	\$5,050	\$4,900	\$4,950	\$5,100	\$5,200	\$5,400
COGS	\$11,186	\$10,896	\$9,073	\$8,840	\$8,916	\$8,916	\$9,106	\$9,415
Inventory Turns	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Months	6.7	6.7	6.7	6.7	6.7	6.9	6.9	6.9
Accounts Receivable	\$7,184	\$7,000	\$6,350	\$6,300	\$6,250	\$6,350	\$6,550	\$6,850
Sales	\$44,030	\$42,400	\$38,630	\$38,435	\$37,940	\$38,765	\$39,940	\$41,660
Receivables Days	60	60	60	60	60	60	60	60
Other Current Assets	\$4,789	\$4,240	\$3,865	\$3,920	\$3,870	\$3,800	\$3,875	\$3,960
% of Sales	11%	10%	10%	10%	10%	10%	10%	10%
Accounts Payable	\$2,274	\$2,300	\$1,900	\$1,850	\$1,900	\$1,900	\$1,900	\$2,000
COGS	\$11,186	\$10,896	\$9,073	\$8,840	\$8,916	\$8,916	\$9,106	\$9,415
Payables Days	74.2	77.0	77.0	77.0	77.0	77.0	77.0	77.0
Other Current Liabilities	\$11,073	\$10,900	\$9,100	\$8,850	\$8,850	\$8,900	\$9,150	\$9,500
% of COGS	99%	100%	100%	100%	99%	100%	100%	101%
Net Working Capital (Ex. Cash, Debt)	\$4,852	\$4,140	\$4,265	\$4,420	\$4,320	\$4,450	\$4,575	\$4,710

Source: Company data, Cowen and Company estimates

Merck Estimated 2013-20 Cash Flow Analysis (\$MM)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P
<u>Operating Activities</u>								
Net Income (Operations)	\$10,442	\$10,317	\$10,192	\$10,918	\$10,592	\$11,244	\$11,866	\$12,584
Depreciation & Amort.	6,988	7,000	6,900	6,950	7,000	7,050	7,050	7,100
Change in Working Capital	(169)	\$712	(125)	(155)	\$100	(130)	(125)	(135)
Other, net	(5,607)	(5,500)	(4,500)	(4,500)	(5,000)	(5,000)	(5,000)	(5,000)
Net Cash Provided By Operations	\$11,654	\$12,529	\$12,467	\$13,213	\$12,692	\$13,164	\$13,791	\$14,549
<u>Investing Activities</u>								
Capital Expenditures	(\$1,548)	(\$1,200)	(\$1,200)	(\$1,250)	(\$1,250)	(\$1,300)	(\$1,300)	(\$1,350)
Investments (net)	(1,693)	(1,500)	(1,000)	(1,000)	(1,000)	(1,000)	(1,000)	(1,000)
Acquisitions (net)	(200)	0	0	0	0	0	0	0
Other, net	293	0	0	0	0	0	0	0
Net Cash Provided By Investing	(\$3,148)	(\$2,700)	(\$2,200)	(\$2,250)	(\$2,250)	(\$2,300)	(\$2,300)	(\$2,350)
<u>Financing Activities</u>								
Long-Term Debt Financings	\$6,467	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Equity Financings	0	0	0	0	0	0	0	0
Net Debt Payments	(1,934)	(500)	(1,000)	(1,000)	(1,000)	(1,000)	(1,000)	(1,000)
Dividend Payments	(5,157)	(5,203)	(5,268)	(5,325)	(5,363)	(5,400)	(5,723)	(6,153)
Share Repurchase	(6,516)	(4,000)	(2,500)	(2,500)	(3,000)	(3,000)	(3,000)	(3,000)
Other, net	1,150	0	0	0	0	0	0	0
Net Cash Provided By Financing	(\$5,990)	(\$9,703)	(\$8,768)	(\$8,825)	(\$9,363)	(\$9,400)	(\$9,723)	(\$10,153)
Impact of Currency	(\$346)	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Net Change in Cash & Equivalents	\$2,170	\$126	\$1,499	\$2,138	\$1,079	\$1,464	\$1,768	\$2,046
Ending Cash & Equivalents	\$15,621	\$15,747	\$17,246	\$19,385	\$20,464	\$21,928	\$23,696	\$25,742

Source: Company data, Cowen and Company estimates

Merck DCF Analysis

9/26/14											
Assumptions											
Share Price	\$59		<i>Output</i>								
			Equity Value		\$184,484						
			Estimated Share Price		\$62						
Discount Rate	9.3%		Net Cash		(\$7,574)						
Shares Outstanding (000)	2,955		Enterprise Value		\$192,058						

MERCK DCF

	2013A	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2021P	2022P	2023P	2024P	2025P	Terminal
Total Revenues	\$44,030	\$42,400	\$38,630	\$38,435	\$37,940	\$38,765	\$39,940	\$41,660	\$43,350	\$45,100	\$46,900	\$48,800	\$50,750	
% Change	-7%	-4%	-9%	-1%	-1%	+2%	+3%	+4%	+4%	+4%	+4%	+4%	+4%	+4%
Cost of Goods	\$11,330	\$10,999	\$9,160	\$8,908	\$8,977	\$8,969	\$9,152	\$9,452	\$9,840	\$10,238	\$10,646	\$11,078	\$11,520	
Gross Profit	\$32,699	\$31,401	\$29,470	\$29,527	\$28,963	\$29,796	\$30,788	\$32,208	\$33,510	\$34,862	\$36,254	\$37,722	\$39,230	
Gross Margin - Total	74.3%	74.1%	76.3%	76.8%	76.3%	76.9%	77.1%	77.3%	77.3%	77.3%	77.3%	77.3%	77.3%	77.3%
SG&A	\$11,673	\$10,615	\$9,530	\$8,660	\$8,800	\$8,750	\$8,900	\$9,250	\$9,667	\$10,057	\$10,459	\$10,882	\$11,317	
% of Revs	26.5%	25.0%	24.7%	22.5%	23.2%	22.6%	22.3%	22.2%	22.3%	22.3%	22.3%	22.3%	22.3%	22.3%
R&D	\$7,124	\$6,845	\$6,550	\$6,600	\$6,400	\$6,500	\$6,600	\$6,800	\$7,153	\$7,442	\$7,739	\$8,052	\$8,374	
% of Revs	16.2%	16.1%	17.0%	17.2%	16.9%	16.8%	16.5%	16.3%	16.5%	16.5%	16.5%	16.5%	16.5%	16.5%
Operating Expenses	\$18,797	\$17,460	\$16,080	\$15,260	\$15,200	\$15,250	\$15,500	\$16,050	\$16,820	\$17,499	\$18,197	\$18,934	\$19,691	
% of Revenues	42.7%	41.2%	41.6%	39.7%	40.1%	39.3%	38.8%	38.5%	38.8%	38.8%	38.8%	38.8%	38.8%	38.8%
Operating Income	\$13,902	\$13,941	\$13,390	\$14,267	\$13,763	\$14,546	\$15,288	\$16,158	\$16,690	\$17,364	\$18,057	\$18,788	\$19,539	
% Operating Margin	31.6%	32.9%	34.7%	37.1%	36.3%	37.5%	38.3%	38.8%	38.5%	38.5%	38.5%	38.5%	38.5%	38.5%
Non-operating income	82	305	170	172	179	187	195	203	205	210	215	220	225	
EBIT	\$13,984	\$14,246	\$13,560	\$14,439	\$13,942	\$14,733	\$15,483	\$16,360	\$16,895	\$17,574	\$18,272	\$19,008	\$19,764	
% of Revs	31.8%	33.6%	35.1%	37.6%	36.7%	38.0%	38.8%	39.3%	39.0%	39.0%	39.0%	39.0%	39.0%	38.9%
D&A	\$6,988	\$7,000	\$6,900	\$6,950	\$7,000	\$7,050	\$7,050	\$7,100	\$7,150	\$7,200	\$7,250	\$7,300	\$7,350	
EBITDA	\$20,972	\$21,246	\$20,460	\$21,389	\$20,942	\$21,783	\$22,533	\$23,460	\$24,045	\$24,774	\$25,522	\$26,308	\$27,114	
% of Revs	47.6%	50.1%	53.0%	55.6%	55.2%	56.2%	56.4%	56.3%	55.5%	54.9%	54.4%	53.9%	53.4%	
Net Interest Income (Expense)	(\$537)	(\$505)	(\$170)	(\$95)	(\$30)	\$35	\$100	\$165	\$175	\$200	\$225	\$250	\$250	
Pre-Tax Income	\$13,447	\$13,741	\$13,390	\$14,344	\$13,912	\$14,768	\$15,583	\$16,525	\$17,070	\$17,774	\$18,497	\$19,258	\$20,014	
Taxes	\$2,927	\$3,369	\$3,198	\$3,425	\$3,320	\$3,524	\$3,717	\$3,941	\$4,080	\$4,248	\$4,421	\$4,603	\$4,783	
Income Tax Rate	21.8%	24.5%	23.9%	23.9%	23.9%	23.9%	23.9%	23.9%	23.9%	23.9%	23.9%	23.9%	23.9%	23.9%
Net Income	\$10,468	\$10,372	\$10,192	\$10,918	\$10,592	\$11,244	\$11,866	\$12,584	\$12,990	\$13,526	\$14,076	\$14,655	\$15,230	
% of Revs	23.8%	24.5%	26.4%	28.4%	27.9%	29.0%	29.7%	30.2%	30.0%	30.0%	30.0%	30.0%	30.0%	30.0%
NOPAT	\$11,057	\$10,877	\$10,362	\$11,013	\$10,622	\$11,209	\$11,766	\$12,419	\$12,815	\$13,326	\$13,851	\$14,405	\$14,980	
Adjustments:														
Capex	(\$1,548)	(\$1,200)	(\$1,200)	(\$1,250)	(\$1,250)	(\$1,300)	(\$1,300)	(\$1,350)	(\$1,400)	(\$1,450)	(\$1,500)	(\$1,550)	(\$1,600)	
Depreciation & Amortization	\$6,988	\$7,000	\$6,900	\$6,950	\$7,000	\$7,050	\$7,050	\$7,100	\$7,150	\$7,200	\$7,250	\$7,300	\$7,350	
Change In Working Capital	(\$169)	\$712	(\$125)	(\$155)	\$100	(\$130)	(\$125)	(\$135)	(\$200)	(\$225)	(\$250)	(\$250)	(\$250)	
Operating Free Cash Flow	\$15,739	\$16,884	\$15,767	\$16,463	\$16,442	\$16,864	\$17,491	\$18,199	\$18,540	\$19,051	\$19,576	\$20,155	\$20,730	\$222,908

Source: Cowen and Company.

MERCK R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Arthritis/Inflammation							
MK-8457			.				Rheumatoid arthritis
Cancer/Oncology/Hematology							
Keytruda			.				Pembrolizumab; approved for melanoma; PII/III NSCLC; combo with crizotinib (PFE) , many other tumors explored
MK-2206			.				Advanced or metastatic solid tumors
Cardiovascular							
Anacetrapib			.		>2015		MK-0859; atherosclerosis; CETP inhibition; 30,000 patient REVEAL Phase III trial completes 1/17
Central Nervous System							
Belsomra					Feb-14		Suvorexant; MK-4305; insomnia; orexin receptor antagonist; approved U.S.; EU strategy under evaluation
Bridion (Sugammadex)			.				MK-8616; reverses neuromuscular block; U.S. CRL from FDA; MRK is conducting hypersensitivity study; anticipates resubmission in 2014
MK-8931			.				BACE inhibitor; Alzheimer's Disease; Phase III initiated 12/13
MK-7622			.				Alzheimer's Disease
Contraception/Women's Health							
MK-8962				.			Corifollitropin alfa injection; infertility; approved EU; filed in U.S.
MK-8175A			.				Next generation ring
MK-8342			.				SCH-900342; medicated IUS; contraception
MK-8342B			.				Next generation ring
Diabetes							
MK-1293			.				Insulin glargine; Types 1 and 2 diabetes
MK-3102			.		>2014		Omarigliptin; once-weekly DPP-4 inhibitor
MK-8835			.				Ertugliflozin; oral sodium glucose cotransporter (SGLT2) inhibitor; licensed from Pfizer
Endocrine/Metabolic/Hormones							
Odanacatib			.		2015		MK-0822; cathepsin K inhibitor; osteoporosis; >16,000 patient, placebo-controlled fracture outcomes trial; study concluded early for efficacy but filing delayed for safety
Infectious Disease							
MK-7009					2014		Hepatitis C; vaniprevir (Japan NDA 2014)
Letermovir (AIC246)		⇒	.				Treatment and prevention of human cytomegalovirus (HCMV) in transplant recipients; oral; ww rights from AiCuris; first of portfolio of agents
MK-3415A			.		2015		CDA-1/CDB-1; combination therapy for treatment of Clostridium difficile (C. difficile) associated diarrhea (CDAD); with BMY and Massachusetts Biologic Laboratories
MK-5172A			.				Hepatitis C; pan-genotypic protease inhibitor; combination of MK-5172 and MK-8742
MK-1439			.				Doravirine; HIV
Rebactam			.				MK-7655; beta-lactamase inhibitor; bacterial infections; FDA designated as a Qualified Infectious Disease Product with Fast Track status in September 2014
Respiratory							
MK-8237							Allergy; house dust mite
MK-1029			.				Asthma
Vaccines							

MERCK R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
V-503 (HPV Vaccine)					Feb-14		Novel vaccine; multivalent HPV vaccine; 9 valent; BLA filing accepted February 2014
V-212				.	>2014		Inactivated VZV vaccine; herpes zoster; autologous hematopoietic cell transplant (NDA 2014); solid tumor and hematologic malignancies (NDA >2014)
V-419 (Pediatric Vaccine)				.	2014		Pediatric hexavalent combination vaccine
V-114			.				Pneumoconjugate vaccine
Total Drugs In Development	0	0	10	14	4		28

Progress since last update in bold; movement marked by arrow

Investor Relations Contact: Joe Romanelli 908-423-5185

Justin Holko 908-423-5088

Price: \$94.13 (09/30/2014)
Price Target: \$95.00

MARKET PERFORM (2)

Steve Scala, R.Ph., CFA

617.946.3923
steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA

617.946.3857
kathy.miner@cowen.com

Jean Perreault

617.946.3967
jean.perreault@cowen.com

Key Data

Symbol NYSE: NVS

52-Week Range: \$95.50 - 72.77

Market Cap (MM): \$254,733.9

Net Debt (MM): \$8,796.0

Cash/Share: NA

Dil. Shares Out (MM): 2,706.2

Enterprise Value (MM): NA

ROIC: NA

ROE (LTM): NA

BV/Share: NA

Dividend: \$2.76

Yield: 2.93%

FY (Dec) 2013A 2014E 2015E

Earnings Per Share

	2013A	2014E	2015E
Q1	\$1.30	\$1.31A	\$1.30
Q2	\$1.29	\$1.34A	\$1.31
Q3	\$1.24	\$1.34	\$1.65
Q4	\$1.18	\$1.16	\$1.54
Year	\$5.00	\$5.15	\$5.80
P/E	18.8x	18.3x	16.2x

Core Basic EPS; excludes amortization and one-time items; pro forma, assumes Alcon acquired 1/1/2010

Consensus EPS - \$5.14 \$5.67

Consensus source: Thomson Reuters

Revenue (MM)

Year	\$57,355.0	\$58,260.0	\$58,180.0
------	------------	------------	------------

Novartis (ADR)

Solid Growth, But Visibility Limited

The Cowen Insight

Recent business reconfiguration boosts confidence in outlook, and the pipeline is gaining visibility.

The positive LCZ696 PARADIGM-HF data is very encouraging and we are fans of Novartis' recent business swaps, given that they bolster an existing area of strength (oncology) and lower exposure to struggling assets (Consumer and Vaccines). However, Novartis also faces challenges including Diovan plain generic competition; competition for Gilenya and Lucentis from Tecfidera and Eylea; uncertain outlook for key pipeline products; and ongoing questions about management's ability to deliver upon the promise of all divisions simultaneously. Pending greater clarity on execution, we maintain our Market Perform rating.

EPS Outlook Improves Starting In 2014

We forecast 3% EPS growth in 2014 and 8-13% annual gains in 2015-20, driven by a multitude of products in the pipeline, expansion to EMs, and cost cutting measures. We estimate flat sales in 2015 and 2016 due to the loss of animal health, vaccines and consumer revenues, partially offset by addition of Glaxo oncology products which also boosts profits. EPS growth in 2014-15 looks achievable despite launch of Diovan plain generics.

Some Pipeline Opportunities Hold Significant Promise, Led By LCZ696

LCZ696 (chronic heart failure) demonstrated very impressive results in the PARADIGM-HF trial and we now estimate sales of \$4B in 2020. LEE011, a highly selective CDK4/6 inhibitor, looks very promising. Its first Phase III trial (MONALEESA-2) began in December 2013 in combination with letrozole (Femara) in patients with HR+/HER2- advanced breast cancer (with no prior therapy). NVS appears to be at a similar stage as PFE assuming that PFE cannot garner approval for palbociclib in the absence of Phase III data, although NVS has shared little data on its compound. More data in both the U.S. and E.U. will be required for Serelaxin (acute heart failure) to move forward, consistent with the views of our physician consultants.

Gleevec Patent Settlement Gives Additional Visibility, Albeit Limited

The Gleevec patent settlement with Sun is a clear positive. Sun may launch a generic on February 1, 2016, and we view it likely that Sandoz will launch its own generic around that time as well. However, the patent settlement extends Gleevec's exclusivity only about 6 months, a surprisingly short amount of additional exclusivity. While Tasigna has been a successful improvement upon Gleevec, it has not replaced even half its sales, leaving Gleevec's \$4B+ in revenue poised for a steep erosion beginning in 2016, representing another significant patent expiration.

Cardiology

Company Optimistic On Heart Failure Portfolio; LCZ Data Impressive; Our Consultants And Regulatory Agencies More Cautious On Serelaxin

The outlook for LCZ696 is very encouraging as the Phase III PARADIGM-HF study was stopped early (end of March 2014) due to strength of interim results. Full data for LCZ696, presented at ESC in late August, showed a 20% reduction in the primary endpoint of death from CV causes or hospitalization for heart failure. Novartis expects to complete its rolling submission by year end. For Serelaxin, inconsistent symptomatic data, the absence of an impact on re-hospitalizations, and only a modest improvement in mortality in the Phase III RELAX-AHF trial, suggest that Serelaxin is not likely to be approved without more convincing data from a larger Phase III trial. The negative FDA AdCom and CHMP opinions reflected the long-standing opinions of our physician experts. Novartis estimates peak sales potential of Serelaxin (acute heart failure) and LCZ696 (chronic heart failure) to be \$2-5B+ combined. The wide range of potential is due to scenarios involving: approval of only one drug versus two, various indications, and various pricing assumptions.

LCZ696: Phase III PARADIGM-HF Shows Impressive Results; Filing To Be Completed By Year End

LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), which provides concomitant inhibition of NEP and the angiotensin receptor. LCZ696 does not appear to cause angioedema, a side effect that has sidelined forerunners in the NEP class. The 8,436 patient Phase III trial, PARADIGM-HF, in patients with heart failure (HF) and reduced ejection fraction (rEF), was stopped early (March 2014) based on strength of interim results (as recommended by the Data Monitoring Committee). Full data, presented in late August, showed a 20% reduction in the primary endpoint. Novartis has initiated a rolling submission in the U.S. for the rEF HF indication which it expects to complete by December 2014. An E.U. filing is expected in Q1:15. A study (PARAGON-HF) in HF patients with preserved ejection fraction (pEF) started in Q3:14. LOE in the U.S. and E.U. is in 2026 and 2030 in Japan. We forecast LCZ696 sales of \$500MM in 2016, \$2,000MM in 2018, and \$4,000MM in 2020.

PARADIGM-HF: Primary Endpoint Reduced By 20%, At High End Of Statistical Forecast Range, But Just Below Survey Expectations

The morbidity and mortality study compared LCZ696 to ace-inhibitor enalapril in heart failure patients. The primary endpoint - death from CV causes or hospitalization for heart failure - occurred in 914 patients (21.8%) on LCZ696 and 1117 patients (26.5%) on enalapril (HR=0.80). Importantly, the difference in favor of LCZ696 was seen early. 558 deaths (13.3%) in the LCZ696 group and 693 (16.5%) in the enalapril group were due to CV causes (HR=0.80). 537 (12.8%) LCZ696 patients were hospitalized for heart failure, versus 658 patients (15.6%) receiving enalapril (HR=0.79). The number needed to treat to prevent one primary event and one death from CV causes was 21 and 32, respectively.

PARADIGM-HF: Primary Endpoint And Components

	LCZ696 (N=4,187)	Enalapril (n=4,212)	Hazard Ratio (95% CI)	P Value
Primary endpoint	914 (21.8%)	1,117 (26.5%)	0.80 (0.73-0.87)	0.0000002
Cardiovascular death	558 (13.3%)	693 (16.5%)	0.80 (0.71-0.89)	0.00004
Hospitalization for heart failure	537 (12.8%)	658 (15.6%)	0.79 (0.71-0.89)	0.00004

Source: ESC 2014

Fewer patients on LCZ696 than on enalapril stopped study medication because of an adverse event (10.7% vs. 12.3%, P=0.03). LCZ696 patients were more likely to have symptomatic hypotension. Angioedema was experienced by 19 patients on LCZ696 and 10 patients on enalapril (P=0.13). No patient required intubation for angioedema.

PARADIGM-HF: Adverse Events

	LCZ696 (n=4,187)	Enalapril (n=4,212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	<0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine ≥ 2.5 mg/dl	139	188	0.007
Cough	474	601	<0.001
Discontinuation for adverse event			
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	--

Source: ESC 2014

The most significant question about the data is the relatively small population of patients in PARADIGM-HF in North America, about 7% of the overall study; this may raise questions given differing background therapies in the U.S. and E.U. But overall, the subgroup data showed strong and consistent results: every single subgroup showed favorable activity for LCZ. There are a few subgroups where p-values are >0.05. These subgroups included Asians, Blacks, Western Europeans, patients with Class III-IV heart failure, and patients on no prior ACE therapy. Importantly, whether or not a patient was on a background of mineralocorticoid receptor antagonists did not impact the results.

PARADIGM-HF Results In Line With Our Cardiologist Survey Expectations

In July, we conducted a survey of 25 cardiologists to determine their expectations for the relative risk reduction likely to be delivered in PARADIGM-HF, as well as their likelihood of prescribing the drug based on various potential outcomes of the trial. On average, the physicians expected the relative risk reduction in PARADIGM-HF to be 23%. 60% of physicians surveyed expected few, if any, safety risks, while 40% expected moderate safety risk. 84% of physicians surveyed believed it was likely that the relative risk reduction benefit will persist even on a background of mineralocorticoid receptor antagonists, which also are associated with risk reduction.

What % Of Patients With CHF With Reduced Ejection Fraction Would Be Prescribed LCZ696 At Various Levels Of Risk Reduction ?

Relative Risk Reduction	<10%	11-20%	21-30%	>30%
% of CHF patients that would be prescribed LCZ696 by CHF specialists	29%	44%	59%	72%
Number of patients prescribed LCZ696, assuming 3.6MM have class II-IV HF with REF	1,044,000	1,584,000	2,124,000	2,592,000
Estimated Daily Price	\$8	\$8	\$8	\$8
Potential Peak Sales (\$B)	\$3.0	\$4.6	\$6.2	\$7.6

Source: Cowen and Company

Phase III PARAGON Trial In Preserved Ejection Fraction Initiated

Novartis began the PARAGON Phase III study of LCZ696 in HF patients with preserved ejection fraction (n=4300) in Q3:14. The primary endpoint is a composite of CV deaths and hospitalizations due to HF. The trial is expected to complete by the end of 2019, although there will be interim looks.

In the Phase II PARAMOUNT study, LCZ696 was the first therapy to significantly reduce NT-proBNP in patients with heart failure with preserved ejection fraction. The PARAMOUNT study showed that after 12 weeks of treatment the reduction of NT-proBNP was 23% greater with valsartan ($p=0.005$). In addition, there was a greater

reduction in left atrial size (cardiac remodeling) in LCZ696 treated patients at the end of the 36-week study ($p=0.003$).

Phase II Data In Hypertension Solid, But Focus On HF

In a 1,000 patient Phase II hypertension trial that comprised 5-10% African Americans, no cases of any severity of angioedema were reported. At the 400mg dose, LCZ696 resulted in superior blood pressure reduction to Diovan. Novartis believes LCZ696 is substantially different than prior failed compounds (BMY's omapatrilat) because it has ARB rather than ACE activity. ACE inhibition is associated with angioedema whereas angioedema is very rare in ARBs, because they don't impact bradykinin. NVS has data in hypertension, but this will not be filed. LCZ696 is formulated as a co-crystalate - the product separates in vivo - but NVS would not say where the separation occurs. It believes the co-crystalate form may confer LCZ696's unique advantages. Novartis believes that LCZ696 has the potential to replace ACE inhibitors as the standard of care in heart failure.

Serelaxin's Early Data Impressive, But RELAX-AHF Will Not Support Approval

In December 2009, Novartis acquired Corthera and its lead product, serelaxin (RLX030) which received fast-track designation in October 2009. Serelaxin (RLX030) is a naturally occurring peptide hormone that acts as a systemic and renal vasodilator. Novartis believes that as many as 2MM patients are candidates annually in the U.S. for RLX030.

In June 2013, the FDA granted breakthrough therapy designation to RLX030. A new analysis of the Phase III RELAX-AHF data was presented at ESC 2013 showing improved symptoms and reduced mortality across multiple subgroups. However, the number of patients in each subgroup was too small for conclusive results. As such, a RELAX -AHF-2 trial was initiated in September 2013, which will enroll approximately 6,400 patients (roughly 25% enrolled through August 2014), and seek to statistically identify the subgroups most responsive to serelaxin. Time to CV death (in 6 month follow-up period) is the primary endpoint. Novartis announced that there is an interim analysis planned after 60% of the events that might fortify a mortality claim. Interim data (at 60% of events) is expected in H2:15, with final data in 2016.

Serelaxin was filed in the E.U. in December 2012 and in the U.S. in May 2013, based on results of the RELAX-AHF trial. In January 2014, CHMP issued a negative opinion on serelaxin citing concerns about demonstrated benefits, how parts of the analysis were conducted, impact of differences in background treatments, and the limitations of the single study. Safety seemed acceptable, but uncertainties around benefits resulted in the negative opinion. Novartis re-submitted a revised filing in Q1:14, and in late May 2014, CHMP re-confirmed their negative opinion indicating that additional data is required. Novartis plans to re-submit its filing as soon as data from the RELAX-AHF-2 study is available. In March 2014, the FDA AdCom also rejected Serelaxin (see details below). Novartis has indicated they will work with the FDA to address its concerns. We estimate serelaxin sales of \$100MM in 2018 and \$300MM in 2020, which are below NVS expectations.

Serelaxin Rejection By FDA AdCom Not Surprising

In line with our physician expert's views, FDA's Cardiovascular and Renal Drugs Advisory Committee voted unanimously (0-11), in late March 2014, against recommending Serelaxin for improving symptoms of acute heart failure. Novartis filed the application for serelaxin on the basis of one Phase 3 trial (RELAX-AHF) of 1,161 acute heart failure patients with systolic blood pressure above 125mmHG at the time

of screening. It sought an indication for improvement of AHF symptoms through reduction of the rate of worsening of heart failure. The primary endpoints of RELAX-AHF were 1) AUC (Area Under the Curve) representing change in patient-reported dyspnea from baseline through day 5 as measured by a 100mm VAS (Visual Analog Scale) and 2) moderately or marked better dyspnea relative to the start of study at 6, 12, 24 hours using 7-point Likert scale. Secondary endpoints included 1) days alive and out of the hospital through day 60 and 2) cardiovascular death or re-hospitalization.

Committee comments included the following:

- Only one trial rather than at least two (or a single trial with data equivalent for two+ independent studies)
- The imputation method drove the results of the trial. The imputation method treated all episodes of worsening heart failure (WHF) equally; no differentiation between patients who had severe cases of WHF and those with easily manageable episodes (i.e., IV diuretics, IV nitrates). Also did not differentiate between long and short WHF episodes.
- Worsening heart failure: signs and symptoms requiring intensified IV therapies or device support. Panelists noted that such worsening signs and symptoms were not adjudicated. WHF was not objectively measured, simply documented by checking a box.
- RELAX-AHF designed to show benefit on dyspnea but NVS seeking broader indication “to improve symptoms of AHF through reduction of rate of WHF”
- Patient-reported updates subjective as were investigator’s decision of treatment for WHF
- Primary endpoint measures took into account only dyspnea; other symptoms were not measured.

CV Death Through Day 180 – RELAX-AHF (ITT Set)

	Statistic	Placebo N=580	Serelaxin N=581
Number of events	n (%)	55 (9.5)	35 (6.0)
Kaplan-Meier estimates for time to cardiovascular death (days)	Probability (95% CI)		
Day 5	0.9 (0.4, 2.1)	0.7 (0.3, 1.8)	
Day 14	2.1 (1.2, 3.6)	0.9 (0.4, 2.1)	
Day 30	3.3 (2.1, 5.1)	1.9 (1.1, 3.4)	
Day 60	4.7 (3.2, 6.8)	3.3 (2.1, 5.1)	
Day 180	9.6 (7.5, 12.3)	6.1 (4.4, 8.4)	
P-value		0.026	
Estimates by Cox model	Hazard ratio (95% CI)		0.63 (0.41, 0.96)
P-value was based on log-rank test by serelaxin vs. placebo			
Hazard ratio < 1.0 favors serelaxin			

Source: Novartis FDA Briefing Document

Consultants Have Been Cautious On RELAX-AHF

Our physician consultants have viewed serelaxin's Phase III RELAX-AHF as an early and ambitious trial. The fact that RELAX-AHF was enriched with hypertensive patients was appropriate given that 60-70% of AHF patients have elevated blood pressure. However, hypertensive AHF patients tend to respond well to currently available, very inexpensive drugs such as diuretics and nitrates.

Serelaxin's failure to achieve a statistical improvement in the LIKERT scale in RELAX-AHF was viewed as concerning. The VAS scale is useful for statistical assessments of dyspnea, but our physician consultant believes the statistical benefit for serelaxin on the VAS scale is of limited clinical utility. Our physician expert views serelaxin's failure to reduce re-hospitalizations in RELAX-AHF as very concerning, as re-hospitalizations in AHF contribute to a poor prognosis and are a considerable burden on the healthcare system. Serelaxin was associated with reduced all-cause death and improved CV mortality in RELAX-AHF, but our consultant views the treatment effect as modest and should be confirmed in an additional trial.

In Pre-RELAX-AHF, the completed Phase II portion of the Phase III program, the objective was proof-of-concept and dose and endpoint selection. In the modified intention-to-treat population, 61 patients were assessed in the placebo group, 40 in the serelaxin 10 µg/kg per day group, 42 in the serelaxin 30 µg/kg per day group, 37 in the serelaxin 100 µg/kg per day group, and 49 in the relaxin 250 µg/kg per day group. Dyspnea improved with serelaxin 30 µg/kg compared with placebo, as assessed by Likert scale (17 of 42 patients [40%] moderately or markedly improved at 6 h, 12 h, and 24 h versus 14 of 61 [23%]; p=0.044) and visual analogue scale through day 14 (8214 mm×h [SD 8712] versus 4622 mm×h [9003]; p=0.053). Length of stay was 10.2 days (SD 6.1) for serelaxin-treated patients versus 12.0 days (7.3) for those given placebo, and days alive out of hospital were 47.9 (10.1) versus 44.2 (14.2). Cardiovascular death or readmission due to heart or renal failure at day 60 was reduced with serelaxin (2.6% [95% CI 0.4-16.8] versus 17.2% [9.6-29.6]; p=0.053). The number of serious adverse events was similar between groups.

Safety Concerns Cap Tekturna Sales Potential

Tekturna, a once-daily direct renin inhibitor, was approved by the FDA in March 2007 and garnered E.U. approval in August 2007 for the treatment of hypertension. Renin is an enzyme that initiates the cascade that ultimately produces the blood pressure regulating peptide angiotensin II. Other anti-hypertensive agents target the renin-angiotensin system (RAS) by inhibiting angiotensin II (ARBs) or angiotensin I (ACE inhibitors). While Tekturna is approved as monotherapy, ~70% of prescriptions were in combination with an ACE inhibitor or ARB.

In December 2011, Novartis reported that Phase III ALTITUDE study was being terminated at the recommendation of the DSMB. ALTITUDE was designed to assess the impact of Tekturna on top of standard of care (ACE inhibitor or ARB) on cardiovascular and renal outcomes in 8,606 patients with type 2 diabetes and renal impairment. The DSMB concluded that patients were unlikely to benefit from the addition of Tekturna and noted an increased incidence of non-fatal stroke, renal complications, hyperkalemia, and hypotension at 18-24 months in the Tekturna arm. In April 2012, FDA updated the Tekturna label to reflect the findings from the ALTITUDE study. The label change includes a contraindication against the use of aliskiren-based products in patients with diabetes or eGFR<60ml/min who are on ACE inhibitors or ARBs. Consistent with this recommendation, Novartis has ceased marketing Valturna (aliskiren and valsartan) combination products.

An increased incidence of hyopkalemia was also observed in other shorter-term ASPIRE-HIGHER trials (ALOFT, AVANT-GARDE, and ASPIRE). While only a 36 week trial, the Tekturna arm of ASPIRE showed similar ADR profile compared to ALTITUDE, with increases in CV ADRs (17.53% for Tekturna vs. 14.86% for placebo), hypotension (6.4% for Tekturna vs. 4.04% for placebo), hyperkalemia (5.21% for Tekturna vs. 1.26% for placebo), and renal dysfunction (1.6% for Tekturna vs. 0.5% for placebo).

In December 2012, Novartis announced that ASTRONAUT had failed to meet its primary endpoints of improvement in cardiac mortality or re-hospitalization when added to an ACE or ARB. We estimate Tekturna sales of \$220MM (-24%) in 2014, \$190MM in 2015, \$170MM in 2016, \$125MM in 2018, and \$75MM in 2020.

ASPIRE Higher Program

Study	Name Definition	Description	Number	Results If Applicable	Presentation/ Expected Completion Date
Biomarker Studies					
ALOFT	ALiskiren Observation of Heart Failure Treatment	Evaluate the safety and efficacy of Tekturna + standard therapy in hypertensive patients with stable heart failure. Change from baseline in the heart failure biochemical markers of N-terminal pro-brain natriuretic peptide (NT-proBNP) and brain natriuretic (BNP) after 12 weeks.	280	Slightly higher but non-significant number of patients receiving Tekturna experienced hyperkalemia. Reductions in BNP (brain natriuretic peptide) nearly five times greater than the standard therapy alone (-61 pg/ml versus -12 pg/ml; p=0.016).	Presented ESC 2007
AVOID	Aliskiren in the Evaluation of Proteinuria in Diabetes	The study included a 3-month open-label run-in period with patients receiving losartan 100mg QD in addition to optimal antihypertensive therapy. After 3 months, patients were randomized to receive 6-months treatment with placebo or Tekturna (150mg QD for 3 month followed by forced titration to 300mg QD for another 3 months) on top of losartan. The primary outcome was reduction in early morning urinary albumin creatinine ratio (UACR) from baseline to end of study.	599	Significant 20% reduction in mean UACR on top of standard therapy compared with placebo after 24 weeks and Tekturna also significantly reduced mean urinary albumin excretion rate (UAER) by 21% compared to placebo (p=0.009, 95% CI: 5-30). Single-measurement serum-potassium of 6.0mEq/L occurred in 4.7% vs. 1.7% (difference not significant) in the Tekturna and placebo groups respectively.	Presented ASN 2007
ALLAY	Aliskiren in Left Ventricular Hypertrophy	Tekturna , Cozaar , and the combination of both agents over 36 weeks in overweight patients with essential hypertension and left ventricular hypertrophy (LVH).	465	Patients in all treatment groups showed a reduction in LV mass index at the 36-week visit. The mean change in LV mass was -4.9 g/m2, -4.8 g/m2, and -5.8 g/m2 in the aliskiren, losartan, and combination therapy groups, respectively (p<0.0001 vs baseline for each group). Despite a numerically greater reduction in LV mass with the combination therapy, this was not significantly greater than losartan alone (p=0.52).	Presented ACC 2008
Pilot Studies					
AVANT-GARDE	Combination with Diovan . Assess improved LV dynamics through NT-pro -BNP measurements in high-risk patients with ACS		1,100	No benefit of early inhibition of the renin-angiotensin-aldosterone system (RAAS) in reducing NT-pro BNP, a biomarker for hemodynamic stress, over eight weeks in patients with acute coronary syndrome (ACS).	Released in 2009
ASPIRE	Assess the effectiveness of Tekturna on the prevention of left ventricular remodeling in high risk ACS patients		800	The combined rates of cardiovascular death, hospitalization for heart failure, recurrent heart attack, stroke and resuscitated sudden death were similar in the Tekturna group and the group given standard therapy. In patients receiving Tekturna in addition to standard therapy there was a higher rate of hyperkalemia, hypotension and kidney dysfunction when compared to the group receiving standard therapy alone.	Presented ACC 2010
Large Outcomes Trials					
ALTITUDE	ALiskiren Trial In Type 2 Diabetic nEphropathy	Assess whether Tekturna, added to conventional therapy, delays heart and kidney complications	8,600	Terminated due to lack of efficacy and increased incidence of non-fatal stroke, hypotension, hyperkalaemia, and renal dysfunction in the Tekturna arm.	2012
ASTRONAUT		Assess the effect of early initiation of Tekturna therapy, compared to standard therapy, in the reduction of cardiovascular death and heart failure re-hospitalization events within 6 months, in CHF patients hospitalized for an episode of acute decompensated heart failure	1,782	Failed to meet primary endpoints of improvement in cardiac mortality or re-hospitalization when added to an ACE or ARB.	2012
ATMOSPHERE	N/A	Assess the effects of Tekturna on cardiovascular morbidity and mortality in patients with acute and chronic congestive heart failure on top of standard therapy	N/A		November 2015
APOLLO	N/A	Assess the effectiveness of Tekturna in preventing cardiovascular morbidity and mortality in elderly patients with or without high blood pressure and other risk factors	N/A	Completed October 2012	2012

Source: Company data; clinicaltrials.gov

Galvus Faring Well Ex-U.S.

Galvus (vildagliptin; DPP-4 inhibitor) was approved for use in T2DM in the E.U. in September 2007. In February 2008, the association of the 100mg dose with liver toxicities required relabeling in the E.U. Galvus is currently approved in the E.U. as monotherapy; in a FDC with metformin (Eucreas), as dual therapy with a thiazolidinedione or sulphonylurea; as triple therapy (with metformin and a sulphonylurea; and with insulin (with or without metformin).

Eucreas (Galvus/metformin fixed-dose combination) was approved in February 2008 and now accounts for the majority of sales in the E.U. and Latin America. Galvus was approved in Japan in January 2010 under the trade name Equa. In Q2:14, Novartis announced that Galvus is no longer reimbursed in Germany, and therefore is essentially off the market. Germany represented 9% of Galvus sales. We forecast Galvus sales of \$1,350MM (+13%) in 2014, \$1,515MM in 2015, \$1,650MM in 2016, \$1,950MM in 2018, and \$2,250MM in 2020.

No Plans To Enter US Market

Novartis filed Galvus (vildagliptin) 50mg and 100mg doses with the FDA in 3/06 and received an "approvable letter" on its February 2007 PDUFA date. The FDA's major concerns included necrotic cutaneous lesions in monkeys at three fold the proposed human dose, acute and symptomatic peripheral edema in humans at 4-6 fold the proposed clinical dose, and potential patient populations who are likely to be at risk for increased drug exposure. The FDA initially requested a 24-week safety study in patients with moderate-to-severe renal impairment that are predisposed to high plasma levels with standard Galvus doses. The FDA also requested additional preclinical characterization of a renally excreted metabolite, LAY151, which was subsequently resolved. In addition, the FDA required a study to address a liver toxicity signal found as part of a Novartis safety review. Novartis stated formally in 2008 that a U.S. resubmission was not planned.

LCQ 908 Pursuing Metabolic Disorders

LCQ908 is a diacylglycerol acyltransferase-1 (DGAT-1) inhibitor. DGAT-1 catalyzes the final committed step in triglyceride synthesis and is believed to play a key role in whole body energy homeostasis. Inhibition of DGAT-1 represents a novel approach to treat metabolic disease. LCQ908 is in Phase III development for the treatment of type 2 diabetes and in patients with severe hypertriglyceridemia. Phase III hypertriglyceridemia studies in patients with familial chylomicronemia syndrome completed recruitment in 2013. Novartis estimates a filing in 2014. Preliminary Phase II data suggests that 40mg of LCQ908 is sufficient to lower baseline plasma triglyceride levels (>4,000mg/dL) by >50% over the course of 21 days. We estimate LCQ 908 sales of \$30MM in 2015, \$50MM in 2016, \$100MM in 2018, and \$150MM in 2020.

Diovan In Decline Due To Generics

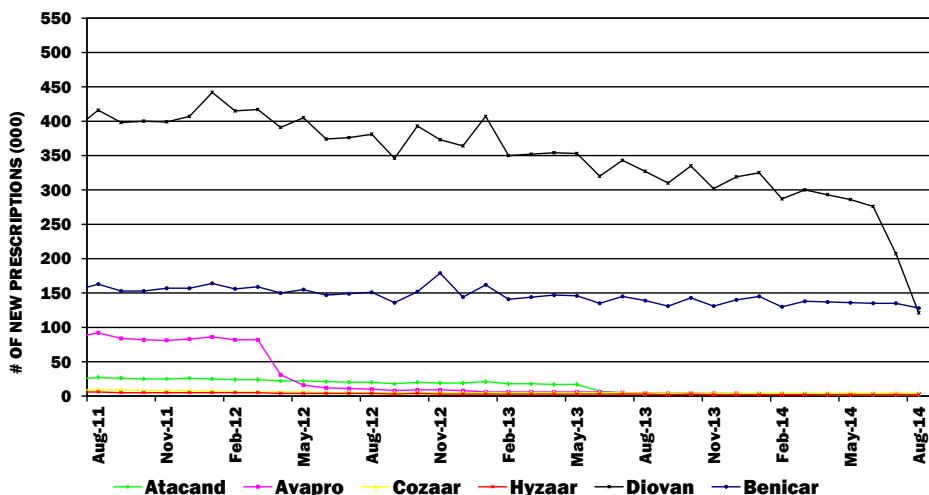
In September 2012, Mylan and Sandoz launched Diovan HCT generics. On June 27th, Ranbaxy was granted FDA approval for its generic version of Diovan and launched immediately. Exforge, a Diovan/amlodipine fixed-dose combination, has grown reasonably ex-U.S. where traditionally fixed-dose combinations have struggled. A fixed-dose Exforge/HCT was launched in the U.S. in 2009. Exforge was approved in Japan in January 2010. Novartis expects amlodipine franchise sales to be \$2B+ post

its U.S. patent expiration; we assume Diovan plus Exforge sales of only \$210MM in 2020.

We estimate Exforge sales of \$1,435MM (-1%) in 2014, \$1,340MM in 2015, \$1,350MM in 2016, \$550MM in 2018, and \$110MM in 2020, pressured by Diovan generics. Exforge's regulatory exclusivity expires in 2017 in Europe and in 2014 in Japan. Diovan's patent expired in 2011 in most European countries (February 2011 in Spain, and May 2011 in France, Germany, Italy and the UK) and will expire in September, 2014 in Japan. We estimate Diovan/HCT sales of \$2.38B (-32%) in 2014, \$1.2B in 2015, \$950MM in 2016, \$350MM in 2018, and \$100MM in 2020.

ARB New Prescription Comparison

ARB NEW PRESCRIPTION COMPARISON



Source: Cowen and Company

Oncology

Acquisition Of Glaxo Products Beefs Up Oncology Portfolio And Helps Deliver Growth Through Gleevec Patent Expiration

In April 2014, Novartis announced that it will be acquiring Glaxo's oncology portfolio which had 2013 sales of approximately \$1.7B, predominantly from Tykerb, Votrient, Promacta, and Arzerra. We expect the transaction, which also includes the sale of non-flu vaccines to and a jv in Consumer with Glaxo, to close effective Q3:15. While these products strengthen the existing oncology franchise, Novartis also expects to launch 10 new oncology products in the next 5 years and garner 6 new indications (see tables below). Admittedly our sales forecasts may not fully reflect the potential of all of these opportunities, particularly LEE011, where Novartis believes it is competitive with Pfizer's palbociclib. Novartis states that Afinitor is ahead of plan and the erosion of Zometa post generics was faster than expected. In December 2013, five year data of Tasigna vs Gleevec was released, and showed continued superiority of Tasigna over Gleevec.

New Product/Indication Launches In Next 5 Years

Drug	Indication	Our 2020 Sales Forecast (\$MM)
BKM120 (pan PI3K)	BC (pivotal), lung, H&N	\$50
CTL019 (CART)	Leukemias, lymphomas; pivotal studies '14	\$500
LBH589	Multiple myeloma	\$350
LCI699	Cushing's	--
LDE225	Basal cell carcinoma, medulloblastoma	\$140
LEE011 (CDK4/6)	BC (Phase III to start 12/13), melanoma	\$1,000
LGX818	Melanoma	\$50
MEK162	Melanoma	\$100
PKC412	AML, mastocytosis	\$125
Jakavi	Polycythemia vera	\$1,400*
Signifor	Acromegaly	\$650*
Afinitor	HER2+, Carcinoid, Lymphoma, TSC Seizure	\$3,325*

* all indications

Source: Company data; Cowen and Company estimates

Gleevec Poised For Modest Decline Through 2015, Post Patent Litigation Settlement

Gleevec (Glivec outside the U.S.) is a selective tyrosine kinase inhibitor (TKI) specifically designed to inhibit bcr-abl, an abnormal tyrosine kinase that is critical to the development of chronic myelogenous leukemia (CML). Gleevec also inhibits receptor tyrosine kinases of platelet-derived growth factor (PDGF) and c-kit (stem cell factor), which is implicated in the development of GI stromal tumors (GIST). Gleevec is approved for treatment of CML, Ph+ ALL, several other rare hematological tumors (worldwide prevalence estimated at 2,000 patients), and to prevent recurrent GIST after surgery. Gleevec was approved for CML in Japan in 2001, GIST in 2002, and mGIST in December 2008. Gleevec was approved for GIST in the E.U. and U.S. in February 2012.

Novartis' head-to-head (ENESTnd) of Tasigna versus Gleevec has set a very high bar for the second-generation TKIs in de novo CML patients. Tasigna resulted in significantly superior MMR at 12-months and its side-effect profile was surprisingly good. Novartis believes that the ENESTnd data are sufficient to generate the switch. In order for Novartis to sustain its CML franchise, it is critical for Tasigna to garner additional first-line share before Gleevec incurs generic competition in early 2016. Tasigna was approved in the first-line in 2009. Wyeth's (now Pfizer) bosutinib is not superior to Gleevec in terms of eliciting CCyR and appears to be associated with greater incidence of serious adverse events. We forecast Gleevec sales of \$4,620MM (-2%) in 2014, \$4,515MM in 2015, \$2,400MM in 2016, \$550MM in 2018, and \$110MM in 2020.

Comparison Of Second-Generation TKI Head-To-Head Studies Vs. Gleevec

	Tasigna (NVS)	Sprycel (BMY)	Bosutinib (PFE)
Efficacy vs. Gleevec	<u>SUPERIOR:</u> Tasigna 400mg BID vs. Gleevec 400mg QD; CCyR 79% vs. 65% ($p<0.001$); MMR 43% vs. 22% ($p<0.001$); Improved time to progression ($p<0.01$).	<u>SUPERIOR:</u> Sprycel 100mg QD vs. Gleevec 400mg QD; CCyR 83% vs. 72% ($p=0.001$); Reduced time to CCyR; MMR 46% vs. 28% ($p<0.001$); Improved time to progression.	<u>EQUIVALENT:</u> Bosutinib 500mg QD vs. Gleevec 400mg QD; CCyR 70% vs. 68% ($p=0.601$); Patients responding to Bosutinib achieved CCyR faster ($p<0.001$); MMR 39% vs. 26% ($p=0.002$); trend towards improving time to progression.
Safety vs. Gleevec	SUPERIOR: Discontinuation rates similar. Tasigna showed less neutropenia (12% vs. 20%), fluid retention, and GI effects (10-20% vs. 30%). Tasigna pts. experienced increased incidence of skin rashes and trend toward ALT elevations.	EQUIVALENT: Sprycel and Gleevec similar incidence of neutropenia, thrombocytopenia, and anemia. Sprycel superior with regards to fluid retention and superficial edema. Sprycel only group to show pleural effusion.	INFERIOR: Incidence of serious adverse effects greater in bosutinib group (25.4% vs. 13.5%). Discontinuation from adverse events greater in bosutinib group (19.4% vs. 5.6%).

Source: Cowen and Company and company data

Composition Of Matter Patent Set To Expire In 2015, But Patent Litigation Settlement Should Delay Generics Until 2016

While the patent on the α -crystalline form of Gleevec expires on July 4, 2015, the β -crystalline form is the only form that is commercially available and the only form studied in clinical trials. The composition of matter patent covering the β -crystalline form of Gleevec does not expire until 2019 in the U.S. In November 2007, Sun filed a Paragraph IV certification against the beta crystal Gleevec patent. In June 2013, Sun sued Novartis for the right to market generic Gleevec in the U.S. In May 2014, Novartis settled patent litigation with Sun permitting Sun to launch a generic version of Gleevec on February 1, 2016. The basic compound patent, which expires in 2015 in the U.S., is not being challenged in the U.S.

Gleevec Patent Estate

U.S. Patent Number	Expiration Date
5521184	January 4, 2015 (July 4, 2015 w/ pedi exclusivity)
6894051	May 23, 2019 (November 23, 2019 w/ pedi exclusivity)
7544799	January 16, 2019 (June 19, 2019 w/pedi exclusivity)
6958335	December 19, 2021 (June 19, 2022 w/ pedi exclusivity)

Source: FDA Orange Book

The beta crystal form has several distinguishing features:

- (1) The beta crystalline form is a compact, powder and non-needle shaped crystal form, which results in more beneficial flow characteristics versus the alpha crystal and other forms. The beta crystal form of Gleevec is easier to handle and process. The beta crystal does not appear to offer efficacy or safety advantages;
- (2) The beta crystalline form is more thermodynamically stable than the alpha form at room temperature, giving superior commercial characteristics for Gleevec (i.e., drug storage);
- (3) The beta crystalline form is also considerably less hygroscopic than the alpha form at 25°C – the beta crystalline form remains dry at 25°C, whereas the alpha crystalline form rapidly takes on water at 93% relative humidity; both the beta and alpha forms of Gleevec become liquids at 97% relative humidity, but the alpha form liquefies much more rapidly – the improved hygroscopicity of the beta form is also an advantage for storing, handling, and processing the material in its final commercial form.

Validation Of '051 And '799 By USPTO Positive For Novartis

Upon initial review, the USPTO rejected the '051 patent based on examiner claims that the beta crystalline form was inherent based on protocols within the reference patent ('184); however, the examiner did not provide evidence to substantiate this assertion. An additional review by the patent board resulted in a complete reversal of the examiners original decision on all counts and the '051 and '799 patents were issued in the absence of expert declaration.

Gleevec Highly Successful In CML

Gleevec shows impressive levels of activity, with response rates over 90% in newly diagnosed CML patients and a high level of patients going into remission. In the common chronic phase of CML, 60% of patients achieve cytogenetic remission. Even in the accelerated phase (where response to chemotherapy is low), 70% of patients remain free of disease progression after one year of treatment. In the most advanced (and hard to treat) phase, blast crisis, median survival is seven months, well ahead of the best available chemotherapy. At seven years 75% of patients have a complete molecular response and 80% have major molecular response; the overall survival was 86%. These data cement indefinite use in Ph+ CML patients.

Resistance to treatment with Gleevec is divided into two categories: primary and secondary. Primary resistance is when a patient fails to achieve a desired response to initial treatment; this occurs in up to 25% of patients with chronic phase CML. Secondary resistance occurs when patients with an initial response to Gleevec ultimately relapse. This proportion has been estimated at 80, 50, and 15 percent at approximately two years for patients in blast crisis, accelerated phase, or chronic phase, respectively.

Bristol-Myers' Sprycel (a bcr-abl inhibitor) is 100x more potent than Gleevec and was approved in resistant CML. Sprycel has made limited impact on Gleevec, in part because of an initial dose-related side-effect profile which includes pleural effusions and myelosuppression. However, Sprycel 100mg once-daily dose was approved and the lack of food effect had made it competitive in the second-line setting. Sprycel's dosing regimen offers comparable efficacy and an improved tolerability profile compared to 70 mg bid dose. However, the 70mg BID dose is required for other resistant CML forms.

Seven-Year IRIS Data In CML Argue For Long-Term Therapy

Seven-year data from the IRIS trial (International Randomized Interferon versus STI571) revealed that after two years of treatment, the rate of disease progression to AP/BC was 0% and the event-free survival rate was 81%. In addition, the estimated overall seven-year survival rate for patients treated with Gleevec was 86%. At year seven, event free survival was 81%. IRIS was an open-label Phase III clinical trial that enrolled 1,106 newly diagnosed patients with Ph+ CML in chronic phase in 177 centers across 16 countries. There were two arms to the study: one group of patients received Gleevec 400 mg per day, while the other received a target dose of interferon (IFN) of 5 MIU/m²/day in combination with cytarabine (Ara-C) 20 mg/m²/day for 10 days each month. Because of tolerability issues, lack of response or loss of response, 65% of patients in the IFN/Ara-C arm crossed over to the Gleevec arm, whereas only 3% of patients in the Gleevec arm crossed over to the IFN/Ara-C arm. Cumulative best responses to Gleevec treatment improved dramatically between the first and seventh years of treatment. Over the period, the number of Gleevec-treated patients showing complete cytogenetic response (or elimination of the abnormal Philadelphia chromosome associated with CML) rose from 70% in the first year to 82% by the seventh year of treatment. The rate of disease progression continued to decline in the seventh year of the study. These data argue for lifetime Gleevec treatment, and aggressive control of bcr-abl levels.

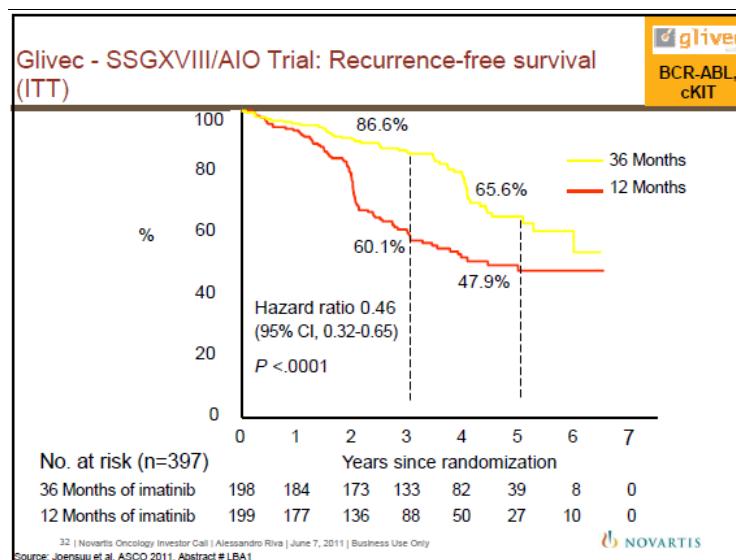
Adjuvant GIST Trial Stopped Early For Overwhelming Efficacy

About 5,000 to 6,000 new patients are diagnosed with GIST each year in the United States. Because symptoms of GIST are no different than other GI complaints such as nausea and vomiting, the cancer is difficult to detect early. Patients initially undergo surgery to remove the tumor but GIST commonly recurs. At ASCO 2007, data from a 644 patient study in primary resectable GIST demonstrated that 97% of those who received Gleevec after surgery were alive after one year with no sign of recurrence, compared to 83% of patients who received placebo ($p < 0.001$). After two years, 90% of Gleevec patients were alive without any sign of the cancer returning compared to 71% of patients receiving placebo. Two trials are ongoing in Europe, a one versus three-year treatment with Gleevec, and surgery only versus two years' treatment with Gleevec.

Extended Duration Gleevec Improves PFS In Adjuvant GIST

Results from the SSGXVIII/AIO trial, released in early 2012, compared 36 months of imatinib to 12 months with follow-up, and demonstrated a significant PFS and OS benefit for extended duration imatinib in patients with previously resected KIT-positive GIST. PFS at three years with 36 months of imatinib was 86.6% compared to 60.1% with 12 months of therapy. Five year PFS was 65.6% with 36 months of therapy compared to 47.9% with 12 months of imatinib. Interestingly, the PFS curves appear to collapse following termination of imatinib therapy, suggesting that extending treatment beyond 36 months may be beneficial in the patient population.

Extended Gleevec Survival Data



Source: Cowen and Company

While three-year OS was similar between treatment groups, five-year survival was 92.0% with 36 months of imatinib compared to 81.7% with 12 months of therapy (HR=0.45, p=0.019). The E.U. approved Gleevec in GIST in February 2012 and the FDA approved a label change to extend Gleevec therapy for GIST at the same time. Novartis estimates that ~30% of Gleevec sales are in GIST.

Gleevec Has Yet To Succeed In Solid Tumors

Novartis has studied Gleevec in several solid tumors. A Phase III trial for glioblastoma multiforme failed to meet its progression-free survival endpoint (PFS) and further development was halted in 2007. Phase II trials for hormone refractory prostate cancer were stopped due to slow patient accruals. Novartis has discontinued trials in breast, small-cell lung, polycythemia vera, and Kit+ AML.

Tasigna A Worthy Heir, But A Challenge To Overtake Gleevec

Tasigna (nilotinib), a twice-daily orally active aminopyrimidine-derivative tyrosine kinase inhibitor, is more potent against CML cells *in vitro* than Gleevec. It was approved by FDA in October 2007 for second-line CML and the EMEA in November 2007 and approved in the first-line in 2009. Tasigna was approved in Japan in December 2010. Like Gleevec, Tasigna functions through competitive inhibition at the ATP-binding site of bcr-abl, leading to the inhibition of tyrosine phosphorylation of proteins that are involved in the intracellular signal transduction that bcr-abl mediates. Tasigna has higher binding affinity and selectivity for the ABL kinase than does Gleevec. Tasigna has a black box warning for QTc prolongation and is associated with QT prolongation of >30 ms or >60 ms in approximately 33% and 2% of patients, respectively with a few reports of sudden death possibly associated with the drug. Abnormalities in potassium and magnesium levels must be corrected prior to Tasigna's initiation and other drugs that may affect the QT interval should be avoided, and caution should be used in patients at risk for QT interval prolongation. Our physician consultants do not believe that the QTc prolongation is a drawback. Tasigna represents 25% of the NVS CML franchise. Improved access to qPCR-based screening

in developing markets has increased prescribing. Tasigna currently has ~33% share of the first-line market and 50% of the second line market.

In the ENESTnd Phase III trials, Tasigna has continued to demonstrate superiority over Gleevec in newly diagnosed Ph+ CML patients. At ASH 2009, Novartis presented the results of the ENESTnd study which demonstrated that Tasigna 300 and 400mg BID were superior to Gleevec 400mg QD. 48-month data was presented at ASH 2012 and showed 68% of patients on Tasigna achieved MMR compared to 49% of patients on Gleevec. Additionally, fewer patients had progressed to advanced stages of CML on Tasigna compared to Gleevec. At ASH 2013, Novartis presented 5 year data which again showed Tasigna patients having higher and more sustained MMR compared to Gleevec. These data are key to help Novartis switch Tasigna into the first-line before Gleevec goes generic in 2015. While CMR is generally accepted as a decent surrogate marker of durable response, our physician consultants state that they will need to see the survival data, which likely will mature over time, before making the switch. A registration study in third-line GIST missed its primary endpoint and Novartis will not file the data. Based on the superior performance of Tasigna in the ENESTnd trial vs. Gleevec, the CHMP granted a positive opinion for Tasigna in first line Ph(+) CML. In December 2010 the European Commission approved Tasigna in first line Ph(+) CML.

We estimate Tasigna sales of \$1.51B (+19%) in 2014, \$1.865B in 2015, \$2.2B in 2016, \$2.85B in 2018, and \$3.5B in 2020.

Tasigna Impressive In First Line CML

Novartis initiated the ENEST (Evaluating Nilotinib Efficacy and Safety in clinical Trials) program to address Tasigna's role with Gleevec. ENESTnd (newly diagnosed) is a randomized trial comparing Tasigna 300 and 400mg BID and Gleevec 400mg QD in de novo CML patients. ENESTcr is comparing Tasigna 400mg BID with Gleevec 400mg BID in CML patients with suboptimal CyR. The primary endpoint is CCyR at 12 months.

Novartis presented the complete results of ENESTnd, the head-to-head study of Tasigna versus Gleevec at ASH 2009. The Phase III trial, ENESTnd, randomized 846 patients in equal proportions to two doses of Tasigna (300 and 400 mg twice daily) or Gleevec 400 mg once daily. The Gleevec dose could be increased, and was boosted in 16% of patients. Major molecular response at 12 months was the study's primary endpoint. There was no difference between Tasigna doses with response rates of 44% and 43% for the lower and higher doses, respectively. Overall, 57%, 54%, and 30% of patients on low-dose Tasigna, high-dose Tasigna, and Gleevec, respectively, achieved a major molecular response at some point before data cut-off. Among 234 patients at high risk (according to Sokal criteria), major molecular response rates at one year were 41%, 32%, and 17% for low-dose Tasigna, high-dose Tasigna, and Gleevec, respectively. Tasigna led to complete cytogenetic responses at one year in about 79% of patients, compared with 65% of those receiving Gleevec ($p < 0.001$). Rates of progression to acute phase disease or blast crisis occurred in a total of three out of 563 patients on Tasigna in the first year of treatment, compared with 11 of 283 patients treated with Gleevec ($p < 0.01$).

Discontinuation rates were similar in the three groups, at 16%, 18%, and 21%. Treatment discontinuation because of adverse events was: 5%, 9%, and 7%. Grade 3-4 neutropenia was seen in 20% of Gleevec patients, compared with 12% and 10% of those on low- and high-dose Tasigna. Gastrointestinal effects were seen in about 30% of Gleevec patients, compared with about 10% to 20% of the Tasigna groups. Fluid retention was also substantially less common with Tasigna. On the other hand, more than 30% of Tasigna patients at both doses developed skin rashes, compared with

11% of the Gleevec group. Bilirubin and alanine aminotransferase elevations were somewhat more common with Tasigna, although these occurred in less than 10% of patients. Grade 3-4 nonhematologic adverse effects were rare, with none seen in more than 3% of patients.

The key secondary endpoint of ENESTnd was durable MMR at 24 months, defined as patients who have MMR when examined at both 12 and 24 months. The 24 month Phase III data was presented at ASH 2010. Rates of MMR were significantly higher in patients treated with Tasigna compared to those treated with Gleevec (67% vs. 44%). Additionally, significantly more Tasigna patients achieved CCyR compared to those taking Gleevec at 24 months (85% vs. 77%). Fewer patients taking Tasigna discontinued therapy as the result of adverse reactions when compared to Gleevec, suggestive of an improved safety profile.

Comparison Of 12-Month Efficacy In DASISION and ENESTnd

	Sprycel Vs. Gleevec			Tasigna Vs. Gleevec			
	Sprycel (N = 258)	Gleevec (N = 258)	P-value	Tasigna 300mg (N=279)	Tasigna 400mg (N=277)	Gleevec (N=280)	P-value
Complete cytogenetic response by 12 mo % (CI)	83 (78-88)	72 (66-77)	0.001‡	80	78	65	<0.001 for both comparisons
Major molecular response by 12 mo % (CI)	46 (40-52)	28 (23-34)	<0.0001‡	44	43	22	<0.001 for both comparisons

‡ This was a post hoc analysis; P values have not been adjusted for multiple comparisons.

Source: Cowen and Company, Company Data

Drug Related Adverse Events That Occurred In At Least 10% Of Treated Patients In DASISION And ENESTnd

Event	Sprycel Vs. Gleevec		Tasigna Vs. Gleevec		
	Sprycel (N = 258)	Gleevec (N = 258)	Tasigna 300mg (N=279)	Tasigna 400mg (N=277)	Gleevec (N=280)
Cytopenia					
Neutropenia	65	58	43	38	68
Thrombocytopenia	70	62	48	49	56
Anemia	90	84	38	38	47
Nonhematologic adverse event					
Fluid retention	19	42	NG	NG	NG
Superficial edema	9	36	NG	NG	NG
Pleural effusion	10	0	NG	NG	NG
Other	5	8	NG	NG	NG
Peripheral edema	NG	NG	5	5	15
Eyelid edema	NG	NG	1	2	13
Periorbital edema	NG	NG	<1	1	12
Diarrhea	17	17	8	6	21
Nausea	8	20	11	19	31
Vomiting	5	10	NG	NG	NG
Myalgia	6	12	10	10	10
Muscle inflammation	4	17	NG	NG	NG
Musculoskeletal pain	11	14	NG	NG	NG
Rash	11	17	31	36	11
Headache	12	10	14	21	8
Fatigue	8	10	11	9	8
Alopecia	NG	NG	8	13	4
Pruritis	NG	NG	15	13	5

Source: Cowen and Company

48-Month ENESTnd Data Continue To Support Tasigna Use

48-month ENESTnd data were presented at ASH 2012. At 48-months of follow-up, fewer patients in the core treatment group progressed to accelerated phase or blast crisis while on treatment with Tasigna at 300 mg twice daily and 400 mg twice daily versus Glivec at 400 mg once daily.

No differences in OS have been observed between treatment arms; however, fewer CML-related deaths have occurred in both Tasigna 300mg twice daily (n=5) and 400mg twice daily (n=4) arms versus Gleevec (n=14) consistent with the significant improvement observed with progression to AP/BC. Nearly twice as many patients had emergent mutations on Gleevec (n=21) versus either Tasigna arm (n=11 in each arm).

The median follow-up for this study was 48 months. Overall, 90% and 89% of patients remained in the study on Tasigna 300 mg twice daily and Glivec 400 mg once daily, respectively.

Rates of discontinuation due to adverse events or laboratory abnormalities continued to be lowest for Tasigna 300 mg twice daily (10%) compared to Tasigna 400 mg twice daily (14%) and Glivec 400 mg once daily (11%).

ENESTcmr Suggests Deeper MMR For Tasigna Compared To Gleevec

ENESTcmr 24-month data were presented at ASH 2012. ENESTcmr was an open-label, randomized, prospective, multi-center Phase III study of Tasigna 400 mg twice daily versus standard-dose Glivec (400 mg or 600 mg once daily) comparing kinetics of CMR for patients with Ph+ CML in chronic phase who had achieved complete cytogenetic response (CCyR) but were still Bcr-Abl positive (i.e., had evidence of residual leukemia) after at least two years of treatment with Glivec. The study enrolled 207 patients. The patients were randomized into one of two treatment arms: Tasigna 400 mg twice daily versus continuing Glivec 400 mg or 600 mg once daily (same dose as at study entry).

The primary endpoint was the rate of confirmed best cumulative CMR by 12 months of study therapy with Tasigna or Glivec. Samples with any detectable level were considered not to be in CMR. The lowest detected Bcr-Abl value was 0.00073%. Secondary objectives included the kinetics of CMR, duration of CMR, progression-free survival and overall survival in both arms. CMR was defined at three levels: CMR ($\text{CMR} \geq 4.5\text{-log}$, undetectable Bcr-Abl by RQ-PCR at a sensitivity of less than 0.0032%), CMR4 ($\text{CMR} \geq 4\text{-log}$, undetectable Bcr-Abl by RQ-PCR at a sensitivity of 0.01% or less) and CMR4.5 ($\text{CMR} \geq 4.5\text{-log}$, undetectable Bcr-Abl by RQ-PCR at a sensitivity of 0.0032% or less).

These data showed that 23% of patients taking Tasigna achieved undetectable disease (24 patients) by 12 months compared to 11% (11 patients) taking Glivec. A majority of patients in both treatment arms received prior Glivec treatment for at least three years before entering the trial. Patients randomized to receive Tasigna were given a new treatment while the others continued to receive a therapy that they had been taking for a minimum of two years.

During this study, discontinuation due to adverse events occurred in 8.9% and 1% for Tasigna- and Glivec-treated patients, respectively. The majority of these were asymptomatic laboratory adverse events. The adverse events seen in ENESTcmr were similar to other studies for patients switched from chronic Glivec therapy to Tasigna.

At 24-months, the difference between groups remained statistically significant with the absolute difference in the number of patients with undetectable CCR-ABL doubling since the 12-month data readout (22.1% on Tasigna vs. 8.7% on Gleevec, p=0.0087).

5-Year ENESTnd Data Continues To Show Tasigna Benefits

At ASH 2013, 5-year ENESTnd data was presented and reaffirmed the superiority of Tasigna over Gleevec in newly diagnosed CML patients. Compared to Gleevec, the Tasigna arms reported: an MR4 difference of 9-14% by year one and 21-24% by year 5; and MR4.5 difference of 6-10% by year one and 21-23% by 5 years. The estimated rates of patients alive at 5 years for Gleevec was 91.6% vs. 93.6% for Tasigna 300mg and 96.0% for Tasigna 400mg. The safety profile was consistent with prior studies.

In the 36 months follow-up of ENESTcmr, Tasigna treated patients led to deeper MMR in patients who switched over after long-term treatment with Gleevec. In patients without MR4.5 at baseline, cumulative incidence of MR4.5 was 46.9% in Tasigna patients vs. 33.3% for Gleevec.

Also presented was data from the LASOR study, which demonstrated higher rates of MMR in patients who failed to achieve a CCyR with front-line Gleevec and then switched to Tasigna vs. those who dose-escalated on Gleevec.

Rapid Zometa Decline Underway Post Launch Of Generics

Zometa (zoledronate) is a second-generation, injectable bisphosphonate for the treatment of hypercalcemia of malignancy (HCM) and for the treatment of bone metastases (secondary tumors) arising from a broad range of tumor types (including prostate and lung cancer, breast cancer, and multiple myeloma). Reduced dosing (versus the prescribed monthly regimen), shorter course of therapy, pricing challenges and concerns with osteonecrosis of the jaw (ONJ) have resulted in a slowing of Zometa's revenues.

Branded Aclasta in the U.S. and Reclast ex-U.S. sales is being negatively impacted post launch of Zometa generics. We forecast Zometa sales of \$265MM (-56%) in 2014, \$115MM in 2015, \$85MM in 2016, \$30MM in 2018, and \$10MM in 2020.

Exjade's Oral Convenience Has Cornered The Iron Chelator Market But Safety Signals Are A Headwind

Exjade (deferasirox) is a once-daily oral iron chelator for the treatment of chronic iron overload. Exjade is approved for adults and children two years and older whose iron overload resulted from frequent blood transfusions for thalassemia and sickle cell disease, rare anemias, and myelodysplastic syndromes (MDS). Exjade offers convenience benefits over desferrioxamine mesylate which often requires infusions lasting eight to 12 hours per night, for five to seven nights a week. Exjade is required to be titrated based on individual iron intake and burden. Exjade is approved in more than 85 countries, including Japan. In July 2008, the CHMP recommended that Exjade's label be updated to reflect reported cases of hepatic failure (sometimes fatal). While most cases of hepatic failure were in patients with severe comorbidities, the CHMP acknowledges that Exjade's role in the liver failure cannot be excluded. Patients are now required to monitor liver function prior to and during initiation of therapy. In addition, upper GI bleeds and renal tubulopathy have also been reported. In February 2010, FDA required Novartis to add a black-box warning for liver and kidney failure as well as excess GI bleeding. The FDA approved Exjade for the treatment of non-

transfusion dependent thalassemia (NTDT) in January 2013. Two new Exjade formulations are in development, a tablet and granules, that are designed to improve GI tolerability and thereby improve patient compliance. Launch of these new formulations is expected in 2015 in the U.S. and E.U. and in ROW in 2016. We forecast Exjade sales of \$935MM (+5%) in 2014, \$985MM in 2015, \$1,025MM in 2016, \$850MM in 2018, and \$500MM in 2020.

Afinitor: Expansion Of Franchise Key To Potential

Afinitor (everolimus) is the first oral mammalian target of rapamycin (mTOR) inhibitor being developed for cancer. Afinitor is approved for the treatment of metastatic renal cell carcinoma, PNET, TS-AML, TSC-SEGA, and ER+/HER2- mBC. Novartis is studying Afinitor in multiple tumor types as depicted in the table below. Novartis believes that Afinitor could be a multibillion dollar opportunity with \$1.5-1.7B of potential sales in breast cancer alone. We estimate Afinitor sales of \$1,560MM (+19%) in 2014, \$1,850MM in 2015, \$2,125MM in 2016, \$2,725MM in 2018, and \$3,325MM in 2020.

Major Afinitor Ongoing Trials

Tumor Type	Trials	Stage	Planned Filing Date
Breast	Afinitor in combination with Herceptin and paclitaxel, as 1st line in HER2 positive locally advanced mBC	Phase III	2014
Gastric cancer	Afinitor +/- best supportive care in patients with advanced gastric cancer after progression on 1 or 2 prior systemic chemotherapies	Phase III	2105
Lymphoma	Afinitor adjuvant therapy in poor risk patients with diffuse large B-cell lymphoma	Phase III	2015
Liver cancer	Combination of Afinitor and Nexavar in patients with advanced HCC	Phase II	Failed

Source: clinicaltrials.gov, Cowen and Company

Breast Cancer Potentially A Large Opportunity But Final OS Data Not Significant

In September 2011, data from the Afinitor Phase III BOLERO-2 trial showed Afinitor + exemestane significantly improved progression free survival compared to exemestane alone in women with ER+/HER2- metastatic breast cancer. Overall survival data favored the Afinitor arm. A more mature interim OS analysis was presented at ASH 2011. After 137 events, 17.2% of patients had died in the everolimus group compared to 22.7% in the placebo arm. The final OS analysis presented in Q1:14 showed Afinitor +exemestane extended OS by 4.4 months (to 31 months from 26.6) compared to exemestane alone. This improvement was not statistically significant. Novartis believes 85,000 women are diagnosed with ER+/HER2- breast cancer annually in the U.S., E.U., and Japan with more than 220,000 eligible patients worldwide. At an average monthly cost of \$6-7K and a median duration of therapy of 7-8 months, Novartis believes that Afinitor has potential to capture 80% of all patients with metastatic breast cancer and has a \$1.5-1.7B opportunity in breast cancer, a decline from prior \$2B guidance reflecting the lack of OS benefit in BOLERO-2. Afinitor is likely to be used as a 3rd or 4th line agent

Afinitor Approved In Advanced HR+/HER2- Breast Cancer

In July 2012, FDA approved Afinitor (everolimus) for the treatment of advanced hormone receptor-positive, HER2-negative breast cancer in combination with

exemestane in letrozole/anastrozole failures. The breast cancer label reflects a 4.6 month PFS benefit (7.8 months for Afinitor vs. 3.2 months for placebo, HR=0.45, p<0.0001) and an improvement in ORR (12.6% for Afinitor vs. 1.7% for placebo) for Afinitor compared to placebo, but also notes that Afinitor has not yet achieved an OS benefit (HR=0.77, 95% CI: 0.57, 10.4). The label sites the most common adverse reactions on Afinitor (incidence ≥ 30%) as stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite, the most common grade 3/4 adverse reactions (incidence ≥ 2%) as stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea, and the most common laboratory abnormalities (incidence ≥ 50%) as hypercholesterolemia, hyperglycemia, increased AST, anemia, leukopenia, thrombocytopenia, lymphopenia, increased ALT, and hypertriglyceridemia. Afinitor 10mg tablets have an AWP of \$320/day. The high cost of Afinitor is not expected to hinder reimbursement given that Afinitor is readily reimbursed at a similar cost in other chronic disease states.

RECORD-1 Stopped Early Due To Overwhelming PFS In RCC

RECORD-1 was a randomized, double-blind placebo-controlled multicenter trial of more than 400 patients with RCC whose cancer worsened despite prior treatment, including Nexavar or Sutent, or both. In addition, prior therapy with Avastin, interferon, and interleukin-2 was allowed. The primary endpoint of RECORD-1 was progression-free survival (PFS) assessed via a blinded, independent central review and defined as the amount of time between randomization and first documented disease progression or death due to any cause. Results of the study demonstrated a statistically significant improvement in PFS for Afinitor compared to placebo (hazard ratio = 0.30 with 95% CI 0.22 to 0.40; p-value < 0.0001; median PFS 4 months vs. 1.9 months, respectively). Secondary endpoints included comparison of overall survival, objective response rate, quality of life, safety, and pharmacokinetics. There was no significant difference in overall survival between the Afinitor and placebo groups (hazard ratio = 0.83 with 95% CI 0.50 to 1.37; p-value = 0.23). The study design allowed patients to be unblinded at the time of radiological disease progression; patients receiving placebo were allowed to cross over to receive Afinitor. There was no significant difference in objective response rate between the Afinitor and placebo groups (1% vs. 0% of responders). However, in a central review among patients evaluable for best percentage change in target lesions (223 and 107 in Afinitor and placebo arms, respectively), tumor shrinkage was observed in 50% of patients receiving Afinitor during the double-blind portion of the study versus 8% of patients receiving placebo. Quality of life measurements taken throughout the study showed no significant difference between the Afinitor and placebo groups. The most frequent adverse events in patients who took Afinitor included mouth sores (40%), feelings of weakness (37%), and rash (25%). There was a low incidence of grade 3 or 4 drug-related adverse events (> 1% of patients listed): mouth sores (3%), lung inflammation (3%), infection (3%), tiredness/feelings of weakness (4%), diarrhea (1%), mucosal inflammation (1%), and difficulty breathing (1%). The trial had a low rate of adverse drug reactions leading to discontinuation among patients who took Afinitor (6%).

Failure Of Study 2325 Prevents Filing For Carcinoid Tumors

Novartis's original NDA was supported by two Phase III trials, Study 2324 (advanced pancreatic neuroendocrine tumor, or PNET) and 2325 (carcinoid), which were designed to use independent review committee (IRC)-determined PFS as the primary endpoint. During an interim efficacy analysis of Study 2325, IRC-determined PFS crossed the futility boundary (p=0.233), while investigator (INV)-determined PFS crossed the efficacy boundary (p= 0.003). Subsequently, Novartis amended Study 2324 to utilize INV-determined PFS and Study 2325 to utilize adjudication committee (AC)-determined PFS. Changes to the analysis of the primary endpoint (PFS)

invalidated FDA's original Special Protocol Assessment. While AC-determined PFS (HR=0.77, p=0.026) in Study 2325 (carcinoid) more closely approximated INV-determined PFS (HR=0.78, p=0.018), FDA considers reanalysis of data a third-interim analysis resulting in an available alpha of 0.0098; the p-value therefore did not achieve statistical significance in either reassessment. Afinitor also negatively impacted OS in Study 2325 (HR=1.22, 95% CI 0.91-1.62).

Afinitor Provides PFS Benefit In PNET Across Analyses

Despite the revision in the PFS analysis in Study 2324 (PNET), improvements in PFS remained similar and significant whether determined by INV (HR=0.35, p<0.001), IRC (HR=0.38, p<0.001), or AC (HR=0.34, p<0.001). Similar to what was observed in Study 2325, Afinitor negatively impacted OS in patients with PNET (HR=1.05, (95% CI 0.91-1.62).

Afinitor Approved In PNET

Phase II data from a study with Afinitor in NET were presented at ASCO 2007. 60 patients were enrolled, 30 patients on 5mg and 30 patients on 10mg. Patients were also treated with depot octreotide (Sandostatin LAR) to help manage complications of the disease, although it has not shown any evidence of being able to control growth of tumors. Half the patients had islet cell tumors and half had carcinoid tumors. The median progression-free survival (for both doses) was 59 weeks. Twenty-seven percent of patients treated with 10mg of Afinitor achieve a partial response and 70% had stable disease, with a median progression-free survival of 62 weeks. At the 5mg dose the partial response rate was 13%, and 73% had stable disease, with a median progression-free survival of 50 weeks. Among patients with carcinoid tumors, the partial response rate was 13% versus a partial response rate of 27% among patients with islet cell tumors. At 64 weeks, the progression-free survival was longer for patients with carcinoid tumors than for patients with islet cell tumors at 50 weeks. Phase III data from RADIANT-2 presented at EMSO 2010 showed Afinitor in combination with octreotide LAR increased time to tumor progression from 11.3 to 16.4 months, but did not provide a survival advantage. Results from RADIANT-3 were presented at the 12th World Congress on Gastrointestinal Cancer 2010. RADIANT-3 was a Phase III trial examining the safety and efficacy of Afinitor vs. best supportive care in patients with advanced pancreatic NET. Afinitor extended PFS from 4.6 months to 11.0 months and reduced the risk of cancer progression by 65% (HR=0.35, 95% CI 0.27-0.45, p<0.001). After 18 months, 24% of patients on Afinitor remained alive vs. 9% of those treated with placebo, demonstrating a significant increase in OS. Based on data from the RADIANT trials, Afinitor received FDA approval in May 2011.

Afinitor Approved In TS-SEGA

Phase II data in TS-SEGA were presented at ASCO 2010. In this open-label study, 28 patients aged three years and above (median age=11, range 3-34) with evidence of established SEGA growth received Afinitor orally at a dose of 3 mg/m²/day (once-daily or on an alternate day regimen), which was subsequently adjusted subject to tolerability to attain a whole blood trough concentration of 5-15 ng/mL. The median duration of treatment was 21.5 months. The study met its primary endpoint of change in primary SEGA lesion volume from baseline to six months (or at the last available assessment if a patient discontinued treatment prior to month 6). Results from the independent central review assessment showed that 75% (21 of 28 patients) experienced a reduction in SEGA volume of 30% or greater from baseline to six months (p<0.001).

Afinitor was associated with a clinically relevant reduction in overall frequency of seizures ($p=0.022$). Of 16 patients with seizures at the start of the study for whom video-EEGs were available, nine experienced decreases in seizure frequency, six reported no change, and one experienced an increase (median change -1.0, $p=0.022$). A reduction was also evident in the proportion of patients experiencing seizures on a daily basis from 7 of 26 patients at baseline to 2 of 25 patients at month six (based on caregiver observation).

Afinitor had a safety profile consistent with previous studies with this drug. The most common adverse events ($\geq 10\%$) included: stomatitis or mouth sores (79%), upper respiratory tract infection (79%), sinusitis (39%), middle ear infection (36%), fever (36%), convulsion (25%), acne-like skin inflammation (25%), diarrhea (25%), cellulitis (21%), vomiting (21%), body tinea or fungal infection (18%), cough (18%), headache (18%), personality change (18%), rash (18%), contact dermatitis (14%), dizziness (14%), gastroenteritis (14%), external ear infection (14%), allergic rhinitis or inflammation of nasal passages (14%), skin infection (14%), acne (11%), constipation (11%), dry skin (11%), gastric infection (11%), hypertriglyceridemia or high blood triglyceride levels (11%), skin disorder (11%) and leukopenia or decreased white blood cell count (11%). Grade three adverse events included convulsion (7%), stomatitis (4%), sinusitis (4%), vomiting (4%), dizziness (4%), leukopenia (4%), pneumonia (4%), aspiration or breathing in a foreign object (4%), viral bronchitis (4%), cyclic neutropenia or cyclical decrease in white blood cell count (4%), sleep apnea syndrome or suspension of breathing while asleep (4%) and tooth infection (4%). A single grade 4 convulsion was reported.

The Phase III EXIST-1 study (EXamining everolimus In a Study of TS) is ongoing and seeks to further explore the potential of everolimus for the treatment of TS. The EXIST-1 is evaluating treatment in patients with SEGAs, including tumor shrinkage, as well as evaluating the effect of everolimus treatment on seizures and skin abnormalities associated with TS. In October 2010, Afinitor was approved for the treatment of SEGA associated with TS.

In April 2012, the FDA approved Afinitor for the treatment of non-cancerous kidney tumors associated with TSC (renal angiomyolipomas), marking the first approval of a medical treatment in this patient population. The accelerated approval was based on the Phase III EXIST-2 study, which found that 42% of patients on everolimus experienced an angiomyolipoma response versus 0% of patients in the placebo arm ($p<0.0001$). The time to angiomyolipoma progression was also statistically longer in patients on everolimus ($p<.0001$). Among the 97% of trial patients with skin lesions, one of the key concerns for the majority of patients with TSC, a 26% response rate was seen with everolimus versus 0% with placebo ($p=0.0011$).

Femara In Decline Post Launch Of Generics

Femara, an aromatase inhibitor indicated for post-menopausal women with ER-positive breast cancer, is indicated in adjuvant treatment of advanced breast cancer. In December 2008, Novartis announced that it had reached a settlement with Mylan about the launch of its generic. Under the terms of the agreement, Novartis gave Mylan a license to market generic Femara 2.5mg prior to the expiration of the relevant U.S. patent. Generics entered the U.S. in June 2011 and the E.U. in May 2011. We forecast Femara sales of \$350MM (-9%) in 2014, \$305MM in 2015, \$105MM in 2016, \$30MM in 2018, and \$10MM in 2020.

Sandostatin Franchise Growing Modestly

Sandostatin LAR (octreotide acetate for injectable suspension), launched in the U.S. in 1999, is a once-monthly injection that reduces and normalizes levels of insulin-like growth factor-1 (IGF-1) and growth hormone in the majority of patients. LAR, a single, intragluteal injection and microsphere delivery system, is indicated for long-term maintenance therapy in acromegalic patients for whom medical therapy is appropriate and who have been shown to respond to and can tolerate Sandostatin. LAR is also indicated to control symptoms, such as severe diarrhea and flushing, of metastatic carcinoid tumors and the profuse, watery diarrhea associated with vasoactive intestinal peptide-secreting (VIPomas) tumors in patients who have responded to and tolerated subcutaneous injections of Sandostatin. Novartis launched LAR as a franchise extension for Sandostatin, but LAR also offered significant dosing convenience; once-monthly versus daily. In April 2005, the FDA approved Sandostatin generics. The LAR patent expired in 2010 in the E.U., although there has been no impact. The patent expires in 2014 and 2015 in the U.S. 85% of the Sandostatin revenues are derived from the LAR formulation with two-thirds of sales ex-U.S. We forecast Sandostatin franchise sales of \$1,640MM (+3%) in 2014, but then declining to \$1,565MM in 2015, \$1,425MM in 2016, \$1,225MM in 2018, and \$1,025MM in 2020.

Signifor A Modest Improvement Over LAR; Approved For Cushing's In The U.S. And E.U.

Signifor (SOM230; pasireotide) is a novel, multi-ligand somatostatin analogue that exhibits high binding affinity to 4 of the 5 somatostatin receptor subtypes sst 1,2,3 and sst 5. Signifor was approved for use in Cushing's in the E.U. in April 2012, and in the U.S. in December 2012. Sandostatin is not indicated in Cushing's. In May 2012, Novartis reported that patients with acromegaly were 63% more likely to achieve full biological control compared to Sandostatin in a Phase III study. Results from a Phase II acromegalic study demonstrated Signifor inhibited free IGF-I (insulin-like growth factor) in a more sustained fashion compared to Sandostatin, implying longer duration of action. Signifor LAR (long acting) was filed for acromegaly in the U.S. and E.U. (received positive CHMP opinion in September 2014). We forecast Signifor sales of \$60MM in 2014, \$150MM in 2015, \$250MM in 2016, \$450MM in 2018, and \$650MM in 2020.

Phase III PASSPORT Trial Demonstrated Signifor Efficacy In Cushing's

Data from the pivotal PASSPORT-CUSHINGS Phase III study in Cushing's disease were released in September 2010. The study evaluated the efficacy and safety of Signifor in 162 patients with persistent or recurrent Cushing's disease, as well as in patients with newly diagnosed Cushing's disease who are not candidates for surgery. Patients with primarily moderate to severe hypercortisolism were randomized to receive Signifor subcutaneous (sc) injection in doses of 600 μ g (n=82) or 900 μ g (n=80) twice daily. The primary endpoint was the proportion of patients who achieved normalization of UFC (urinary free cortisol) after six months without dose up-titration relative to randomized dose. UFC is typically used to diagnose and monitor Cushing's disease. In this test, urine is collected over 24 hours to assess average cortisol secretion. The primary endpoint was met for the higher dose tested (900 μ g sc twice daily). Secondary endpoints included safety, time to response, response duration and changes from baseline in clinical signs, symptoms, tumor volume and health-related quality of life. After six months, the primary efficacy responder rate was 26.3% (95% CI, 16.6 to 35.9) and 14.6% (95% confidence interval [CI], 7.0 to 22.3), respectively, for the 900 μ g and 600 μ g groups. Based on pre-specified criteria (lower bound of 95% CI >15%), the 900 μ g group met the primary endpoint and the 600 μ g group did not meet

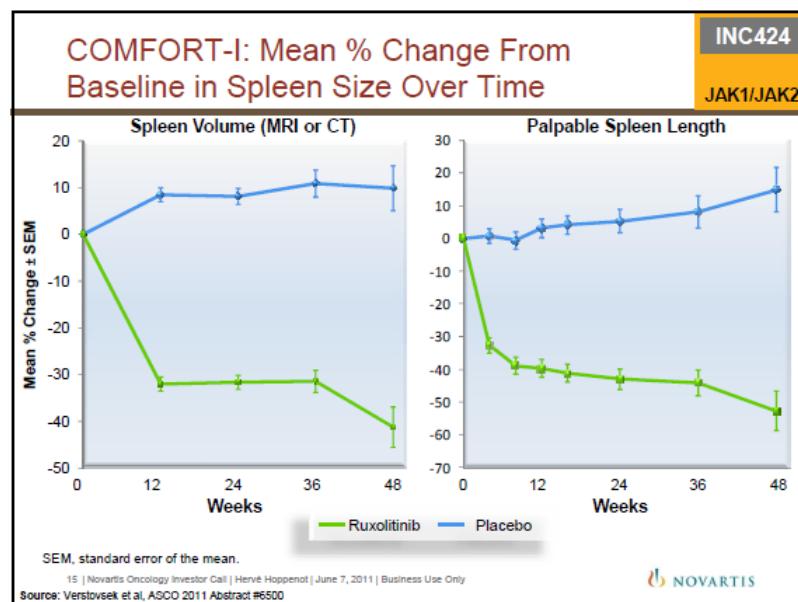
the primary endpoint. After 12 months, the proportion of responders regardless of dose up-titration was 13.4% and 25.0%, respectively, for the 600 μ g and 900 μ g groups. The median reduction in UFC after six months was 47.9% for both groups. The median reduction in UFC after 12 months was 67.6% (600 μ g) and 62.4% (900 μ g). Patients who showed little to no improvement in UFC levels (<50% reduction from baseline) by month two were unlikely to show improvement by month six or 12. The most frequently reported adverse events suspected by the investigators to be related to the study drug were diarrhea (58%), nausea (46.9%), hyperglycemia (38.9%), cholelithiasis (29.6%), abdominal pain (20.4%), diabetes mellitus (17.9%), fatigue (11.7%) and increased glycosylated hemoglobin (10.5%), with most events being Grade 1-2. Overall, the tolerability profile of Signifor is similar to other somatostatin analogs with the exception of the greater degree of hyperglycemia, which appears manageable with early detection and appropriate intervention following established treatment guidelines. As may be expected with a treatment that lowers cortisol levels in Cushing's disease, 13 (8.0%) patients experienced adverse events associated with cortisol levels below the normal range. This was managed by dose reduction without loss of efficacy.

Jakafi/Jakavi (INC424/ruxolitinib) Marketed In U.S. And E.U. For Myelofibrosis

Jakafi/Jakavi (ruxolitinib) was approved by the FDA for the treatment of myelofibrosis in November 2011. In August 2012, Jakavi (ex-U.S. name for Jakafi) was approved by the EMA for the treatment of myelofibrosis. In February 2013, NICE issued draft guidance recommending against the use of Jakavi to treat disease-related splenomegaly or symptoms in adults with chronic idiopathic myelofibrosis, post-polycythemia vera, or thrombocythemia myelofibrosis. Novartis does not believe there are inherent differences between the U.S. MF population and ex-U.S. patients. Ex-U.S. pricing is likely to vary by geography, depending on reimbursement, but \$60,000/year is a good target. In March 2014, Novartis reported that Jakafi met the primary endpoints of its Phase III trial (RESPONSE) in polycythemia vera (rare blood cancer) patients resistant/intolerant to hydroxyurea by maintaining hematocrit control and reducing spleen size; full data will be provided later this year. Novartis filed for this indication in the E.U. in June and a Japan filing is expected in H2:14. We estimate Jakafi/Jakavi sales of \$295MM (+81%) in 2014, \$460MM in 2015, \$650MM in 2016, \$1,050MM in 2018, and \$1,400MM in 2020.

Jakafi was evaluated in 2 pivotal Phase III trials (COMFORT-1 and COMFORT-2) versus either placebo or best available treatment. Both trials met the primary endpoint of >35% reduction in spleen volume at Week 24 or 48. COMFORT-I showed an OS benefit (HR=0.50, p=0.04) with median 51 week follow up. Remarkably, this was achieved despite the fact that 111 of the 154 placebo patients crossed over to the Jakafi arm (40 crossed over before unblinding, 71 after unblinding, and 38 discontinued). OS benefit was similar in all subgroups analyzed, including presence or absence of Jak mutation, risk category, and degree of baseline symptoms. Our consultants view these data as solid evidence of Jakafi's ability to modify the natural history of disease.

Reduction Spleen Size In COMFORT-1



Source: Novartis

In COMFORT-1, 41% of patients on ruxolitinib achieved a >35% reduction in spleen volume at Week 24 compared to 0.7% of placebo treated patients. Results for the primary endpoint in COMFORT-2 were similar at Week 48 with 28.5% of patients achieving >35% reduction in spleen volume compared to 0% of patients on best available therapy. Additionally, greater than 97% of patients on ruxolitinib experienced some reduction in spleen volume in COMFORT-2. Measures of quality of life including fatigue, pain, dyspnea, sleep, appetite, and diarrhea were improved by ruxolitinib whereas patients on best available therapy experience worsening in all of these parameters. Hematologic ADRs were more frequent with ruxolitinib when compared to either placebo or best available therapy; however, the mean number of transfusions required was balanced between groups. In COMFORT-2, patients' symptoms before and after dose interruption were shown. Patients experienced a total symptom score (TSS) benefit of about 25% for the 2 week period ahead of interruption. After interruption, symptoms returned to baseline over a period of 7-10 days and stayed there. Hence, there was no hyper-rebound. Additionally, SAEs after treatment interruption were identical on the ruxolitinib (3 of 49 patients, 6%) and placebo arms (3 of 54 patients, 6%). There was no AE signal dependency on various doses withdrawn, though the presenter suggested physicians might consider tapering off drug. Discontinuation due to AEs was also identical on ruxolitinib vs. placebo at 11%.

Survival Data Positive For Both COMFORT 1 And 2

Updated survival data from Jakafi's two Phase III trials in myelofibrosis were presented at ASH 2012 (HR=0.51 in COMFORT 2 and HR=0.58 in COMFORT 1, p<0.05 for each). Three year data for COMFORT-2 at EHA 2013 confirmed this trend with Jakafi demonstrating a 52% reduction in the risk of death (HR=0.48, p=0.009). Incyte's experts believe the OS benefit is driven by Jakafi patients being healthier overall, and better able to fight off infection and other ailments. However, other experts remain unconvinced of the drug's disease modifying properties. Until this debate is settled, we expect Jakafi adoption to be driven primarily by physicians' firsthand experience with the tremendous symptomatic benefits of therapy.

Data Increasingly Suggest Lower Starting Doses May Be Optimal

A higher than expected early discontinuation rate has tempered Jakafi's initial rollout. Data from multiple trials indicated that a 10mg dose (vs. the labeled 15mg or 20mg starting dose) may be more tolerable and as efficacious. Specifically, updated data from the TALPAZ trial demonstrated the viability of a dose escalation regimen in patients with low platelet counts, and follow up data from COMFORT 1 and 2 showed good efficacy and patient persistence (>50% of patients out to 28+ months) on doses as low as 10 mg.

Hematologic ADRs In COMFORT Trials

		Thrombocytopenia & Anemia: Most frequent AEs Generally manageable & rarely led to discontinuation		INC424 JAK1/JAK2	
		COMFORT-I		COMFORT-II	
		Ruxolitinib (N = 155)	Placebo (N = 151)	Ruxolitinib (N = 146)	BAT (N = 73)
All Grades	Thrombocytopenia	69.6%	30.5%	66.4%	26.0%
	Anemia	96.1%	86.8%	81.5%	49.3%
Grade 3 or higher	Thrombocytopenia	12.9%	1.3%	8.2%	6.8%
	Anemia	45.2%	19.2%	38.4%	20.5%

Source: Verstovsek et al, ASCO 2011 Abstract #6500 & Harrison et al, ASCO 2011 Abstract # LBA6501

NOVARTIS

Source: Novartis

Zykadia Receives Accelerated Approval in ALK+NSCLC

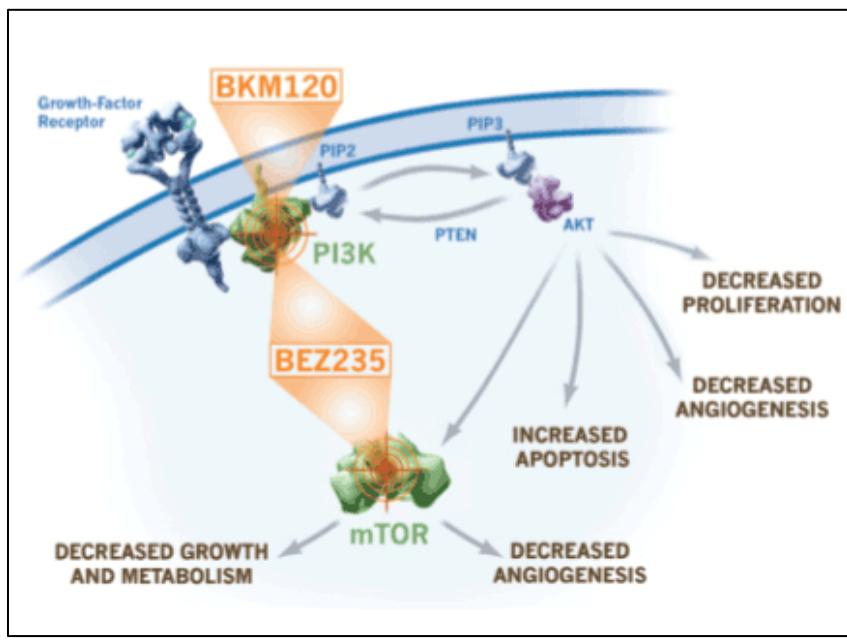
Zykadia (ceritinib/LDK378) is an ALK-inhibitor which has demonstrated activity in crizotinib-resistant NSCLC. In April 2014 (four months ahead of its PDUFA date), the FDA granted accelerated approval to Zykadia for patients with ALK+ NSCLC who were previously treated with crizotinib (Xalkori). It is estimated that 2-7% of patients with NSCLC are ALK-positive. Xalkori is the only other approved ALK tyrosine kinase inhibitor. A Phase I study, published in the March 2014 NEJM, showed that ALK+ NSCLC patients (n=114) treated with 400mg (or up to 750mg) of ceritinib per day achieved a 58% ORR and a median PFS of 7 months (range 5.6 -9.5 months). Novartis has two Phase II trials with Zykadia ongoing and two Phase III trials in progress, including one for chemo-naïve, crizotinib-naïve NSCLC, with a targeted 2016 filing date for this indication. Studies are also ongoing to optimize dose and GI tolerability; the company has indicated they expect a downward trend in dose. We estimate Zykadia sales of \$15MM in 2014, \$40MM in 2015, \$75MM in 2016, \$150MM in 2018, and \$250MM in 2020.

Several Early Stage Oncology Drugs Appear Promising

- **LEE011**, a highly -selective CDK4/6 inhibitor, started its first Phase III trial (MONALEESA-2) in December 2013 in combination with letrozole (Femara) in patients with HR+/HER2- advanced breast cancer (with no prior therapy for

advanced disease). Estimated enrollment is 500 and completion date is January 2017, with the primary endpoint of PFS. According to ClinTrials, LEE011 is in 10 additional Phase I/II trials evaluating its use in other tumor types, including solid tumors, melanoma, and malignant rhabdoid tumors, as well as in combination with various other anti-cancer agents including PI3Ki, fulvestrant, afinitor, and exemestane. Novartis hopes to file for breast cancer in 2016.

- **TKI258** (dovitinib lactate) is a multikinase inhibitor targeting VEGFR and FGFr. FGF appears important in breast and urothelial cancers and myeloma. TKI258 has been shown to be orally available and to be a potent inhibitor of VEGFR and GFGs in-vivo. Studies in AML and MM were terminated but TK1258 is currently being evaluated in Phase II studies for metastatic renal cell carcinoma (mRCC) patients refractory to approved targeted therapies, resistant prostate cancer, advanced urothelial cancer, and melanoma. A favorable response for dovitinib was demonstrated in patients with FGF pathway amplifications. Phase II studies in solid tumors are underway and the company is targeting 2017 for filing.
- **BKM120** is a pan PI3K inhibitor in development for the treatment of NSCLC, breast cancer, prostate cancer, GIST, and glioblastoma. Based on encouraging activity in Phase I/II studies in patients with heavily pretreated breast cancer, Novartis has advanced BKM120 to Phase III studies in HR+ AI-resistant, mTOR- naïve and mTOR-refractory breast cancer. The company anticipates breast cancer filing in 2015 and solid tumors 2018+.



Source: Company data

- **BYL719** is a PI3Kalpha-specific inhibitor. Novartis believes that the alpha (p100 α) isoform of PI3K is associated with the progression of various tumors. Clinical trials will be directed towards patients with PI3KAA mutations who are most likely to respond to BYL719. The drug is in Phase I/II trials with filing expected 2018+.
- **LDE225** (sonidegib), a smoothened inhibitor/hedgehog signaling inhibitor, is in Phase II for locally advanced basal cell carcinoma, Phase III for medulloblastoma, and Phase I/II for solid tumors. LDE225 was filed in 2012 for Gorlin Syndrome and advanced basal cell carcinoma was filed in the E.U. in Q2:14. Gorlin syndrome (basal cell nevus syndrome or nevoid basal cell carcinoma syndrome) is a rare, autosomal

dominant cancer syndrome. Gorlin patients have since been integrated into the BCC trials programs. In February 2014, Novartis announced that LDE225 met its primary endpoint (ORR) in its Phase II BOLT trial in basal cell carcinoma. Full data presented at ASCO 2014 showed an ORR of 41.8% for the 200mg dose and 32.5% for the 800mg dose. The side effect profile was consistent with hedgehog inhibitors; the most common grade 3-4 AEs were increased CPK and lipase and hypertension. Overall side effects were less frequent in the 200mg (30.4%) vs the 800mg arm (56%). LDE225 has a half-life of 60 hours and provides a dose dependent reduction in the expression of the hedgehog target gene, Gli1. Novartis has identified a 5-gene signature that is predictive of response in patients with hedgehog activation. We estimate LDE225 sales of \$40MM in 2015, \$60MM in 2016, \$100MM in 2018, and \$140MM in 2020.

- **LBH589** (panobinostat), an oral, multitargeted deacetylase inhibitor (DACi), is in Phase III for multiple myeloma and Hodgkin's lymphoma. Novartis originally planned Cutaneous T-Cell Lymphoma to be the first indication. However, it has discontinued development in CTCL in pursuit of HL and MM. DACis have been shown to have multiple effects in tumor cell lines: decreased oncoprotein expression (e.g., Bcr-Abl, HER-2), decreased angiogenesis, induction of apoptosis, induction of cell-cycle arrest, and decreased tumor cell motility and invasion. By interfering with the hallmarks of cancer, pan-DAC inhibitors have potential in many hematologic and solid malignancies, including lymphomas, chronic myeloid leukemia, multiple myeloma, breast cancer, and prostate cancer. LBH589 was identified as a potent DACi, which induced cell death of tumor cell lines but not normal cells.

Top-line results from the Phase III study in multiple myeloma (PANORAMA-1) were announced in December 2013 and showed that LBH589 in combination with bortezomib and dexamethasone met its primary endpoint of extending PFS in patients with relapsed or relapsed and refractory MS compared to bortezomib and dexamethasone alone. Novartis filed for relapse/refractory multiple myeloma in March 2014 in the U.S., May 2014 in the E.U., and June 2014 in Japan. Novartis estimates peak sales at \$500MM. We forecast LBH589 sales of \$100MM in 2015, \$150MM in 2016, \$250MM in 2018, and \$350MM in 2020.

The Phase II data for LBH589 in Hodgkin's lymphoma (HL), presented at ASH 2010, demonstrated substantial disease control and tumor reduction in HL patients who had relapsed or become treatment refractory post-stem cell transplant. 82% of study participants achieved disease control and 74% achieved tumor reduction at the 9.6 month follow-up. Up to 35% of all HL patients relapse or become refractory post-stem cell transplant. Based on previous discussion with FDA and given that this is an unmet medical need, Novartis believed a filing based on Phase II data in relapsing or treatment refractory NHL patients post-stem cell transplant would be accepted. In the end, FDA ruled that a single arm Phase II study was not sufficient and did not accept the filing. A Phase III first-line trial for HL began in April 2010.

- **Cell Therapy.** Novartis has three efforts in cell therapy, including CTL019 (leukemias, lymphomas), FCRx (solid organ transplant), and HSC835 (leukemias, leukodystrophies, hemoglobinopathies). In July 2014, CTL019 received Breakthrough Therapy designation for the treatment of pediatric and adult patients with relapsed/refractory ALL. Pivotal studies for CTL019 are expected to start in Q4:14 with U.S. filing targeted for 2016. There is a pipeline of CAR (chimeric antigen receptor) technology, including those directed at mesothelioma and pancreatic cancer and glioma, a second generation CART (entered clinic in late Q4:13), and multiple other programs in earlier stages. In February 2014, Novartis acquired privately-held CoStim which is expected to strengthen efforts in this area.

Glaxo Oncology Products Acquired As Of Q3:2015 Expand Portfolio BRAF And MEK Inhibitors Marketed; Combination A Meaningful Advantage

Tafinlar (dabrafenib) and Mekinist (trametinib) were approved by FDA in May 2013. Tafinlar is indicated as a single-agent oral treatment for unresectable melanoma or metastatic melanoma in adult patients with BRAF V600E mutation. Tafinlar is not indicated for the treatment of patients with wild-type BRAF melanoma. Mekinist is indicated as a single-agent oral treatment for unresectable or metastatic melanoma in adult patients with BRAF V600E or V600K mutations. Mekinist is not indicated for the treatment of patients who have received a prior BRAF inhibitor therapy.

The combination received accelerated FDA approval in January 2014 for the treatment of unresectable or metastatic melanoma in patients with BRAF V600E or V600K mutations. The accelerated approval is contingent on the results of the ongoing Phase III trials. The combination application in the E.U. was withdrawn in March 2014 and will be re-submitted when additional Phase III data are available. Tafinlar was approved in the E.U. in September 2013. Mekinist was approved in the E.U. in July 2014. We estimate Tafinlar sales of \$160MM in H2:15, \$420MM in 2016, \$675MM in 2018, and \$925MM in 2020. We estimate Mekinist sales of \$140MM in H2:15, \$375MM in 2016, \$625MM in 2018, and \$875MM in 2020.

Combo Results Promising

In January 2014, Glaxo reported positive top-line results for the COMBI-d Phase III trial which compared the combo of dabrafenib plus trametinib to dabrafenib plus placebo as 1st-line therapy in melanoma patients with unresectable or metastatic BRAF V600/K mutations. The primary endpoint of PFS was met; patients are now being followed for OS. The most common AEs (>20%) were pyrexia, fatigue, nausea, headache, chills, diarrhea, arthralgia, rash, hypertension, and vomiting. Full data will be reported later this year or early next.

In July 2014, the second Phase III study, COMBI-v, evaluating the combo compared to Zelboraf, was stopped early by the IDMC based on an interim analysis which demonstrated an OS benefit that crossed the pre-specified efficacy stopping boundary. Safety profile of the combo arm was consistent with existing profile. Secondary endpoints include PFS, ORR, and response duration. Detailed OS data expected to readout late 2014 or early 2015.

Trametinib is also being evaluated in combination with Pfizer's palbociclib in a Phase I/II study of patients with advanced metastatic melanoma (patients with BRAF V600 wild type melanoma including NRAS mutations). Study 200344 is a dose-escalation, open-label study which will also evaluate the effect on biomarkers.

Dabrafenib Efficacy Similar To Roche's Zelboraf In BREAK3

In BREAK3, patients with treatment naive V600E mutant melanoma (Stage III/IV) were randomized 3:1 to receive dabrafenib 150mg BID or DTIC 100mg/m² IV every 3 weeks. Dabrafenib met its primary endpoint of improvement in investigator-assessed PFS compared to DTIC (PFS of 5.1 months for dabrafenib vs. 2.7 months for DTIC, HR=0.3, p<0.0001). A PFS benefit was maintained across all subgroups with the exception of patients ≥65 years old, the lack of significance in this patient population likely was the result of variability across a small sample size (53 patients ≥65 y/o compared to 197 patients <65 y/o). The PFS benefit for dabrafenib in BREAK3 is nearly identical to what was observed in Roche's Phase III BRIM3 trial for Zelboraf (PFS for Zelboraf of 5.3 months vs. 1.6 months for DTIC). OS data for dabrafenib has not yet matured; OS for

Zelboraf in BRIM3 was 13.6 months. A detailed description of the efficacy data in BREAK3 is below:

Dabrafenib Efficacy In BREAK3

	Investigator Assessed		Independent Review	
	Dabrafenib	DTIC	Dabrafenib	DTIC
PFS, mo	5.1	2.7	6.7	2.9
CR, n (%)	6 (3%)	0	6 (3%)	1 (2%)
PR, n (%)	93 (50%)	12 (19%)	87 (47%)	3 (5%)
ORR (CR + PR), n (%)	99 (53%)	12 (19)	93 (50%)	4 (6%)

Source: ASCO 2012

Adverse Event Profile Differentiates Dabrafenib From Zelboraf

Dabrafenib was well tolerated in BREAK3 with only 3% of patients discontinuing treatment as the result of adverse events. Interestingly, the side effect profile of dabrafenib is distinctly different than that of Zelboraf. Only 7% of patients on dabrafenib developed keratoacanthoma (KA) or squamous cell carcinoma (SCC) compared to 11% and 19% of patients on Zelboraf in BRIM3. Additionally, only 3% of patients on dabrafenib experienced photosensitivity compared to 41% of patients on Zelboraf in BRIM3. Dabrafenib has previously shown intracranial disease control in >80% of patients with a median OS of >31 weeks, which may further differentiate dabrafenib from Zelboraf. The adverse event profile for dabrafenib in BREAK3 is detailed below:

AEs Occurring In ≥5% Of Patients In BREAK3

AE	Dabrafenib, n (%)			DTIC, n (%)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Skin	Hyperkeratosis	95 (51)	1 (<1)	1 (<1)	--	--
	Palmar-plantar hyperkeratosis	39 (21)	4 (2)	--	1 (2)	--
	SCC/KA	13 (7)	9 (5)	--	--	--
GI	Nausea	18 (10)	--	--	21 (36)	--
	Vomiting	8 (4)	--	--	12 (20)	--
Hematologic	Neutropenia	2 (1)	1 (<1)	--	9 (15)	3 (5)
	Thrombocytopenia	1 (<1)	1 (<1)	--	5 (8)	1 (2)
	Leukopenia	1 (<1)	--	--	3 (5)	1 (2)
Other	Arthralgia	30 (16)	1 (<1)	--	--	--
	Fatigue	32 (17)	2 (1)	--	13 (22)	--
	headache	32 (17)	--	--	2 (3)	--
	Pyrexia	28 (15)	5 (3)	--	--	--
	Asthenia	26 (14)	--	--	7 (12)	--

Source: ASCO 2012

Dabrafenib First To Demonstrate CNS Benefit

BREAK-MB evaluated dabrafenib in Stage IV melanoma patients with one or more brain mets without prior brain therapy (Cohort A) or with progression following prior brain therapy (Cohort B) with V600E/K mutations. Patients received dabrafenib 150mg BID. Of 127 patients enrolled, 41 (Cohort A, n=24; Cohort B, n=17) had reached the 8-week disease assessment. Unconfirmed OIRR in Cohort A was 10/19 (53%; 95% CI

28.9–75.6%) for V600E and 1/5 (20%; 95% CI 0.5–75.6%) in V600K. In Cohort B unconfirmed OIRR was 6/15 (40%; 95% CI 16.3–67.7%) in V600E and 1/2 (50%; 95% CI 1.3–98.7%) in V600K. 19% of patients in Cohort A reported an SEA compared to 25% in Cohort B. One patient in Cohort A died from a cerebral hemorrhage and one patient in Cohort B died from a fatal seizure. The most common adverse events were headache, hyperkeratosis, rash, fatigue, nausea, and pyrexia. Our physician consultants are impressed with the efficacy of dabrafenib in this population.

Trametinib Demonstrates OS Advantage In METRIC

Trametinib met its primary PFS endpoint in its Phase III METRIC trial comparing trametinib to chemotherapy in patients with metastatic melanoma who had received one prior regimen of chemotherapy (PFS for trametinib was 4.8 months vs. 1.5 months for chemotherapy, HR=0.45, p<0.0001). Additionally, an overall survival benefit was observed for trametinib at the interim analysis (81% of patients on trametinib alive at 6-months vs. 67% on chemotherapy, HR=0.54, p=0.0136). The most common adverse events reported in the trametinib arm were rash (57%), diarrhea (43%), fatigue (26%), and peripheral edema (26%). Other adverse events associated with trametinib were hypertension (15%), chorioretinopathy (<1%), and a decrease in ejection fraction/ventricular dysfunction (7%). Adverse events in METRIC are detailed below:

Adverse Events In METRIC

Adverse Event	Trametinib, n=211	Chemotherapy, n=99
Rash	121 (57%)	10 (10%)
Diarrhea	91 (43%)	16 (16%)
Peripheral Edema	54 (26%)	3 (3%)
Fatigue	54 (26%)	27 (27%)
Dermatitis acneiform	40 (19%)	1 (1%)
Nausea	38 (18%)	37 (37%)
Alopecia	36 (17%)	19 (19%)
Hypertension	32 (15%)	7 (7%)
Contipation	30 (14%)	23 (23%)
Vomiting	27 (13%)	19 (19%)

Source: ASCO 2012

Tykerb Forecast To Experience Moderate Growth Through 2020

Tykerb (lapatinib), an oral, small molecule, dual HER2/EGFR inhibitor was approved in March 2007 for use in combination with Xeloda for the treatment of patients with HER2-positive metastatic breast cancer who have received prior therapy including an anthracycline, a taxane, and Herceptin. In June 2008, the EC granted conditional marketing authorization for Tykerb. U.S. approval was supported by a single Phase III trial in 392 refractory HER positive metastatic breast cancer patients. The study showed a time to disease progression benefit for Tykerb plus Xeloda (36.9 weeks) versus Xeloda monotherapy (19.7 weeks, p=0.00016). Although this trial enabled Tykerb to receive FDA approval, Tykerb may not represent a significant advance for patients with Herceptin-refractory breast cancer, as it is widely assumed (though unproven) that Herceptin would also show benefit in this setting. Our consultants report limited use of Tykerb in their HER2 positive metastatic breast cancer patients. While they note that Tykerb is a viable alternative in patients no longer benefiting from Herceptin, they have tended to continue using Herceptin in the majority of their patients post-progression as they see no reason to switch to Tykerb and note Tykerb's safety profile may on the margin be differentially worse than that of Herceptin. Versus Herceptin, Tykerb holds theoretical advantages in terms of oral administration, lower

cardiotoxicity, and efficacy in treating CNS metastases. However, consultants note that these advantages are purely speculative. Consultants assert that oral dosing is not a significant advantage in the treatment setting as compliance with a five pills/day regimen cannot be assured and every three week Herceptin infusions are hardly inconvenient. As a result, patients have not clamored for Tykerb.

In December 2009 at the SABSC, Glaxo presented data from a Phase III study comparing Tykerb alone to Tykerb + Herceptin in patients who had failed a median of three Herceptin based therapies. Despite Glaxo's positive presentation of the study, Tykerb alone was inferior to the combination. In February 2012, Glaxo submitted a sNDA to the FDA for Tykerb in combination with trastuzumab for the treatment of patients with HER2+ breast cancer who have received prior trastuzumab containing regimens. While the filing is based on a successful study that demonstrated a trend towards survival, the study was small and was not intended for registration.

In June 2008, the European Commission granted conditional marketing authorization for Tyverb (E.U. name). Tyverb suffered a setback in October 2008 when the U.K.'s NICE in its second appraisal document suggested that Tyverb was not cost-effective and should only be used in the clinical trial setting. In July 2009, Glaxo won an appeal requiring NICE to reexamine its decision. In June 2010, NICE issued an appraisal determination against funding of Tykerb in combination with Xeloda for treatment of advanced breast cancer. In April 2009, Glaxo announced the submission of simultaneous regulatory applications for Tykerb as first-line therapy combined with anti-hormonal therapy for patients with hormone-sensitive, metastatic (or advanced) breast cancer in Europe and the United States, based on the EGF30008 study. In January 2010, FDA approved Tykerb in combination with Femara (AI) for first-line metastatic breast cancer. E.U. approval was also received in 2010. The first-line indication could provide a modest boost to sales given that between 25% and 30% of breast cancers over express HER2 receptors and 60% to 70% of all breast cancer cases in Europe and the U.S. are HR positive. In August 2013, Tyverb received EC approval for the additional indication of use with trastuzumab in patients with HER2-positive, HR-negative metastatic breast cancer.

Tykerb is in several Phase III studies including adjuvant breast, gastric, and head and neck squamous cell (resectable) cancers. We estimate Tykerb sales of \$200MM in H2:15, \$410MM in 2016, \$445MM in 2018, and \$475MM in 2020.

NeoALTTO Shows Potential Of Dual HER2 Inhibition

In January 2012, final data from the Phase III NEO-ALTTO study, evaluating lapatinib, trastuzumab, and the combination in the neo-adjuvant setting, were published in the Lancet. Women with HER2+ primary breast cancer with tumors greater than 2cm in diameter were randomly assigned to oral lapatinib (1500mg), i.v. trastuzumab (loading dose 4mg/kg2, subsequent doses of 2mg/kg), or lapatinib (1000mg) plus trastuzumab. Anti-HER2 therapy alone was given for the first 6 weeks; weekly paclitaxel (80mg/kg/m²) was then added to the regimen for an additional 12 weeks, before definitive surgery was undertaken. After surgery, patients received adjuvant chemo followed by the same targeted therapy as in the neoadjuvant phase to 52 weeks. The primary endpoint of the study was the rate of pathological complete response. The pCR rate was significantly higher in the group given lapatinib and trastuzumab (51.3%; 95% CI 43.1-59.5%) compared to trastuzumab alone (29.5%; 95% CI 22.4-37.5%); difference 21.1% (95% CI 9.1-34.2%, p=0.0001). No significant differences in pCR between the lapatinib and trastuzumab arms were observed. The addition of lapatinib increased the frequency of grade 3 diarrhea and grade 3 liver-enzyme elevations.

Together these data suggest that dual inhibition of HER2 may be a valid approach for the treatment of HER2+ breast cancer in the neoadjuvant setting.

ALTTO Trial Of Tykerb In The Adjuvant Setting Failed

In May 2007, GlaxoSmithKline and the National Cancer Institute initiated the 8,000-patient worldwide ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) Phase III study evaluating Tykerb vs. Herceptin vs. Tykerb/Herceptin combination vs. Herceptin followed by Tykerb, in HER 2+ adjuvant patients. An interim review of the ALTTO study showed that Tykerb as monotherapy was unlikely to meet the non-inferiority PFS endpoint vs. Herceptin. As a result, the Tykerb monotherapy arm of the trial was discontinued. The trial continued to compare Tykerb plus Herceptin to Herceptin alone.

At ASCO 2014, final results of ALTTO trial were presented. The Phase III study of Tykerb and Herceptin did not meet the primary endpoint of improved disease free survival (DFS) compared to single agent therapy with Herceptin as adjuvant treatment for HER2 positive early breast cancer. This result is not overly surprising.

Promacta Growth Helped By Expanded Indication in HCV Patients

Promacta (eltrombopag) was approved by FDA in November 2008 for the short-term treatment of idiopathic thrombocytopenia purpura (ITP) based on two short-term therapy six-week studies: a 114 patient Phase III trial and a 117-patient Phase II trial. In early 2011, Promacta received approval for chronic immune (idiopathic) thrombocytopenic purpura. Promacta has a favorable label with few restrictions. Promacta has a REMS program similar to that approved with Amgen's Nplate (approved July 2008). It only allows prescribers, pharmacies, and patients registered with the program to prescribe, dispense, and receive Promacta. Besides a black-box warning for hepatotoxicity, there are no other major restrictions. The average cost per month is approximately \$3,600. Assuming similar efficacy and safety data between Promacta and the Nplate, orally-delivered Promacta is likely to be favored by the majority of patients. Nplate's weekly subQ injection will likely be used in less compliant and sicker patients. In December 2008, the Phase III RAISE data, in chronic ITP, were presented at ASH and confirmed Promacta's efficacy and safety. In April 2010, Revolade (European trade name) was approved in Europe. Studies in chronic liver disease were suspended, clipping a large market opportunity.

Promacta was approved for the treatment of thrombocytopenia in adults with chronic HCV infection in November 2012. In August 2014, the FDA approved Promacta for the treatment of cytopenias in patients with severe aplastic anemia (SAA) who have an inadequate response to immunosuppressants. We forecast Promacta sales of \$240MM in H2:15, \$535MM in 2016, \$685MM in 2018, and \$835MM in 2020.

Indication For Thrombocytopenia In HCV Patients Gained In 2012

Full results from ENABLE1 were presented at AASLD 2011. In ENABLE 1, patients who received eltrombopag along with Pegasys® (peginterferon alfa-2a) and ribavirin antiviral therapy achieved a statistically significant improvement in the primary endpoint of sustained virologic response (SVR). 23% of patients in the eltrombopag group achieved SVR compared to 14% of patients receiving placebo ($p=0.0064$). Serious adverse events were reported in 20% of eltrombopag and 15% of placebo patients. During the entire study period death occurred in 2% of patients in the eltrombopag and 3% in the placebo group. Thromboembolic events were reported in 2% of eltrombopag patients and 2% of placebo patients. Elevations in liver enzymes

were similar in both groups. Events consistent with worsening of liver function were reported in 13% of eltrombopag patients and 8% of placebo patients.

Complete data from ENABLE 2 were presented at EASL 2012. The ENABLE 2 trial met its primary endpoint of improved SVR, with 19% of eltrombopag patients and 13% of placebo patients achieving SVR ($p=0.0202$). Serious adverse events were reported in 20% of eltrombopag and 15% of placebo patients. Death occurred in 4% of patients in the eltrombopag and 2% of placebo group. Thromboembolic events were reported in 4% of eltrombopag patients and less than 1% of placebo patients. Elevations in liver enzymes were similar in both groups. Events consistent with worsening of liver function were reported in 15% of eltrombopag patients and 8% placebo patients.

Arzerra (Ofatumumab) Approved For First Line CLL

Arzerra is a fully human anti-CD20 monoclonal antibody being developed for both oncology (CLL, follicular non-Hodgkin's lymphoma, DLBCL) and autoimmune (multiple sclerosis, PII) indications. In April 2010, Arzerra achieved conditional marketing authorization in the E.U. for refractory CLL. Arzerra was launched in Japan in May 2013. Approval in first-line CLL was received in the U.S. in April 2014 and in the E.U. in July 2014.

In July 2014, positive results were announced from an interim look at the Phase III study (PROLONG) of Arzerra used as maintenance therapy in relapsed CLL. The IDMC interim analysis showed that Arzerra treatment met the primary endpoint of PFS. The study evaluated 532 patients with rCLL, comparing Arzerra maintenance (two initial doses a week apart, then one dose every 8 weeks for up to 2 years) to no further treatment. Detailed data will be presented at a future medical meeting. We estimate Arzerra sales of \$110MM in H2:15, \$250MM in 2016, \$320MM in 2018, and \$390MM in 2020 for all indications.

CLL Data Mixed

In May 2013, GSK announced top-line results from a pivotal Phase III trial of Arzerra in combination with chlorambucil in patients with previously untreated CLL. Patients randomized to Arzerra plus chlorambucil had a PFS of 22.4 months compared to 13.1 months on chlorambucil alone ($HR=0.57$, $p<0.001$). There were no unexpected safety findings.

Interim data from a single-agent, multi-cohort study evaluating PCI-32765 in CLL/SLL patients with relapsed/ refractory disease or with treatment-naive disease who were 65 years of age or older were presented at ASCO 2011. At a median follow-up of 6.3 months, 67% of patients with treatment-naive disease had achieved an overall response by standard criteria, with an additional 19% of patients achieving a nodal response. At a median follow-up of 7.8 months in the cohort of relapsed/ refractory patients treated with 420mg qD, the rate of overall objective response was 48% with an additional 41% of patients having achieved a nodal response. The initial response assessment at two months in patients with relapsed/refractory disease appeared similar between the 420mg qD and 840mg qD doses. Additionally, achieving response appeared to be independent of poor-risk features, such as del (17p), del (11q), and lack of mutation in the immunoglobulin heavy chain variable region gene. At the time of the interim analysis, only three patients had experienced disease progression, and 81% of relapsed/refractory patients in the more mature 420mg QD cohort were on treatment and free-of-progression at six months.

However, in June 2014, Glaxo reported that a Phase III study (n=122) of Arzerra vs physicians choice in bulky fludarabine-refractory CLL did not meet PFS endpoint. The median PFS was 5.36 months for Arzerra vs 3.61 months for physicians choice (HR = 0.79, p= 0.267). Full efficacy and safety data will be presented at a future time. The current approved indications in the U.S. and E.U. do not include bulky fludarabine-refractory patients.

Phase III Study In DLBCL Vs. Rituxan Misses Endpoint

In December 2009, Genmab—Arzerra's licensor—initiated a Phase III head-to-head study (ORCHARRD) of Arzerra versus Rituxan, in 410 patients with diffuse large B-cell lymphoma who are refractory to or have relapsed following first-line treatment with Rituxan in combination with a chemotherapy regimen containing anthracycline and are eligible for autologous stem cell transplant (ASCT). In May 2014, Glaxo announced that Arzerra + chemo did not meet the primary endpoint of improved PFS vs. Rituxan + chemo. There were no differences in AE's leading to discontinuation, Gr 3+ AEs or SAEs between the two arms. However, the Arzerra arm did report more dose interruptions and delays (due to infusion reactions) and also had increased levels of serum creatinine.

Votrient (pazopanib) Approved For mRCC And Sarcoma; OS Data Does Not Support Use In Ovarian Cancer

Votrient is an oral, once-daily angiogenesis inhibitor targeting multiple tyrosine kinases including VEGFR, PDGFR and c-kit. Votrient was approved in October 2009 for mRCC. There are now many drugs approved for kidney cancer. Votrient was approved in mRCC on a Phase II study and a randomized double-blind placebo-controlled Phase III monotherapy trial. The Phase III data presented at ASCO 2009 demonstrated that the median progression-free survival or PFS in the Votrient treated group was 9.2 months compared to 4.2 months in the placebo group (HR 0.46, 95% CI 0.34,0.62; p<0.0000001). The interim analysis showed that there was no statistically significant difference in OS. The hazard ratio for overall survival was 0.73 (95% CI: 0.53 - 1.00) with a one-sided p-value of 0.02 (>0.004, significance level allocated for the interim OS analysis).

In December 2010, Glaxo won the backing of the U.K. National Institute for Health and Clinical Excellence (NICE). Glaxo provides Votrient at the reduced cost of £2,000 per month (a 12.5% discount). Votrient was approved with a black box warning for severe and fatal hepatotoxicity. FDA briefing documents for the ODAC panel in October 2009 highlighted the high incidence of hepatic laboratory abnormalities and four cases fulfilled Hy's Law (about 0.4%). Significantly, three hepatic deaths related to or associated with Votrient were also observed in the clinical trials.

Studies are progressing in myeloma, prostate, GIST, and NSCLC. In March 2014, Glaxo withdrew its E.U. application for maintenance therapy in advanced ovarian cancer as interim OS data did not support a positive benefit-risk in this indication. We estimate Votrient sales of \$520MM in H2:15, \$1,250MM in 2016, \$1,700MM in 2018, and \$2,100MM in 2020 for all indications.

Side Effect Profile May Be Differentiating Factor

Votrient is differentiated from Sutent by a superior side-effect profile. This was conclusively demonstrated in the PISCES trial where blinded patients and physicians overwhelmingly preferred Votrient to Sutent (61% of patients and 70% of physicians preferred Votrient vs. 22% of patients and physicians who preferred Sutent). While PISCES was not designed to compare the efficacy of Votrient relative to Sutent, no

statistical differences in response rate between the two agents was observed. The COMPARZ trial was a head-to-head efficacy study comparing Votrient to Sutent in RCC; data was presented at ESMO 2012. In COMPARZ, 110 patients were randomized to receive either pazopanib or sunitinib for 4-weeks followed by 2-weeks off treatment. Treatment was continued in both arms until progression, unacceptable toxicity or voluntary withdraw. The primary endpoint was PFS. Secondary endpoints included OS, ORR, and QoL. The PFS ratio for Votrient vs. Sutent was 1.047 (95% CI, 0.898-1.220); predefined criteria for non-inferiority was the upper bound of a two-sided 95% CI of 1.25. Median PFS was 8.4 months for pazopanib compared to 9.5 months for sunitinib. The secondary endpoint of ORR showed an ORR of 31% in the pazopanib arm versus 25% in the sunitinib arm ($p=0.032$). An analysis of OS showed that Votrient provided an OS of 28.4 months compared to 29.3 months on sunitinib ($p=0.275$).

PALETTE Trial The Basis For Sarcoma Approval

Pazopanib has demonstrated activity in patients with advanced STS. In the PALETTE trial, the efficacy and safety of pazopanib versus placebo in second and third line treatment were evaluated in metastatic STS. PALETTE included several types of STS including leiomyosarcoma, synovial sarcoma, and other forms of STS; adipocytic sarcomas were excluded based on a lack of efficacy in Phase II studies. Patients were randomized 2:1 to pazopanib (500mg BID) or placebo. Pazopanib met its primary PFS endpoint compared to placebo (4.6 months for pazopanib vs. 1.5 months for placebo, HR=0.31, $p<0.0001$). The PFS treatment effect was consistent across all STS types. Pazopanib did not meet the secondary OS endpoint (11.9 months for pazopanib vs. 10.4 months for placebo, HR=0.83, $p=0.1782$). The average treatment duration for pazopanib was 16.4 weeks compared to 8.1 weeks for placebo with the majority of placebo patients discontinuing therapy as the result of disease progression. The most common ADRs were fatigue, diarrhea, nausea, weight loss, and hypertension. A mild decrease in ejection fraction was observed in the pazopanib group along with reversible elevations in LFTs. In April 2012, the FDA approved Votrient for the treatment of advanced soft tissue sarcoma in patients who had received prior chemotherapy. The label limits the treatment of patients with adipocytis STS or gastrointestinal stromal tumors.

Hycamtin Should Grow Modestly Despite Generic Competition In Some Markets

Hycamtin i.v. is approved for SCLC and ovarian cancer. In October 2007, the FDA approved Hycamtin capsules for the treatment of relapsed SCLC. In the pivotal Phase III program, Hycamtin significantly improved overall survival, 25.9 versus 13.9 weeks (best supportive care) in SCLC relapsers not eligible for IV therapy. Hycamtin is the only oral agent approved for relapsed SCLC. SCLC constitutes 15% of lung cancers; however, most patients respond to first-line intravenous chemotherapy. Hycamtin has been approved and launched in more than 70 countries. We forecast Hycamtin sales of \$45MM in H2:15, \$100MM in 2016, \$130MM in 2018, and \$160MM in 2020.

CNS

Gilenya Facing Formidable New Oral Competitors

Gilenya (fingolimod; formerly FTY720) is a sphingosine-1-phosphate receptor modulator. In September 2010, the drug became the first FDA-approved DMARD therapy for MS that is dosed orally (1x/day). Novartis licensed the compound from Mitsubishi Pharma and targeted development toward transplant rejection. This indication was subsequently abandoned in favor of MS. Gilenya's pivotal program

included three Phase III studies in MS. Two Phase III trials were two-year double-blind RRMS studies that compare Gilenya at doses of 0.5mg and 1.25mg with placebo, one in the U.S. (FREEDOMS II) and the other ex-U.S. (FREEDOMS I). The FREEDOMS II trial had an additional prespecified 300-patient safety analysis, requested by the FDA, to monitor ophthalmic (macular edema was seen in transplant studies), pulmonary function and cardiovascular adverse events (bradycardia associated with hypertension changes). The third study is a one-year active comparator trial, TRANSFORM, which compared the 0.5mg and 1.25mg doses of Gilenya with Avonex. A fourth Phase III study, INFORMS, is evaluating Gilenya in 971 patients with PPMS, and will likely report in Q4:14. We forecast Gilenya sales of \$2,460MM (+27%) in 2014, \$2,830MM in 2015, \$3,100MM in 2016, \$3,600MM in 2018, and \$4,200MM in 2020.

Gilenya Program Overview

Study	Design	Comparator	Population	Duration	Number of participants
2201 (completed)	Phase II	Placebo	Relapsing MS	6 months	281*
2201F1 (ongoing)	Long-term open-label extension	–		Until FTY720 on market	250*
TRANSFORMS 2302 (completed)	Phase III	IFN beta-1a (Avonex®) IM weekly	RRMS	1 year (+extension)	1292*
FREEDOMS 2301 (completed)	Phase III	Placebo	RRMS	2 years (+ extension)	1272*
FREEDOMS II 2309 (ongoing)	Phase III	Placebo	RRMS	2 years (+ extension)	1083*
INFORMS 2306 (ongoing)	Phase III	Placebo	PPMS	3+ years	~650†
1201** (ongoing)	Phase II	Placebo	Relapsing MS	6 months (+ extension)	~168*

* Randomized

† Registration study required for Japan

‡ Target enrolment number

FN beta 1a IM, interferon beta 1a intramuscularly; MS, Multiple Sclerosis; PPMS, primary progressive MS; RRMS, relapsing remitting MS

Source: Novartis

Safety Concerns Prompted Required ECG Monitoring

In November 2011, a 58 year-old patient on a beta blockers and calcium channel blocker died of 1st degree heart block within 24 hours of receiving their first dose of Gilenya. While this death represented the first of its kind in more than 28,000 patients on drug, similar reports have also been reported across the E.U. In January 2012, reports of ten deaths, including six unexplained deaths, three heart attacks, and one death due to disruption of heart rhythm were reported by the EMA.

Novartis provided details on the labeling updates for Gilenya in the E.U. and U.S. post reports of several CV-related deaths in patients on Gilenya. In the E.U., the final labeling changes reflect temporary changes that had been in place for several months, including requirements for continuous ECG monitoring and hourly BP/HR monitoring. The new U.S. label requires an ECG prior to the first dose and 6-hours after the first dose, hourly BP/HR monitoring, and restricts the patient population that is appropriate for Gilenya. The U.S. label previously did not require ECG monitoring. Details of the label changes are below:

Gilenya Label Changes

	CHMP Recommendation	FDA Labeling Change
ECG Monitoring	ECG before first-dose, minimum of 6-hours real-time ECG monitoring recommended after first dose	ECG before and after first-dose observation
HR/BP Monitoring	Hourly	Hourly
Overnight Monitoring	Patients who may be less tolerant of or are more likely to develop significantly slowed or abnormal heart rate because of certain underlying conditions or concomitant medications	Certain pre-existing cardiac conditions or those taking certain concomitant medications would require overnight monitoring following administration of first dose of medication
Patient Considerations	Contraindicated in patients with serious AV block, sick sinus syndrome, active ischemic heart disease, uncontrolled BP, QTc prolongation, unstable angina and severe heart failure	Contraindicated in patients with history or presence of certain cardiac conditions, including heart attack or stroke in the past six months, second- and third-degree AV block and other serious cardiac rhythm disturbances, and in patients treated with certain anti-arrhythmic drugs.

Source: Company data

Our U.S. physician experts had already implemented ECG monitoring prior to the first dose and routinely measure BP/HR hourly post the first dose. They believe that adding an ECG 6-hours post the first dose is cumbersome, but doable at a medical center. Additional monitoring requirements could be a barrier to prescribing for community neurologists who are already nervous about using Gilenya and the risk of sudden death. ECG monitoring may also present a logistical barrier in the community by limiting physicians' ability to conduct first dose observations in the waiting room.

Our physician experts note that only a small portion of their MS patients present with prolonged QTc intervals, are at higher risk of rhythm disturbances, or are on concomitant HR lowering drugs. When treating patients with beta blockers or calcium channel blockers for migraine or hypertension, medications are held the day before, the day of, and the day after the first dose observation. At this point, our physician experts will not treat any patient with Gilenya if the ECG is anything but normal or if the patient is taking any cardiac or heart rate lowering drugs. They will not be monitoring any patients overnight. A patient cannot come back from sudden death and there are no predictors for who is likely to experience such an event.

Despite safety signals, monitoring requirements, and the lack of long-term experience, Gilenya market share remains solid (8.9% share of the MS market in the U.S. during May 2014, up 13% Y/Y).

Gilenya Uncertainties Increase Appeal Of New Entrants

Additional monitoring and patient restrictions for Gilenya make other treatment options appear more attractive, including BIIB's Tecfidera (BG-12; FDA approved on 3/27/13). Our experts believe Gilenya will be a niche drug, although they are uncertain of what that niche will be. Our physician experts recognize that Tysabri (BIIB, ELN) carries a small risk of a potentially fatal disease, but note that the efficacy is exceptionally solid and that patients are willing to take a calculated risk that can be further stratified by JCV status. Our experts do not believe Gilenya's efficacy is strong

enough to justify the potential CV risk. They will continue to use Gilenya conservatively and in young, healthy patients with no comorbidities and no concomitant medications.

FREEDOMS I Surprises With Better-Than-Expected Side-Effect Profile

In September 2009, Novartis released the FREEDOMS I data. FREEDOMS I confirmed the 0.5mg dose's effectiveness. Gilenya demonstrated solid efficacy at both doses studied (0.5 mg and 1.25 mg), including a positive impact on relapse rate and disability progression. More surprising, the drug's safety profile appeared better than that observed in earlier trials, and the lower dose of Gilenya appears to have a superior safety profile relative to the higher dose.

The efficacy data from FREEDOMS are in line with cladribine's Phase III CLARITY data. Novartis suggested that given dose-dependent efficacy in this trial (vs. none in TRANSFORMS), a lower Gilenya dose may not be effective. However, the FDA's advisory panel expressed interest in seeing data on lower doses in the post-marketing setting.

FREEDOMS I Disposition

	FTY720		
	1.25 mg	0.5 mg	Placebo
Randomized, N	429	425	418
Discontinued study drug, n (%)	131 (31)	80 (19)	115 (28)
Discontinued study, n (%)	97 (23)	56 (13)	86 (21)
Completed study, n (%)	332 (77)	369 (87)	332 (79)
Completed on study drug, n	297 (69)	345 (81)	303 (72)
Completed off study drug, n	35 (8)	24 (6)	29 (7)

Source: Company data

Comparison Of Relapse Data Across Gilenya, Tysabri, And Cladribine Two-Year Studies

	FTY720 FREEDOMS			Study 1801		Tysabri Study 1802		Cladribine CLARITY		
	FTY720 0.5mg	FTY720 1.25mg	Placebo	Tysabri	Placebo	Tysabri + Avonex	Placebo + Avonex	Low Dose	High Dose	Placebo
Annualized relapse rate, mean	0.18	0.16	0.40	0.25	0.74	0.36	0.78	0.14	0.15	0.33
Relative risk reduction	54%	60%		66%		54%		58%	55%	

Source: Cowen and Company, prescribing information

Gilenya 0.5mg demonstrated a favorable safety profile, but higher rates of bradycardia and basal carcinoma. Infection rates were higher with the 1.25mg dose and no disseminated viral infections were seen. Infection rate with 0.5mg was similar to placebo. While serious adverse events were more balanced in FREEDOMS than in TRANSFORMS, Gilenya has a proven mechanistic association with bradycardia and macular edema. Gilenya's appeal will depend likely on the longer-term incidence of CV side effects, infections, and cancers.

FREEDOMS I Serious Adverse Events

	FTY720		Placebo
	1.25 mg	0.5 mg	
Safety population, N	429	425	418
All SAEs, n (%)	51 (11.9)	43 (10.1)	56 (13.4)
Infections and infestations	11 (2.6)	7 (1.6)	8 (1.9)
Cardiac disorders	7 (1.6)	7 (1.6)	4 (1.0)
Bradycardia	3 (0.7)	4 (0.9)	1 (0.2)
AV block first degree	1 (0.2)	0 (0.0)	0 (0.0)
AV block second degree	1 (0.2)	0 (0.0)	1 (0.2)
Eye disorders	6 (1.4)	1 (0.2)	1 (0.2)
Macular edema	3 (0.7)	0 (0.0)	0 (0.0)
Neoplasms, benign or malignant	5 (1.2)	5 (1.2)	11 (2.6)
Basal cell carcinoma	1 (0.2)	4 (0.9)	2 (0.5)
Breast cancer	1 (0.2)	0 (0.0)	3 (0.7)
Malignant melanoma	1 (0.2)	0 (0.0)	1 (0.2)
Other malignant	1 (0.2)	0 (0.0)	3 (0.7)
Death	1 (0.2)	0 (0.0)	2 (0.5)

Source: Novartis

Freedom II Confirms Gilenya's Efficacy

In December 2011, Novartis announced data from the Phase III 2309 Freedom II study showing patients with relapsing-remitting multiple sclerosis treated with Gilenya had a statistically significant 48% reduction in annualized relapse rates at 24 months compared to placebo. Study 2309 is the third Phase III clinical trial to demonstrate a significant reduction of relapse rates with Gilenya treatment in patients with RRMS.

A reduction of brain volume loss, a pre-defined key secondary endpoint for study 2309, also achieved statistical significance for Gilenya-treated patients compared to placebo. Brain volume loss is valued as a predictor of long-term disability.

Gilenya-treated patients had a 17% and 28% reduction in three-month and six-month confirmed disability progression, compared to placebo as measured by EDSS, respectively, which were not statistically significant. A post-hoc analysis of the data showed that this result is likely due to a high variability in EDSS measurements among patients with low baseline scores (i.e. 0.0 and 1.0).

A subsequent analysis that applied a more rigorous definition of EDSS disability progression reduced the impact of this variability. Specifically, Gilenya-treated patients showed approximately a 34% reduction of six-month confirmed disability progression compared to placebo when a 1.5 point increase in EDSS was used to define progression in patients with baseline EDSS scores of zero, rather than the pre-specified 1.0 point increase. This disability reduction outcome is in range with what was seen in previous clinical trials. Further, study 2309 showed a statistically significant difference from placebo in the Multiple Sclerosis Functional Composite (MSFC), an alternative disability scale pre-defined in the clinical trial.

TRANSFORMS Data Raised Questions About Safety

In April 2009, data from Novartis's Phase III TRANSFORMS trial, a one-year head-to-head study evaluating two doses of Gilenya vs. Biogen's Avonex were presented at the annual AAN meeting. TRANSFORMS was a worldwide double-blind study that enrolled 1,292 patients. The study had three arms: oral Gilenya 0.5 mg and 1.25 mg once-daily, and Avonex once-weekly (given by intra-muscular injection). The study met its primary endpoint for both doses of Gilenya, with an annualized one-year

relapse rate of 0.16 and 0.20 for the 0.5mg and 1.25mg doses, respectively, a statistically significant reduction of 52% and 38% ($p < 0.001$) for the 0.5 and 1.25mg doses versus the Avonex control arm (relapse rate of 0.33).

While Gilenya's efficacy was impressive and TRANSFORMS established the viability of a lower dose of Gilenya (0.5mg), the trial failed to assuage concerns over side effects. There were three deaths (herpes encephalitis, varicella, and a progressive neurological condition of unclear etiology) on the higher dose of Gilenya. While the lower dose appeared to be associated with less infectious risk, opportunistic infections (varicella reactivation) were observed in this relatively short-term study. Almost as concerning, seven patients (approximately 1%) in the Gilenya arms developed skin cancer (4 BCC, 3 melanoma) vs. two cases in the control arm, and four patients in the Gilenya-treated group developed breast cancer (two high-dose, two low-dose) vs. none on Avonex. Lastly, Gilenya-treated patients experienced transient reductions in heart rate, increases in blood pressure (1-3 mmHg), elevations in liver enzymes, and increased rates of macular edema. These data received a lukewarm reception at AAN.

TRANSFORMS Study: Key Safety Findings

	FTY720 0.5mg N=429 n (%)	FTY720 1.25mg N=420 n (%)	Avonex N=431 n (%)
Any Adverse Event	369 (86.0)	380 (90.5)	395 (91.6)
Headache	99 (23.1)	96 (22.9)	88 (20.4)
Nasopharyngitis	88 (20.5)	93 (22.1)	88 (20.4)
Fatigue	44 (10.3)	59 (14.0)	45 (10.4)
Influenza-like illness	15 (3.5)	15 (3.6)	159 (36.9)
Pyrexia	18 (4.2)	15 (3.6)	77 (17.9)
Myalgia	14 (3.3)	14 (3.3)	44 (10.2)
Transient increase in HR		Yes	
Increase in blood pressure at 12 months		Yes (average of 1-3mmg)	
Raised ALT changes, %		7-8%	2%
Macular edema, n (%)		8 (0.94)	1 (0.2)
Skin cancers, n		7†	1
Serious infections (death), n	0	2	0
ITT Population			
† (4 basal cell carcinomas, 3 melanomas evenly distributed across the two arms)			

Source: Cowen and Company

Second-Gen BAF312 In Phase III Trials

Novartis moved its second generation S1P1,5-receptor modulator BAF312 (siponimod) into Phase III studies in 2012. This decision comes following positive efficacy data from a Phase II dose finding study. The study showed that BAF312 reduced brain MRI lesions by 80% when compared to placebo. Relapses were infrequent and appeared to be reduced with treatment (ARR 2.0 vs. 0.58 for placebo, $p = 0.044$). BAF312 was generally well tolerated with an initial dose titration, with the most frequent adverse events being headache, bradycardia, dizziness, and nasopharyngitis. Novartis does not expect filing until 2018+.

Extavia A Moderate Success

In a deal reached with Bayer (which gained commercial rights to interferon beta 1b via its acquisition of Schering AG), Novartis (which acquired Chiron, the developer of interferon beta 1b) gained rights to launch its own drug identical to Betaseron under the brand name Extavia. As part of the agreement, Bayer purchased the former Chiron manufacturing facility in California from Novartis and agreed to supply Novartis with the interferon beta-1b formulation in return for double-digit royalties. Novartis launched Extavia in Europe in early 2009 and in the U.S. late 2009. In the U.S., Extavia is priced at \$292/vial versus \$347/vial for Betaseron. We estimate Extavia sales of \$170MM (+7%) in 2014, \$185MM in 2015, \$200MM in 2016, \$230MM in 2018, and \$260MM in 2020.

Fanapt A Minor Player In Schizophrenia

Fanapt (iloperidone) is a dopamine type 2 (D2) and serotonin type 2 (5-HT2A) receptor antagonist antipsychotic agent. Fanapt is indicated in the U.S. for the acute treatment of schizophrenia in adults and was launched in January 2010. Novartis acquired the license to commercialize Fanapt in the U.S. and Canada from Vanda Pharmaceuticals. While our consultants have low expectations for Fanapt in the U.S. because of its undifferentiated profile, it appears that the strategic rationale behind the license was the development of a SubQ formulation. In February 2010, Vanda announced that it received a notice of allowance for its patent application of a microsphere, long-acting injectable formulation of Fanapt. We estimate Fanapt sales of \$90MM (+29%) in 2014, \$110MM in 2015, \$130MM in 2016, \$170MM in 2018, and \$210MM in 2020.

Exelon Franchise In Decline Due To Generics

Novartis has marketed Exelon (rivastigmine) in Europe since late 1998 and in the U.S. since mid-2000 for the treatment of Alzheimer's disease. As an oral dosage, Exelon's challenges include twice-daily dosing and nausea, although the latter is less problematic with careful titration. Exelon blocks 62% of acetylcholinesterase in the CNS when given at a 6 mg dose twice daily. It has 35% bioavailability, generates peak activity at six hours, and has 12-hour duration of activity. Among the 725 patients completing a Phase III study, 55% in a high-dose group showed statistically significant improvement in ADAS-cog from baseline, compared with 45% of placebo-treated patients. In another Phase III study (402 patients), moderate-to-marked improvement in ADAS-cog occurred in 43% of patients in the high-dose group, 31.5% in the low-dose group, and 30% on placebo. Side effects include nausea, vomiting, diarrhea, anorexia, abdominal pain, weight loss, headache, dizziness and fatigue. In 2006, Exelon became the only cholinesterase inhibitor to be approved for mild to moderate Parkinson's disease dementia (PDD) in addition to AD in both the U.S. and E.U. The approvals were based on the results of the EXPRESS study, a large-scale, randomized, well-controlled study involving 541 patients from 12 study centers in Europe and Canada.

The transdermal formulation of Exelon may help improve upon the oral's side-effect profile by reducing the nausea. The transdermal formulation was launched in the U.S. in August 2007 and was approved in the E.U. in September 2007 based on the IDEAL study. The patch showed efficacy similar to the highest doses of Exelon capsules as well as significant improvement, compared to placebo, in memory and the ability to perform everyday activities. In addition, the IDEAL study demonstrated a sharp reduction in reported gastrointestinal side effects (nausea and vomiting) compared to

the oral form of the medication. Patent expirations began in 2011 and continued through 2013 in all other major markets. We estimate Exelon sales of \$1,010MM (-2%) in 2014, \$940MM in 2015 (U.S. patent expires on higher strength patch in 8/15), \$650MM in 2016, \$450MM in 2018, and \$275MM in 2020.

Comtan/Stalevo In Decline Due To Generic Competition

Comtan (entacapone) is used in the treatment of Parkinson's disease as an adjunct to levodopa/carbidopa therapy. Stalevo is the combination of Comtan, levadopa and carbidopa. Novartis is the exclusive licensor of Comtan from European-based Orion Pharmaceuticals. Comtan is a selective and reversible inhibitor of catechol-O-methyltransferase (COMT). When Comtan is given in conjunction with levodopa and an aromatic amino acid decarboxylase inhibitor, such as carbidopa, plasma levels of levodopa are greater and more sustained than after administration of levodopa and an aromatic amino acid decarboxylase inhibitor alone. It is believed that, at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease.

Patent protection for entacapone, the active ingredient in Comtan, expired in Europe in 2012 and in the U.S. in October 2013 (patent No. 5,466,194). We forecast Comtan/Stalevo sales of \$370MM (-8%) in 2014, \$325MM in 2015, \$290MM in 2016, \$225MM in 2018, and \$165MM in 2020.

Ophthalmology

Lucentis Leads Wet AMD But Sales Pressured By New Entrants Despite Broadened Label

Lucentis (ranibizumab; NVS has OUS rights) is a pan anti-VEGF antibody fragment, and while the VEGF165 isoform is thought to account for most VEGF activity in AMD, blocking all VEGF activity in the retina appears to translate into superior clinical activity. In June 2003, Novartis licensed ex-North American rights for Lucentis from Genentech. Final FDA approval was received in June 2006 with the European approval in January 2007. Genentech estimates that the average wet AMD patient will require five to seven injections per year. Lucentis' Phase III (RESTORE) for diabetic macular edema (DME) demonstrated that around 40% of Lucentis patients substantially improved vision by 10 letters or more on an eye-chart, compared to 16% with laser therapy alone. Lucentis was approved in the E.U. for use in DME in January 2011 based on data from the RISE trial. The RISE trial showed significantly more patients on Lucentis with DME achieved an improvement in vision (BCVA) of at least 15 letters on the eye chart at 24 months compared to the control group. Novartis states that there are ~500K patients treated ex-U.S. for DME compared to 560K for AMD. In addition to wet AMD and DME, Lucentis is approved for BRVO (branch retinal vein occlusion), CRVO (central retinal vein occlusion), and myopic CNV (myopic choroidal neovascularization).

Avastin substitution has been a barrier to Lucentis' commercial success in the U.S. Compounding pharmacies reconstitute the significantly cheaper Avastin (\$40 versus \$2,000 a dose) for intraocular injection despite its lack of FDA approval for AMD. Novartis believes there is less impact and managed to secure NICE reimbursement-allowing it to drive U.K. sales. In July 2014, the French government endorsed a new budget that allows use of Avastin in AMD. In September 2011, five cases of blindness associated with Avastin-related infections highlighted the risk of infection with

repackaged intravitreal injections of Avastin. As a result of perceived safety concerns, U.S. V.A. hospitals have stopped using Avastin to treat AMD. Our clinical consultants believe that monthly dosing with Avastin is likely to create the highest risk for endophthalmitis, noting that no infections were observed in the PRN arm of the CATT study. Our consultants therefore anticipate using whatever therapy allows for the fewest number of yearly injections and are willing to sacrifice 1 to 2 letters of visual acuity for greater duration of action.

While not supported by clinical data, our consultants note that the ophthalmology community believes that REGN's Eylea may have a greater duration of action and increased efficacy compared to Lucentis. A pre-filled syringe of Lucentis, specifically designed for intraocular injection, was launched in Germany in March 2014, followed by launches in Japan, France, and other E.U. countries. We estimate Lucentis sales of \$2.515B (+6%) in 2014, \$2.595B in 2015, \$2.7B in 2016, \$2B in 2018, and \$1.5B in 2020, post its 3/18 patent expiration.

Longer Acting Agents The Biggest Challenge For Lucentis

The Comparison of AMD Treatments Trial (CATT) enrolled about 1,600 patients (across 40 U.S. centers) with newly diagnosed AMD. Patients were randomized to one of four arms: (1) Lucentis dosed once every four weeks; (2) Avastin dosed once every four weeks; (3) Lucentis with variable dosing; and (4) Avastin with variable dosing. The regimens were based upon the fact that Avastin is generally given on a variable basis and Lucentis had only been formally tested in a fixed regimen. The primary endpoint was change in visual acuity at one year, and secondary objectives including change in lesion size, fluid found on OCT and cost. Full 12-month data from CATT were presented at the 2011 ARVO conference and showed Avastin and Lucentis similar in terms of efficacy in the monthly arms at one year; however, Avastin was not as effective as Lucentis at reducing retinal thickness, a secondary endpoint of the study. Additionally, Avastin PRN dosing was similar to Lucentis PRN. While a higher rate of SAEs occurred in the Avastin arm (24% vs. 19%), this did not concern our physician consultants as there were similar rates of typical anti-VEGF SAEs, diversity of SAE types and hospitalization causes, and the lack of a dose relationship to Avastin.

Two-year CATT data was presented in April 2012 and subsequently published in the journal *Ophthalmology*. Visual acuity was similar between Lucentis and Avastin. While the mean gain was largest on monthly compared to as-needed treatments, patients receiving monthly injections were more likely to experience endophthalmitis. Rates of serious systemic events were higher with Avastin than Lucentis, although the majority of the excess events in the Avastin group have not previously been associated with systemic anti-VEGF therapy. Two-year data are similar to what was observed with 12-months of treatment, in-line with our consultants' expectations.

There are three key findings in the two-year results:

- Mean visual acuity gain was similar for Avastin and Lucentis through year two (Avastin-Lucentis difference of -1.4 letters, p=0.21)
- The mean gain was greater for monthly treatment than for as-needed treatment (difference -2.4 letters, p=0.046), although the magnitude of the difference at 2.4 letters was less than what our consultants have in the past said was borderline clinical significance
- The proportion of patients who had SAEs was again higher for Avastin than Lucentis (39.9% vs 31.7%, p=0.009), although similar to the one year data, the

excess events have not been associated previously with systemic anti-VEGF therapy. Moreover, while the cumulative incidence of SAEs on Avastin compared to Lucentis increased, the annualized frequency difference actually decreased in year 2 compared to year 1.

With the year two data producing a spread of just 2.4 letters, we think the results are overall very consistent with our physicians' expectations and unlikely to dramatically change physicians' use of as-needed vs monthly dosing. Moreover, this publication highlights the dramatic difference in the number of intraocular injections received by the monthly group (26 over two years) compared to the as-needed groups (12.6 ± 6.6 for Lucentis PRN compared to 14.1 ± 7.0 on Avastin PRN), and noted that 10 of 11 cases of endophthalmitis observed in the trial occurred in patients being dosed monthly.

While CATT data is unlikely to change clinical practice, Lucentis faces competition from agents that clinicians perceive to have a longer duration of action such as Eylea (REGN). Agents which may be dosed every 3-4 months are currently in development and are likely to change the standard of care if approved in 2016.

Fovista OUS Rights Acquired

In May 2014, Novartis acquired the ex-U.S. right to Fovista (anti-PDGF aptamer) from Ophthotech for a \$200MM upfront payment and additional milestone payments plus undisclosed royalties. Ophthotech will retain U.S. marketing rights. Fostiva is the most advanced anti-PDGF in development and is being evaluated in combination with other anti-VEGF agents in wet AMD. In Phase II studies, a Fostiva + Lucentis combination showed significantly improved visual acuity in wet AMD patients. Phase III studies of the combo are ongoing with data expected in 2016.

Respiratory

Novartis expects peak sales potential of Onbrez (indacaterol; LABA; approved U.S. and E.U.), Seebri (glycopyrronium; LAMA; approved E.U. and Japan), and Ultibro (FTC of indacaterol/glycopyrronium; LABA/LAMA; launched in Germany, Netherlands, and Japan, with U.S. filing expected Q4:14) to be \$2-4B in total.

Onbrez Breezhaler Marketed In E.U.; U.S. Approved At Lower Dose

Indacaterol (Onbrez/Arcapta in U.S.), an ultra-long-acting beta-2 agonist (uLABA), is marketed as a monotherapy for COPD and in development as a combination therapy for both COPD and potentially asthma. Indacaterol's major advantage over existing long-acting inhaled beta-2 agonists is its long duration of action (24 hours) over currently approved twice-daily LABA such as GlaxoSmithKline's Serevent (salmeterol) and Foradil (formoterol). Phase III data suggest incremental FEV1 improvement with no increased toxicity; however, exacerbation rates over 52-weeks appear similar to formoterol. Six-month Phase III data versus Spiriva, presented at ERS 2009, demonstrated a modest but significant benefit over Spiriva in the TDI and MRC scores. The FEV1 benefit seen at 12 weeks in the study did not improve over time. Safety appears robust and a thorough QTc study demonstrated a small but not clinically relevant increase in QTc signal at 600ug, 2-times the highest dose approved in the E.U. A transient cough on administration has been noted. Novartis opted to use a single-dose dry powder inhaler device which is inferior to Glaxo's devices but likely comparable to Spiriva's.

In December 2009, the EMA approved indacaterol 150 and 300ug for COPD. Novartis received a CRL from the FDA in October 2009 and resubmitted the NDA in Q3:2010 following the completion of an additional dose finding optimization study. The study included two lower doses, particularly 75ug to address FDA concerns over Cmax-associated toxicity FDA approved the 75ug dose in July 2011.

We estimate Onbrez Breezhaler sales of \$235MM (+22%) in 2014, \$310MM in 2015, \$400MM in 2016, \$500MM in 2018, and \$600MM in 2020.

Onbrez Breezhaler Demonstrates Efficacy On Par With Spiriva In Phase III

Results from a blinded Phase III head-to-head study (INTENSITY) showing that once-daily Onbrez Breezhaler (indacaterol) was as effective as tiotropium in improving lung function in patients with COPD, while providing greater clinical benefits in terms of reduced breathlessness, lower use of rescue medication and improved health status were released in November of 2010. A total of 1,598 patients with moderate-to-severe COPD were enrolled in the blinded, double-dummy study in which they received once-daily treatment with either Onbrez Breezhaler 150 mcg or tiotropium 18 mcg. The study met its primary endpoint by demonstrating non-inferiority of Onbrez Breezhaler to tiotropium after 12 weeks in terms of lung function, measured by forced expiratory volume of breath in one second (FEV₁). Results showed that baseline-adjusted trough FEV₁ at 12 weeks was 1.44 L with Onbrez Breezhaler and 1.43 L with tiotropium (mean of 23 hrs., 10 mins. and 23 hrs., 45 mins. post-dose, p<0.001 for non-inferiority). FEV₁ superiority to tiotropium, one of the secondary endpoints, did not reach statistical significance.

Onbrez Breezhaler showed superiority to tiotropium on other secondary endpoints relating to key patient outcomes. Breathlessness improved significantly more with Onbrez Breezhaler than tiotropium (total scores of 2.01 vs. 1.43 in transition dyspnea index, p<0.001). Onbrez Breezhaler patients used less albuterol rescue medication (change of -1.40 vs. -0.85 puffs/day, p<0.001) and had a higher percentage of days without rescue medication use (46.1 vs. 41.4, p=0.004). Patients using Onbrez Breezhaler reported significantly better health status than those on tiotropium (mean change of -5.1 vs. -3.0 in St George's Respiratory Questionnaire, p<0.001).

Data Versus Spiriva Demonstrate Modest Benefit

In May 2009, Novartis released top-line 12-week data from the INHANCE study of 2,059 patients with COPD versus open-label Spiriva 18ug. The primary endpoint was trough FEV₁ after 12 weeks. The full 26-week data were presented at ERS 2009. Adjusted mean trough FEV₁ at Week 12 was 1.46L with indacaterol 150µg and 300µg; both doses were significantly more effective versus Spiriva (1.42L; p≤0.01) and versus placebo (1.28L; p<0.001). The clinically relevant threshold (120mL versus placebo) was exceeded by indacaterol (180mL, both doses) and Spiriva (140mL). For both indacaterol doses, trough FEV₁ was improved at 24 hours after first dose (≥110mL vs. placebo, p<0.001) and maintained to Week 26 (≥170mL vs. placebo, p<0.001). Indacaterol (both doses) increased FEV₁ at 5 min post-dose after the first dose (120mL vs. placebo, p<0.001); at subsequent visits, FEV₁ at 5 min post-dose was increased by ≥170mL vs. placebo (p<0.001). Subgroup analysis of Week 12 trough FEV₁ showed that efficacy was similar in patients aged less than 65 years versus greater than 65 years: 190 and 170mL versus placebo, respectively for indacaterol 150µg, and 180 and 170mL versus placebo for indacaterol 300µg (all p<0.001).

The mean transition dyspnea index (TDI) total score achieved the minimal important difference (≥ 1 versus placebo) at Week 26 with indacaterol 150 µg (Δ = +1.00 vs. placebo, p<0.001) and with indacaterol 300 µg (Δ = +1.18 vs. placebo, p<0.001).

Improvement in the TDI at Week 26 with Spiriva was $\Delta = +0.87$ vs. placebo ($p < 0.001$). The percent of patients with a clinically important improvement from baseline (≥ 1 unit) at weeks 12 and 26 were 59 and 62% with indacaterol 150 μg ($p < 0.001$ vs. placebo), 66 and 71% with indacaterol 300 μg ($p < 0.001$ vs. placebo, $p \leq 0.01$ vs. Spiriva), and 55 and 57% with Spiriva ($p < 0.01$ vs. placebo). At 26 weeks, the modified Medical Research Council (mMRC) dyspnea score improved by ≥ 1 in 34% of patients receiving indacaterol 150 μg , 37% receiving indacaterol 300 μg and 35% receiving Spiriva ($p < 0.05$ vs. placebo for all).

Ultibro LABA/LAMA Data In COPD Impressive; Approved In E.U. And Japan; U.S. Filing Expected Late 2014

Ultibro Breezhaler (QVA149) is the once-daily fixed-dose combination of QAB149 (Onbrez: LABA indacaterol) and NVA237 (Seebri: LAMA glycopyrronium) being developed for COPD. Data from Phase III trials, presented at ERS 2012 and 2013, demonstrated improvements in lung function and SOB in COPD patients. E.U. approval was granted in September 2013 along with approval in Japan. Ultibro has been approved in 40 countries and launched in 13 to date. The E.U. rollout has been very successful.

Our physician experts believe that dual bronchodilators will offer superior improvements in lung function and dyspnea and sees LAMA/LABA combinations supplanting LABA/ICS combinations as first-line therapy in COPD. While our consultant believes that LAMAs are very safe drugs, a meta-analysis linking tiotropium use to an increased incidence of cardiovascular events forced FDA to mandate that the appropriate dose and dosing regimen be determined for all LAMAs. Novartis has yet to establish the best dose for NVA237, a requirement which has delayed the development of NVS237 and combinations. Novartis has committed to conducting additional BID dosing studies for QVA149 in the U.S. at the request of FDA. Our consultants do not believe the 75 μg dose of indacaterol will be efficacious in a LAMA/LABA combination and therefore think approval in the U.S. could be difficult. Novartis anticipates a U.S. filing in Q4:14 for Ultibro. We estimate Ultibro sales of \$105MM in 2014, \$260MM in 2015, \$400MM in 2016, \$600MM in 2018, and \$800MM in 2020.

Phase III Study Demonstrates Superiority Over Seretide

At ERS 2014 (September), data from the Phase III LANTERN study ($n=744$; 56 OUS sites) was presented which showed once-daily Ultibro reduced exacerbations by 31% compared to twice daily Seretide (GSK; ICS/LABA) in patients with moderate-to-severe COPD. Ultibro also significantly increased lung function compared to Seretide at 26 weeks. The data suggest Ultibro to be an effective once-daily, non-steroid option for patients.

Seebri U.S. Filing Targeted For Late 2014

NVA237 (Seebri, glycopyrronium) is a once-daily inhaled LAMA approved for COPD in the E.U. in October 2012 and in Japan in September 2012. In the U.S., establishment of best dose has been the mitigating factor. The company now anticipates a U.S. filing in Q4:14. Seebri is also in Phase III trial for once-daily use in asthma. We estimate Seebri sales of \$150MM in 2014, \$230MM in 2015, \$300MM in 2016, \$400MM in 2018, and \$500MM in 2020.

New Analysis At ERS 2013 Further Supports Efficacy of QVA149 And NVA 237

At ERS 2012, three Phase III trials were presented from QVA149's IGNITE program, ILLUMINATE, ENLIGHTEN, and SHINE. All three trials met their primary endpoints and established QVA149 as an effective method of achieving dual bronchodilation in patients with moderate-to-severe COPD. In September 2012, Novartis announced that QVA149 met its primary endpoint of reduced rate of COPD exacerbations compared to NVA237 alone in its Phase III SPARK trial; however, QVA149 did not demonstrate a statistically significant improvement in exacerbations versus open-label tiotriptip.

Additional analysis presented at ERS 2013 of the IGNITE trial program (which includes 11 international studies in more than 10,000 COPD patients) showed statistically significant improvements in bronchodilation with QVA149 versus comparator and symptomatic improvements (SOB, exercise tolerance, rescue medication use) versus placebo. Data was also presented from the BLAZE study showing that QVA149 provided improvements in SOB compared to tiotropium. Data from the SPARK study (of glycopyrronium) showed similar efficacy and safety to tiotropium.

QVA149 An Effective Treatment For Moderate-To-Severe COPD

Once daily QVA149 significantly improves lung function, and symptoms compared to twice daily fluticasone/salmeterol in COPD patients: The ILLUMINATE Study. ILLUMINATE is part of the IGNITE clinical trial program, which is composed of 10 studies and encompasses more than 5,700 patients. ILLUMINATE was a 26-week double-blind, placebo-controlled 2,144 patient study comparing the efficacy of QVA149 (LAMA/LABA) to Advair with the primary endpoint of FEV₁ AUC_{0-12h} at 26-weeks. Current guidelines prefer LAMA/LABA combinations over LABA/ICS in patients with minimal exacerbations; however, post hoc analyses of several clinical trials suggest ICS may have benefits in these patients beyond bronchodilation. ILLUMINATE is the first trial to directly compare a LAMA/LABA combination to a LABA/ICS in patients without a history of exacerbations within the last year. Patients in ILLUMINATE must also be >40 years old, have >10 year pack-year history of smoking, and a post-bronchodilator FEV₁ >40% and <80% predicted and FEV₁/FVC <0.7. 33% of QVA149 patients and 37% of Advair patients received ICS at baseline.

QVA149 met its primary endpoint of superior FEV₁ AUC_{0-12h} at 26-weeks compared to Advair, demonstrating more than a 140mL improvement ($p<0.001$). QVA149 also demonstrated superior FEV₁ AUC_{0-12h} at Day 1 (70mL improvement, $p<0.001$) and Week 12 (120mL improvement, $p<0.001$).

Ultibro FEV₁ Comparison

	QVA149 (L)*	FP/SAL (L)*
Day 1	1.60	1.68
Week 12	1.59	1.71
Week 26**	2.54	1.68

*All difference statistically significant ($p<0.001$)

**Primary endpoint

Source: Company data, ERS 2012

Lung function in patients on QVA149 was also superior to Advair as measured by serial FEV₁ on Day 1, Week 12, and Week 26 ($p<0.01$ at all-time points assessed). Peak FEV₁ was also superior for patients on QVA149 compared to those on Advair.

Ultibro Peak FEV₁ Comparison

	QVA149 (L)*	FP/SAL (L)*
Day 1	1.69	1.76
Week 12	1.68	1.82
Week 26	1.67	1.82

*All difference statistically significant ($p < 0.001$)

Source: Company data, ERS 2012

No major differences in FEV₁ were observed between 5-and-30 minutes post treatment, suggesting QVA149 has a rapid onset of action; FEV₁ on QVA149 was superior to Advair at both of these time points ($p < 0.001$). QVA149 demonstrated <90mL improvement at Week 12 and <100mL improvement at Week 26 vs. Advair in pre-dose trough FEV₁ ($p < 0.001$). QVA significantly improved patient reported TDI scores (0.59 pts. at Week 12, $p < 0.05$ and 0.76 pts. at Week 26, $p < 0.01$) and demonstrated a numerical improvement in SGRQ at 26 weeks (-1.39, NS). Patients on QVA149 utilized significantly less rescue medication over the duration of the study compared to Advair (-0.39, $p < 0.05$).

The incidence of adverse events was lower with QVA149 (55.4%) vs. Advair (60.2%). Pneumonia was only reported in the Advair group (4 patients, 1.5%). Discontinuations were more frequent on Advair compared to QVA149. The incidence of serious adverse events was similar between treatment groups (5.0% on Advair vs. 5.3% on QVA149). One death was reported on Advair.

Benefits of dual bronchodilation with QVA149 once daily versus placebo, indacaterol NVA237, and tiotropium in patients with COPD: The SHINE study. The SHINE study was a 2,144 patient Phase III study to compare QVA149, indacaterol, NVA237, and open-label tiotropium (18ug) to placebo for the treatment of moderate-to-severe COPD. The primary endpoint was trough FEV₁ with QVA149 vs. indacaterol and NVA237 at 26 weeks. QVA149 demonstrated statistically superior bronchodilation over placebo, indacaterol, NVA237, and placebo that were sustained over the course of 26-weeks.

Ultibro Least Squares Mean Treatment

	QVA149-PBO	QBA149-IND	QVA149-NVA	QVA149-TIO
Day 1				
Trough FEV1 (mL)	190*	80*	80*	80*
FEV1 AUC 0-4h (mL)	220*	60*	30*	80*
Week 26				
Trough FEV1 (mL)	200*	70*	90*	80*
FEV1 AUC 0-4h (mL)	340*	110*	140*	130*
FEV1 AUC 0-24h (mL)	320*	110*	110*	110*
Peak FEV1 0-4h (mL)	330*	120*	120*	130*
Transition Dyspnea Index focal score	1.09*	0.26	0.21	0.51**
SGRQ total score	-3.01*	-1.09	-1.18	-2.13**
Rescue medication use	-0.96*	-0.30**	-0.66*	-0.54*

* $p < 0.001$

** $p < 0.05$

Source: Company data, ERS 2012

The safety profile of QVA149 was comparable to that of placebo without any serious drug-related adverse events.

QVA149 administered once daily provides significant improvements in lung function over 1 year in patients with COPD: The ENLIGHTEN study. The goal of this 338 patient Phase III study was to evaluate the efficacy of QVA149 (indacaterol/NVA237, LABA/LAMA) in the treatment of COPD. Patients were randomized 2:1 to receive QVA 149 (100/50ug) or placebo via a single-dose dry powder inhaler for 52-weeks. While the primary endpoint for the study was safety, only efficacy data were reported. QVA149 significantly increased REV1 and FVC versus placebo at all-time points assessed. p-values for all comparisons below are <0.001.

Ultibro Efficacy In COPD

	Day 1	Week 3	Week 6	Week 12	Week 26	Week 39	Week 52
FEV1 (mL)	156	246	268	235	271	231	248
30 min. post-dose	201	267	276	256	275	277	257
60 min. post-dose							
FVC (mL)							
30 min. post-dose	221	333	340	268	353	290	291
60 min. post-dose	254	328	340	286	338	334	319

Source: Company data, ERS 2012

Foradil Small In The U.S., Off Patent In Foreign Markets

Foradil (formoterol fumarate) is a long-acting bronchodilator that offers onset of action within five minutes and 12-hour relief of symptoms for patients with asthma and COPD, which includes chronic bronchitis and emphysema. It was first registered and launched in Europe in 1994. U.S. approval was granted in 2001, and in 2002 Novartis licensed Foradil to Schering-Plough but maintained rights in the rest of the world. Foradil Aerolizer is a single-dose dry powder inhaler available in the U.S., while a metered-dose inhaler is available in some countries. Foradil Certihaler was approved in the U.S. in December 2006, and previously was approved in 27 other countries. Certihaler is a novel, breath-activated multi-dose dry powder inhaler technology developed by SkyePharma. Foradil Certihaler was launched in Germany and Switzerland in September 2005, but was withdrawn due to a patient mishandling issue and is not currently marketed there. Merck now books U.S. sales and pays a royalty to Novartis. Foradil's composition-of-matter patent has expired in major countries, leading to a decline in WW revenues.

In May 2009, Schering and Novartis announced a restructuring of their respiratory collaboration. Schering assumed exclusive rights to develop and commercialize the twice-daily fixed-combination of mometasone plus formoterol (MFF) using a pMDI device. Novartis assumed development responsibility for the once-daily QAB149 indacaterol/mometasone combination. The agreement provides for a royalty sharing arrangement based on sales. We forecast ex-U.S. Foradil sales plus U.S. royalty of \$185MM (-10%) in 2014, \$150MM in 2015, \$125MM in 2016, \$75MM in 2018, and \$25MM in 2020.

Xolair Expanded Outside Respiratory With CSU Approval

Xolair is a humanized monoclonal antibody designed to bind to the IgE circulating in the bloodstream, inhibiting the release of inflammatory chemicals that cause the symptoms of asthma. Reducing IgE levels also helps to improve inflammation of the airways, making Xolair the first non-steroidal therapy that is proven to have a major anti-inflammatory effect in allergic asthma. Xolair was developed jointly by Novartis,

Genentech, and Tanox, and was approved by the FDA in June 2003 for children older than 12 years. Xolair's price of \$10K/patient per year in the U.S. and injectable formulation have constrained the drug's use to the most refractory of asthma patients (approximately 10% of patients). In October 2005, Novartis received European approval of Xolair as add-on therapy in patients with severe persistent allergic asthma, not controlled by other available treatments.

In July 2007, Xolair's U.S. label was updated with a "black box" warning related to an associated risk of anaphylaxis. Three cases of anaphylaxis were reported among the 3507 patients exposed to Xolair in clinical trials; post-marketing studies suggested an incidence rate of approximately 0.2%. Approximately 89% of these patients had pulmonary involvement, 14% had hypotension or syncope, and 15% required hospitalization. Cardiovascular irregularities were also raised as concerns. In August 2009, Xolair was approved in Europe for children aged 6-11 years. In November 2009, an FDA advisory committee voted against recommending Xolair for use in children between 2 and 11 years with moderate to severe asthma and allergies.

In March 2014, Xolair was approved, in the U.S. and E.U., for use in chronic spontaneous/idiopathic urticaria (CSU/CIU), a condition which the company believes has a WW prevalence of 0.5-1%, with 1.6MM patients in the U.S. plus EU5. CSU is a skin condition characterized by red, swollen, itchy, and sometimes painful hives that can spontaneously present and re-occur. Xolair was shown to be safe and effective in studies (GLACIAL, ASTERIA II) which supported approval. Xolair is the only approved therapy for the up to 50% of CSU patients who do not respond to antihistamines. We forecast Xolair sales of \$775MM (+26%) in 2014, \$820MM in 2015, \$875MM in 2016, \$975MM in 2018, and \$1,075MM in 2020.

Dry Powder Inhaler To Extend The TOBI Franchise

TOBI (inhaled tobramycin solution) is the only FDA-approved inhaled medication for cystic fibrosis with *P. aeruginosa* infections in people age six and older with lung function within a certain range. It improves lung function, reduces the number of days in the hospital and the need for IV antibiotics. TOBI was acquired through the Chiron acquisition. TOBI is nebulized twice-daily in repeated cycles of 28 days on drug followed by 28 days off drug. TOBI has dominated the U.S. and ex-U.S. CF markets since its launch in 1997 and 1999 respectively. A second-generation dry powder version, TIP, was approved in the E.U. in September 2009 and in the U.S. in March 2013. TIP utilizes a handheld device designed to reduce administration time and increase convenience. We assume tobramycin replaced by TIP in Q4:10 in the E.U. and in 2012 in the U.S. We estimate sales of TIP of \$360MM (+55%) in 2014, \$420MM in 2015, \$475MM in 2016, \$575MM in 2018, and \$675MM in 2020.

Immunology And Infectious Disease

Ilaris Approved In E.U. For Gout, For CAPS And SJIA In U.S.

Ilaris (canakinumab), an IL-1B mAb, is marketed for cryopyrin-associated periodic syndromes (CAPS). CAPS is comprised of three disorders of increasing severity: FCAS, MWS and neonatal-onset multisystem inflammatory disease (NOMID). There are believed to be approximately 300 cases in the U.S., but many patients may remain undiagnosed due to poor disease recognition. Ilaris is in multiple parallel trials for neonatal multiple inflammatory disease, systemic onset juvenile idiopathic arthritis (U.S. prevalence of 11,000 patients), gout, COPD and diabetes. Development in RA was discontinued. Muckle-Wells syndrome is a rare, inherited disease caused by

mutations in a gene, leading to elevated levels of IL-1. Symptoms of the disorder range from itching skin rashes and daily fevers to conjunctivitis and swollen joints. Only a few hundred people worldwide are believed to suffer from Muckle-Wells syndrome, so recruiting patients was thought to be a major challenge. In November 2012, Novartis reported Phase II data showing that ACZ885 reduced attack frequency by ≥50% in patients with familial Mediterranean fever and provided sustained symptom relief in patients with TNG-receptor associated periodic syndrome. Ilaris has been granted orphan drug designation for SJIA in the U.S., E.U. and Switzerland. Novartis received approval for SJIA in May 2013 in the U.S. and in September 2013 in the E.U., and plans to file in secondary prevention of CV events and diabetes in 2017. We estimate Ilaris sales of \$190MM (+60%) in 2014, \$210MM in 2015, \$230MM in 2016, \$270MM in 2018, and \$310MM in 2020.

Ilaris FDA Approved For Systemic Juvenile Idiopathic Arthritis

In May 2013, FDA approved Ilaris for the treatment of SJIA based on the results of Phase III studies where 84% of Ilaris treated patients demonstrated a significant improvement in ACR30 (vs. 10% on placebo). In the open-label portion of the Phase III program, 62% of patients were able to substantially reduce their use of steroids and 46% were able to completely eliminate steroids. The risk of flare for patients in the Ilaris group was reduced by 64% compared to those on placebo (HR=0.36, 95% CI 0.17-0.75).

Ilaris Receives Approved For Gout In E.U.; Future Of Ilaris For Gout In U.S. Uncertain

In June 2011, the FDA Arthritis Advisory Committee voted 11-1 against the approval of the 150mg dose of Ilaris (canakinumab) for the “treatment of gouty arthritis attacks in patients who cannot obtain adequate response with NSAIDS or colchicines” and voted 12-0 against approval for the indication of “extending the time to next attack and reducing the frequency of subsequent attacks.” While the AdCom agreed the drug was effective, concerns over an increased incidence of infection and uncertainty surrounding recurrent dosing created an unfavorable risk-benefit ratio. In June 2011, FDA issued a CRL for Ilaris in gout requesting additional data. In April 2012, the Arthritis Advisory Committee voted 11-0 against recommending approval of Regeneron’s IL-1 β inhibitor, Araclyst, for the treatment of gout in patients initiating urate-lowering therapy. The panel was concerned that patients were exposed to Araclyst for only 16 weeks during its clinical trials, while patients could be on the drug significantly longer in clinical practice. FDA’s continuing concerns surrounding the safety profile of IL-1 β inhibitors remain an overhang for Ilaris in the gout indication. In January 2013, Ilaris received a positive CHMP opinion for acute gouty arthritis in patients for whom current treatments are unsuitable or ineffective.

Ilaris Viewed As Effective In Gout...

Ilaris (150mg) met the primary endpoint of demonstrating a significantly greater reduction in VAS pain score at 72 hours compared to triamcinolone in two pivotal Phase III trials (additional 11.4 point reduction in VAS pain score compared to 40mg triamcinolone). Additionally, the 150mg dose of Ilaris rapidly reduced CRP and markers of IL-1 β driven inflammation, resulting in decreased joint tenderness, swelling, and erythema. The committee voted 11-1 that Ilaris is efficacious in treating gouty arthritis attacks in patients with an inadequate response to NSAIDS or colchicine. While the committee expressed some concern that lower doses of Ilaris were not investigated in Phase III studies, Phase II dose-ranging studies showed the 150mg dose to be superior to lower dose for pain relief, which the panel ultimately viewed as supporting selection of the 150mg dose. In both Phase III studies, Ilaris reduced the likelihood of recurrent flares compared to triamcinolone within 12 weeks

of starting therapy (HR=0.45-0.48, p=0.0003-0.0014). Experts attribute the reduced incidence of flares to the sustained action of the drug; the half-life of Ilaris is 26 days. The committee voted 8-4 that Ilaris demonstrated substantial evidence to support the additional claim of extending the time to the next gouty attack and reducing the frequency of subsequent attacks. Those that voted against this additional claim did not dispute that Ilaris prevented the time to the next attack, but were uncertain whether there was sufficient data to support an efficacy claim for subsequent attacks.

...But Safety Is A Different Story

The committee voted 11-1 that Ilaris did not possess a safety profile that supported approval for the treatment of gouty arthritis attacks. AdCom members were concerned with the safety profile of Ilaris for use in disease that is not life threatening such as gout. While the panel recognized that other immune-modifying antibodies have been approved with similar safety profiles, they noted that Ilaris is not a disease modifying drug and that it only provides symptomatic relief. An increase in serum urate, an increased incidence of infections, and the potential for declining renal function with Ilaris were of particular concern, especially given the frequency of other co-morbid conditions in severe gout populations. Several analyses suggested that the incidence of SAEs may increase with repeated dosing, although these data were derived from a relatively small sample size (43 gout patients from Phase III had received >2 doses of Ilaris and been followed for 6-months). Given the lack of data for recurrent dosing in severe gout patients amidst significant safety concerns, the panel voted 12-0 that the Ilaris safety profile is not sufficient to support approval for reducing gouty arthritis flares.

Certain Populations May Benefit, Additional Data Necessary

The AdCom agreed that new drugs are necessary to alleviate pain in patients who are intolerant or unresponsive to NSAIDs and colchicine. These patients currently receive corticosteroids and must be free of flares prior to beginning urate lowering therapy. AdCom members generally agreed that Ilaris would be a valuable addition to their armamentarium for patients who do not respond to NSAIDs and colchicine and whose flares are not managed with corticosteroids. Such patients commonly receive multiple courses of steroids which increases their susceptibility to infection. The infection risk associated with using Ilaris in place of corticosteroids may therefore be more acceptable in this patient population. The ability of Ilaris to reduce the time to next flare may also facilitate bridging to urate lowering therapies in these patients, which has proved a considerable challenge with corticosteroids alone. A majority of the panel suggested that trials in patients refractory to both NSAIDs and corticosteroids, may be required. The panel also recommended obtaining additional safety data for extended periods of treatment with recurrent dosing (continuing to follow the patients from Phase III studies for up to six months was viewed as acceptable by some committee members).

Secukinumab Shows Promise In Psoriasis And Uveitis; Less Impressive In Arthritis

Secukinumab (AIN457) is a monoclonal antibody neutralizing Interleukin-17A, a key pro-inflammatory cytokine expressed by TH17 cells. In a proof-of-concept study in 36 patients with severe chronic psoriasis, patients randomized to intravenous AIN457 demonstrated a 56% placebo-corrected PASI decrease at 12 weeks. Some of these patients demonstrated a sustained response at six months. AIN457 is also in Phase III development in uveitis and Phase II for rheumatoid arthritis. Phase III data from the FIXTURE trial, released in Q3:13, showed AIN457 superior to Enbrel in moderate-to-severe plaque psoriasis. Other Phase III trials (FEATURE, JUNCTURE) showed similar results but with secukinumab provided in convenient dosing forms (pre-filled syringes,

autoinjector pen). Top-line Phase III data in psoriatic arthritis (FUTURE 1 and 2 trials) was announced in September 2014 with secukinumab meeting the primary endpoint of ACR20. Key secondary endpoints were also met and the drug was well tolerated. Full data will be presented at a future medical meeting. Novartis expects to file for psoriatic arthritis in 2015.

A Phase IIIb (CLEAR) study of secukinumab vs. Stelara in psoriasis is enrolling patients (completed enrollment expected H2:14); the primary endpoint is PASI90 measured at Week 16. Novartis filed secukinumab for moderate-to-severe plaque psoriasis in the U.S., E.U., and Japan in Q4:13 (Japan filing also included psoriatic arthritis). An FDA Adcom will review secukinumab for severe plaque psoriasis on October 20th, 2014. FDA action is expected by January 2015 and a CHMP opinion in Q4:14. We estimate secukinumab sales of \$150MM in 2015, \$300MM in 2016, \$800MM in 2018, and \$1,200MM in 2020.

Fixture Study Shows Secukinumab Superiority To Enbrel In Psoriasis

The FIXTURE study of 1,306 moderate to severe plaque psoriasis patients demonstrated superiority of secukinumab (both 150mg and 300mg doses) to Enbrel (50mg) at Weeks 12 and 52 for both co-primary endpoints (PASI 75 and IGA 0/1). Results showed 54% of patients treated with 300mg secukinumab achieved PASI90 at Week 12 compared to 21% on Enbrel; 72% of secukinumab 300mg patients achieved PASI90 by Week 16; and 24% of secukinumab patients experienced completely clear skin at Week 12 vs. 4% for Enbrel. Symptoms were shown to resolve sooner on secukinumab and efficacy was sustained to a greater degree than with Enbrel (65% had PASI 90 at Week 52 for secukinumab vs. 33% for Enbrel). The most common side effects were nasopharyngitis and headache. Serious side effects were seen in 6% of 300mg secukinumab patients and 6% of Enbrel patients.

Secukinumab Meets Psoriasis Endpoint In Phase II Study

In October 2011, Novartis announced that secukinumab significantly improved skin clearance in three Phase II trials in patients with moderate-to-severe plaque psoriasis. 150mg of SQ secukinumab, administered once every four weeks, resulted in 81-83% of patients achieving at least a 75% improvement in their symptoms (PASI 75) after 12-weeks ($p<0.001$). Secukinumab was nearly three times more effective than placebo at reducing moderate-to-severe plaque psoriasis on the hands and/or feet when given every week during the first month of treatment (54.3% of patients vs. 19.2% respectively, $p=0.005$), as measured by the Investigator's Global Assessment.

Secukinumab Fails To Meet Primary Endpoint In Phase II RA Study

A Phase II study of 237 patients on methotrexate was designed to compare monthly SQ injections of secukinumab (25mg, 75mg, 150mg, and 300mg) to placebo for the treatment of RA. The primary endpoint of the study was proportion of patients achieving ACR20 at Week 16. After Week 16, responders on secukinumab remained on the same dose whereas doses were escalated in non-responders at Week 20 and all placebo patients were switched to secukinumab 150mg. Patients were continuously followed through Week 52.

ACR20 responder rates at Week 16 were numerically greater for secukinumab 75mg, 150mg, and 300mg (47%, 47%, and 54%) compared to placebo (36%), but did not achieve statistical significance. In a subset analysis, patients who did achieve ACR20 at Week 16 maintained or improved their response through weeks 24 and 52. Non-responders that experienced dose-escalation post-Week 16 did not achieve additional benefit at either Week 24 or 52. No dose dependent adverse events were observed.

Aclasta In Decline Due To Generic Competition

Reclast/Aclasta is marketed in the U.S. as a once-yearly infusion to treat postmenopausal osteoporosis (PMO), to increase bone mass in men with osteoporosis, and to treat and prevent osteoporosis caused by steroids (glucocorticoids). In the E.U., Aclasta is approved for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture, including those with a low trauma hip fracture. Additionally, the CHMP approved Aclasta for the treatment of glucocorticoid-induced osteoporosis in 2009. In June 2009, FDA approved Aclasta to prevent postmenopausal osteoporosis for two years with a single dose.

Efficacy is excellent but market penetration limited as the majority of patients treated for osteoporosis are seen by their primary care doctors (who typically do not have infusion centers). In addition, physician reimbursement for the infusion is minimal. Our physician consultants believe that Aclasta is the second-line agent of choice in osteoporosis, especially with the availability of Fosamax generics and other non-intravenous options. The composition patent expired in March 2013. We forecast Aclasta sales of \$20MM (-94%) in 2014, \$25MM in 2015, \$15MM in 2016, \$5MM in 2018, and \$5MM in 2020.

Generics

Sandoz Poised For Moderate Growth

Sandoz's growth was fueled by its expansion into third-world markets while the U.S. business suffered several manufacturing and regulatory setbacks. Novartis management believes that generics growth in emerging markets is a critical component of its overall growth strategy. As a result of effective EM penetration strategies, Novartis has grown 4-5 times the market rate in Central and Eastern Europe, the Middle East and Turkey, and outpaced the market by twofold in Asia-Pacific. According to Novartis, Emerging Markets CAGR for 2011-13 was +9.2% for Sandoz versus +7.7% for the market. Sandoz is also specializing in difficult-to-make generics, including metoprolol, fentanyl, and inhaled bronchodilators, and generic biologics with the recent approval of Binocrit (epoetin alpha) and is currently the industry leader in biosimilars with 56% market share (and a very high GPM)

In September 2009, Novartis completed the acquisition of specialty European generics company, EBEWE for €925MM. EBEWE's focus on oncology injectables complemented Sandoz's competence in specialty and difficult-to-make generics. In May 2012, Sandoz acquired Fougera Pharmaceuticals. The acquisition made Sandoz the world's largest manufacturer of generic dermatology products. While a majority of Fougera's \$620MM in sales came from the U.S., Sandoz has utilized the Fougera platform to distribute generic dermatology products globally.

We forecast Sandoz revenues of \$9.6B (+5%) in 2014, \$10.075B in 2015, \$10.5B in 2016, \$11.5B in 2018, and \$12.55B in 2020.

Product Updates

Generic Copaxone: Sandoz, through its Momenta partnership, was first to file on Teva's Copaxone. The 30-month stay expired in 2011. The Copaxone litigation trial was held in September 2011. In June 2012, the Southern District Court of New York ruled in favor of Teva over Momenta/Sandoz and Natco/Mylan regarding Teva's Copaxone patents. Teva has nine patents covering Copaxone, seven of which are Orange-book

listed composition patents that expired in June 2014, and two are process patents (one expired in June 2014 and one will expire in September 2015). The Court ruled that ANDAs from Momenta/Sandoz and Natco/Mylan infringe all of the asserted claims of Teva's patents, none of which are invalid or unenforceable. Momenta appealed the decision, and estimated it will take 12-18 months from the initial verdict before another verdict is reached. We view Teva's patents as formidable, especially in light of the fact that MNTA would need to invalidate 100% of the claims in order to gain early market entry. However, regardless of any court decision, these patents will expire in 2-3 years. Hence the bigger challenge to bringing a Copaxone generic to the market may be FDA approval.

In late August, 2014, the FDA accepted for review Momenta's 3x/week generic copaxone. The company estimates it could be on the market as early as Q1:2017.

Factors that Novartis would consider before it entered a potential patent litigation settlement include: 1) the success of the 3x/ week formulation (which has been quite successful); 2) timing of FDA approval of a biosimilar; and 3) Supreme Court deliberation. It expects to have more visibility in the next 6 months on at least some of these points.

Generic Advair: In March 2010, Sandoz altered its agreement with Vectura, handing over full U.S. rights to generic Advair (V315). V315 is in development for asthma/COPD. In August 2011, Sandoz acquired the rights to V315 in the rest-of-world.

In April 2010, Sandoz acquired Oriel Therapeutics. The acquisition gave Sandoz rights to Oriel's U.S. generic respiratory platform, which includes three development projects as well as the FreePath drug delivery system and Solis multi-dose DPI. Sandoz appears to be more aggressive than some of its competitors in pursuing generic respiratory devices. In December 2013, Sandoz' generic Advair (AirFluSal) received marketing approval in Denmark, followed by approvals in Germany, Sweden, Hungary, Romania, Bulgaria, and South Korea. AirFluSal is currently approved in 10 countries total.

Novartis is not saying whether or not it has filed a generic Advair in the U.S. It apparently does not consider such a filing material. Novartis also states that, because it is following a J pathway, clinical trials it is conducting do not necessarily show up on www.clinicaltrials.gov.

Biosimilars: Sandoz currently has 8 ongoing Phase III trials covering 6 molecules: etanercept in psoriasis, rituximab in follicular lymphoma, pegfilgrastim in breast cancer (2 studies), filgrastim in breast cancer, epoetin alfa in CKD (2 studies), and most recently, adalimumab (Humira). Some of these trials are fully enrolled (300-1,000 patients/trial) while others are still enrolling.

For Humira, Novartis is conducting a Phase III trial in psoriasis. It indicated that it has an agreement with FDA on a pathway for extrapolation to other indications without clinical data. However, should an RA trial ultimately be required, it would take about 2 years for data to be generated. It appeared to us that Novartis will conduct an RA trial of Humira. Novartis says that it has carefully analyzed Humira's patents beyond the substance patent.

Acceptance of biosimilars overall is much better in northern Europe than in southern Europe. Selling biosimilars is keyed to a salesforce and achieving adequate share of voice. In traditional generics in emerging markets, NVS does not believe it will have

the issues Sanofi had in Brazil because it has rigorous controls and a deep understanding of inventory.

PharmaDerm (branded dermatology): In July 2014, Sandoz entered a partnership with Anacor to market Kerydin (tavaborole) in the U.S. (onychomycosis – nail fungus). Sandoz will pay \$40MM upfront, \$25MM in January 2015 (post launch); Sandoz will retain first \$50MM in profits and then split profits equally. The collaboration provides the 60+ PharmaDerm sales reps with a newly approved product (July 2014) in a therapeutic area needing treatment alternatives.

Alcon

Sales Acceleration A Key Focus

Novartis' acquisition of Alcon in 2010 created a leader in ophthalmology, fortifying the non-pharma businesses and providing synergy opportunities. The Alcon Division includes a surgical (lasers) division, CIBA Vision (contacts, solutions), and pharmaceutical ophthalmology products (ex Lucentis). Eye care is expected to continue to grow substantially with Alcon expected to outperform market trends. Growth in eye care will be driven by the aging population, significant unmet medical need in AMD and glaucoma, and the development of eye diseases in emerging markets. Both developed and emerging markets are expected to benefit from increased utilization by aging demographics. Alcon views share development in glaucoma, growing cataract procedures in emerging markets, developing advanced technology intraocular lenses, building out the Vision Care capability, and expanding daily disposable technology as key near term priorities.

At its June 2014 analyst meeting, Novartis stated that it is not happy with recent top-line trends in Alcon. All segments- surgical/medical device, pharma, and vision care - should contribute to a sales reacceleration. Margin improvement appears less a focus given the need to support new products. In pharma ophthalmics, LOEs are a challenge over the next 5 years, but life cycle extensions have been successful thus far. In surgical/medical equipment, the company indicated that more work is needed in disposables, although the technology gap has closed versus the competition. While resources among the three businesses may be adjusted based on opportunities and challenges, it does not appear that resources overall for Alcon will change significantly. Alcon believes there are interesting M&A opportunities in ophthalmology and believes it is best positioned to win the best deals.

We forecast Alcon revenues consolidated by Novartis of \$10.975B (+5%) in 2014, \$11.625B in 2015, \$12.45B in 2016, \$13.8B in 2018, and \$15.15B in 2020.

Alcon New Products Key To Targeted Above-Market Growth

With its integration complete, Alcon is relying on an array of new products across all three business units – Surgical, Ophthalmic Pharma, and Vision Care – to reach the 2013-2018 CAGR goal of >5%, ahead of estimated 5% market growth. Surgical growth is tied to the rollout of the new Centurion phaco system which in turn will drive growth of the new line of more profitable IOLs. Ophthalmic Pharma gains will be driven by expansion of glaucoma combination drops, penetration of Jetrea (VMT), and eventual entry into the retinal segment with 1-3 new products (wet AMD, GA). In Vision Care, line expansion of Dailies (toric, multi-focal, water gradient SiHy), AirOptix silicone hydrogel (colors) and focused efforts to build share in Japan are key drivers.

Ophthalmic Market Growth Pegged At +5%

Demographics, new products, and EM inroads are key drivers to market growth over the next five years.

Ophthalmic Market (U.S. \$B)

	2013	2018	CAGR	Comments
Vision Care	\$9	\$11	4%	- Shift to disposable contacts & SiHy - Continue to penetrate EMs
Surgical	\$9	\$13	7%	- Cataract procedures grow w/aging population - More use of advanced IOLs; nex-gen equipment
Ophth Pharma	\$19	\$25	5%	- Continued expansion of retina therapies - Increase in glaucoma combo products - Unit volume growth from demographics
Total	\$37	\$49	5%	

Source: Company data

Alcon Surgical: New System To Drive Shift To New IOLs

Last week, Alcon began the U.S. launch of its nex-gen phacoemulsion system, Centurion. The Centurion allows for the use of smaller and more advanced IOLs (ReSTOR Toric, ReSTOR 2.5D multi-focal, and Intrepid minimally invasive). Alcon is the U.S. leader in the cataract market with its Infiniti system, and it seeks to both upgrade these systems to Centurion as well as capture share from competitors. Alcon will also be introducing a new pre-operative device, Verion, which will enable more accurate eye/lens measurements and be part of a complete Cataract Refractive Suite. Alcon views this roll-out of equipment as an investment which will lead to the sale of the more profitable lenses.

Alcon Ophthalmic Pharma: New Products Drive 5% Growth Expectation

Alcon is the leader in most areas of U.S. ophthalmic pharmaceuticals - glaucoma, infection/inflammation, allergy, retina care, and #2 in dry eye. In the glaucoma area, generics have pressured sales, but Alcon believes a shift to combination drops (Simbrinza – U.S. approved May 2013; E.U. approved July 2014) can boost growth. Alcon's dry eye products (Systane line) have been growing 9% over the past couple years, ahead of the market's estimated 4% gains. Alcon feels addressing the under-diagnosis of dry eye represents the greatest opportunity for growth. Jetrea (approved March 2013 in E.U.; Alcon has OUS commercial rights from ThromboGenics) is indicated for treatment of vitreomacular traction (VMT), an age-related, sight-threatening eye disease. There are an estimated 250-350K potential patients in the E.U.

Three products in the pipeline (more than 3 years away) that Alcon hopes will enable it to build presence in the retina market are RTH258 (formerly ESBA 1008; wet AMD), LFG316 Complement Inhibitor (geographic atrophy), and the Replenish delivery system (wet AMD). Alcon estimates the WW sales for wet AMD, DME and RVO was \$6.4B in 2013, and will reach \$10.2B in 2018, a +10% CAGR. RTH258 has a potentially longer duration of action than current anti-VEGFs; it is in Phase II trials for wet AMD, but may also be evaluated in DME and RVO. LFG316, for geographic atrophy, is currently in Phase II with readout expected in 2015. Replenish is a drug delivery pump

that is surgically attached to the eye (like a tiny insulin pump) that can deliver one or more drugs on a programmed basis. FIH studies are complete, proof-of-concept studies to be conducted next for patients with wet AMD.

Alcon Vision Care: Portfolio Expansion

Alcon estimates the WW soft contact lens market to be \$7.6B in 2013, growing at a 4% rate. Alcon is the #2 company in the market, behind JNJ. Alcon is the leader in lens care products, a market estimated at \$1.4B, growing at 1%, and under pressure from the increasing use of daily wear contacts. Alcon's key goal is to expand its portfolio of product offerings. For the Dailies line, Alcon will now include toric and multi-focal options. Regulatory approvals have been received and Alcon launched the full line in the U.S., E.U., Japan, Canada, and Australia in H1:2014. For the AirOptix silicone hydrogel lenses, Alcon is adding a colors line; CE mark was received in October 2013 and U.S. approval in Q1:14. Alcon has also introduced Dailies Total 1 for the water gradient/SiHy segment; early response to this product has been very favorable. It is the #1 premium disposable lens in Italy in less than a year, and in the U.S. it has gained 20 share points in a limited launch, which was constrained by capacity limitations that Alcon is now addressing. Alcon is also focused on Japan where it holds an 8% share of the daily disposables (largest segment in Japan), which is well below its 25-35% share in other markets. Alcon is expanding its salesforce in Japan among other efforts. In July 2014, Alcon announced an agreement with Google to develop their "smart lens" technology (sensors, microchips, etc) initially in the areas of diabetes and presbyopia.

Vaccines

All But Flu Vaccine Sold To Glaxo

In April 2014, Novartis announced the divestiture of its Vaccine business (ex flu) to Glaxo. The transaction, which also includes a joint venture of Consumer products with Glaxo, is expected to be completed by the end of H1:2015. Novartis has indicated they intend to sell the influenza vaccine separately, but no details/timing for this transaction have been provided. Several varieties of companies could be interested, including: 1) those with a vaccine business but not flu (MRK, PFE); 2) those with subscale flu businesses (CSL, Baxter, Takada); or 3) companies, such as biotechs, that are tangentially involved. Flu sales were \$500MM in 2013. We forecast Vaccine sales of \$1,510MM (+6%) in 2014, \$1,100MM in 2015, \$550MM in 2016, \$650MM in 2018, and \$750MM in 2020.

Consumer

Consumer Business Shifted To JV With Glaxo

In April 2014, Novartis announced that it would be JV'ing its consumer business with Glaxo (who will be the majority partner). Novartis will own a 36.5% share of the joint venture and recognize income as part of "income from associated companies". Novartis has a put option (3 year blackout, expires after 20 years) that can be exercised partially or in full. We estimate sales for H:15 of \$2,040MM and equity income to Novartis from the joint venture to be \$613MM in H2:15, \$641MM in 2016, \$699MM in 2018, and \$759MM in 2020.

EPS Growth Prospects Bolstered By Restructuring Moves

EPS Forecast To Be Up 3% In 2014 On 2% Revenue Growth

We estimate EPS to be up 3% to \$5.15 in 2014 on revenue growth of 2% to \$58.26B. We factor in a 0.7pp decline in gross PM, due in part to Diovan generic competition. MSG&A and R&D are forecast to be flat resulting in a 0.3pp increase in operating margin to 25.0%. A \$39MM increase in non-operating income, a 0.3pp increase in the tax rate, and a slight decline in the share count lead to the forecasted 3% EPS gain.

Novartis 2014 Guidance (at CER) Versus Our Expectations

	NVS Guidance	Our Forecasts*
Group sales	Low- to mid-single digit growth	+2%
Pharma sales	In line with 2013	-1%
Alcon sales	Mid-to-high-single digit growth	+5%
Vaccines	NA	+6%
Sandoz sales	Mid-to-high-single digit growth	+5%
Consumer sales	NA	+7%
Core operating income	Mid-to-high single digit growth	+2%
Tax rate	14%	14.1%

*Cowen estimates reflect existing exchange rate movement

Bold= revised

Source: Cowen and Company

EPS Forecast To Be +9-13% In 2015-17

2015 revenues are forecast to be flat reflecting the sale of Animal Health and joint venture of Consumer, which we assume becomes effective Q3:15. Sales growth of 0 to +4% is estimated for 2016-17. We estimate 13% EPS growth in 2015 and 9-10% in 2016 and 2017. This assumes an increase in gross profit margin reflecting the elimination of the lower margin Consumer and Vaccine sales and addition of higher margin oncology products, roughly flat R&D spend, slightly declining MSG&A as a percentage of sales, annual increases in non-operating income including a \$580MM jump in 2015 as equity income from the consumer jv kicks-in, a flat tax rate of roughly 14.2%, and a flat share count. All told, we forecast EPS of \$5.80 (+13%) in 2015, \$6.40 (+10%) in 2016, and \$7.00 (+9%) in 2017.

Novartis 2013-15 Divisional Core P&L Build Up (\$MM)

	2013			2014E			2015E	
	Net Sales	Op. Inc.	O.M.	Net Sales	Op. Inc.	O.M.	Net Sales	Op. Inc.
Pharmaceuticals	\$32,214	\$9,523	29.6%	\$31,846	\$9,590	30.1%	\$33,340	\$10,595
Vaccines	1,422	(229)	-16.1%	1,510	(297)	-19.7%	1,100	(230)
Sandoz	9,159	1,541	16.8%	9,599	1,528	15.9%	10,075	1,750
Consumer health	4,064	298	7.3%	4,330	449	10.4%	2,040	110
Alcon	10,496	874	34.5%	10,974	3,809	34.7%	11,625	3,925
Consolidated Net Sales	\$57,355	\$14,191	24.7%	\$58,259	\$14,544	25.0%	\$58,180	\$15,735
Core income from associated companies		877			965			1,435
Financial income		(48)			(130)			(80)
Interest income		(683)			(650)			(590)
Non-Op Inc./(Exp)		\$146			\$185			\$765
Pretax Income (% of sales)		\$14,337	25.0%		\$14,729	25.3%		\$16,500
Tax Rate		13.8%			14.1%			14.2%
Core Net Income (% of sales)		\$12,235	21.3%		\$12,547	21.5%		\$14,040
Core EPS Basic			\$5.00			\$5.15		\$5.80
Shares Basic (MM)			2,442.0			2,432.8		2,420.0

* 2013 restated to exclude Diagnostics Division, which was divested on January 9, 2014

Source: Company data, Cowen and Company

Solid Growth Appears On Tap In 2018-20

Patent expirations/loss of exclusivity of Lucentis and Exforge should temper sales growth in 2018. Revenues are expected to be +3% in 2018 and EPS up 8% to \$7.55. We forecast 2018 gross profit margin to increase 0.6pp (to 76%) and operating profit margin to be up 1.2pp to 32.2%. We also anticipate an increase in non-operating income, and tax rate and share count to be flat. Growth should accelerate in 2019 and 2020 with revenues forecast to increase 6-8% and EPS 11-13%. We estimate EPS of \$8.40 in 2019 and \$9.45 in 2020.

Novartis 2013-20 EPS Breakout

2013*	2013-16						2013-20		2014-20		Comments
	2014E	2015P	2016P	2017P	2018P	2019P	2020P	CGR	CGR	CGR	
Telgna	0.15	0.18	0.22	0.26	0.30	0.33	0.37	0.41	22%	16%	15% - Nilotinib; 1st and 2nd line CML; cKIT melanoma 2012; GIST study discontinued
Lucentis	0.28	0.29	0.30	0.32	0.33	0.23	0.20	0.18	3%	-6%	-8% - AMD; Ex-US/Japan rights; pat exp. 3/18; E.U. off-label Avastin use small; DME approved 2012; RVO approved 2011; Eylea a competitive challenge
Exjade	0.10	0.11	0.12	0.12	0.12	0.10	0.08	0.06	4%	-8%	-10% - Oral tablet for iron overload; label expansion into myelodysplastic syndrome; patent expiration 2017
Neoral	0.09	0.08	0.07	0.06	0.06	0.05	0.05	0.04	-7%	-9%	-9% - Cyclosporine; ROW majority of sales; generic but substitution minimal
Exelon	0.12	0.12	0.11	0.08	0.06	0.05	0.04	0.03	-11%	-17%	-19% - Patch driving growth, 60% of franchise; Aricept generics 11/10 clip oral sales
Dioven	0.41	0.28	0.14	0.11	0.08	0.04	0.02	0.01	-32%	-40%	-41% - Pat exp 2/11 Spain, Portugal, Brazil; 11/11 other EU; Japan 9/14 (\$1B+); NVS guided to \$2B+ ex-U.S. sales in >2014 for valsartan franchise
Gleevec	0.55	0.54	0.53	0.28	0.13	0.06	0.03	0.01	-15%	-41%	-46% - CML, GIST; alpha crystal pat. exp. 7/15 (includes pedi), beta crystal patent exp. 2019; settlement with Sun allows launch on Feb 1, 2016
Exforge	0.17	0.17	0.16	0.16	0.16	0.09	0.03	0.01	0%	-31%	-35% - Diovan+amlodipine
Zometa	0.07	0.03	0.01	0.01	0.01	0.00	0.00	0.00	-49%	-44%	-42% - U.S. patent expired 03/13
Femera	0.04	0.04	0.04	0.01	0.01	0.00	0.00	0.00	-30%	-41%	-45% - Aromatase inhibitor; exp. 12/10; U.S. generics June 2011; EU generics May 2011
Other Pharma	0.10	0.24	1.20	2.24	2.84	3.56	4.39	5.37	67%	78%	68%
Alcon	1.22	1.28	1.36	1.46	1.54	1.61	1.69	1.77	5%	5%	6% - Alcon robust growth & profitability
Sandoz	1.07	1.12	1.18	1.23	1.29	1.35	1.40	1.47	5%	5%	5% - Fougera Pharma added sales of \$430MM growing at double digit; 6 biosimilars in development including Humira, Enbrel, Rituxan, EPO
Consumer	0.47	0.50	0.24	0.00	0.00	0.00	0.00	0.00	NM	NM	NM - Excludes animal health as of end Q115, sold to LLY for \$5.4B; excludes consumer as of end Q215; JV with GSK, income to associates line
Vaccines	0.12	0.18	0.13	0.06	0.07	0.08	0.08	0.09	-26%	-9%	-11% - Divested blood transfusion dx unit 1/9/14; divested vaccines ex flu as of end Q215 to GSK for \$5.25B + \$1.8B in milestones
Basic EPS	\$5.00	\$5.15	\$5.80	\$6.40	\$7.00	\$7.55	\$8.40	\$9.45	5%	10%	11% - Versus industry averages of +4%, +6% and +8%
% Change	-5%	3%	13%	10%	9%	8%	11%	13%			

* 2013 restated to exclude Diagnostics Division, which was divested on January 9, 2014

Source: Cowen and Company estimates

Novartis 2013-20 Quarterly Core P&L Buildup (\$MM)

	Sales Total \$MM	% Chg	Gross P.M. % Rev	SG&A \$MM	% Rev	R&D \$MM	% Rev	Core Operating Inc \$MM	% Rev	Non-op. Inc. \$MM	Pretax Income \$MM	% Rev	Reported Tax Rate %	Core Net Income \$MM	Core EPS	Chg %	Shares (MM)
Q1	\$13,879	1%	73.7%	\$4,197	30.2%	\$2,279	16.4%	\$3,652	26.3%	\$107	\$3,759	27.1%	14.6%	\$3,186	\$1.30	2%	2,441
Q2	14,354	0%	73.6%	4,367	30.4%	2,374	16.5%	3,692	25.7%	51	3,743	26.1%	14.8%	3,156	1.29	-6%	2,453
Q3	14,196	3%	72.5%	4,207	29.6%	2,359	16.6%	3,554	25.0%	(5)	3,549	25.0%	13.7%	3,029	1.24	-7%	2,442
Q4	14,926	1%	71.5%	4,720	31.6%	2,601	17.4%	3,293	22.1%	(7)	3,286	22.0%	12.0%	2,863	1.18	-7%	2,432
2013*	\$57,355	1%	72.8%	\$17,491	30.5%	\$9,613	16.8%	\$14,191	24.7%	\$146	\$14,337	25.0%	13.8%	\$12,235	\$5.00	-5%	2,442
Q1	\$14,022	1%	73.3%	\$4,199	29.9%	\$2,396	17.1%	\$3,657	26.1%	\$100	\$3,757	26.8%	14.5%	\$3,212	\$1.31	1%	2,440
Q2	14,637	2%	73.2%	4,384	30.0%	2,330	15.9%	3,797	25.9%	16	3,813	26.1%	13.9%	3,253	1.34	4%	2,436
Q3E	14,525	2%	71.5%	4,170	28.7%	2,335	16.1%	3,790	26.1%	45	3,835	26.4%	14.1%	3,259	1.34	8%	2,430
Q4E	15,075	1%	70.5%	4,692	31.1%	2,574	17.1%	3,300	21.9%	24	3,324	22.0%	14.1%	2,822	1.16	-1%	2,425
2014E	\$58,260	2%	72.1%	\$17,445	29.9%	\$9,635	16.5%	\$14,544	25.0%	\$185	\$14,729	25.3%	14.1%	\$12,547	\$5.15	3%	2,433
Q1E	\$14,190	1%	72.8%	\$4,225	29.8%	\$2,480	17.5%	\$3,565	25.1%	\$130	\$3,695	26.0%	14.2%	\$3,150	\$1.30	0%	2,420
Q2E	14,850	1%	72.1%	4,530	30.5%	2,415	16.3%	3,675	24.7%	80	3,755	25.3%	14.5%	3,177	1.31	-2%	2,420
Q3E	14,240	-2%	74.4%	3,865	27.1%	2,250	15.8%	4,395	30.9%	280	4,675	32.8%	14.0%	3,984	1.65	23%	2,420
Q4E	14,900	-1%	73.7%	4,310	28.9%	2,490	16.7%	4,100	27.5%	275	4,375	29.4%	14.0%	3,729	1.54	32%	2,420
2015E	\$58,180	0%	73.3%	\$16,930	29.1%	\$9,635	16.6%	\$15,735	27.0%	\$785	\$16,500	28.4%	14.2%	\$14,040	\$5.80	13%	2,420
2016P	\$58,025	0%	74.8%	\$16,445	28.3%	\$9,385	16.2%	\$17,265	29.8%	\$965	\$18,230	31.4%	14.2%	\$15,495	\$6.40	10%	2,420
2017P	\$60,580	4%	75.4%	\$17,045	28.1%	\$9,520	15.7%	\$18,785	31.0%	\$1,160	\$19,945	32.9%	14.2%	\$16,938	\$7.00	9%	2,420
2018P	\$62,525	3%	76.0%	\$17,450	27.9%	\$9,655	15.4%	\$20,160	32.2%	\$1,355	\$21,515	34.4%	14.2%	\$18,269	\$7.55	8%	2,420
2019P	\$66,340	6%	77.0%	\$18,240	27.5%	\$10,115	15.2%	\$22,425	33.8%	\$1,525	\$23,950	36.1%	14.3%	\$20,322	\$8.40	11%	2,420
2020P	\$71,730	8%	77.8%	\$19,430	27.1%	\$10,835	15.1%	\$25,280	35.2%	\$1,685	\$26,965	37.6%	14.4%	\$22,865	\$9.45	13%	2,420

* 2013 restated to exclude Diagnostics Division, which was divested on January 9, 2014

Source: Company data, Cowen and Company estimates

Novartis Quarterly Product Sales Buildup 2013-15 (\$MM)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E	
Cardiology																
LCZ696																
Galvus	\$267	\$289	\$316	\$328	1,200	308	328	350	365	1,350	350	370	390	405	1,515	
Serelaxin																
LCQ908														15	15	30
Diovan U.S.	430	452	411	386	1,679	414	366	100	100	980	75	75	50	50	250	
Diovan Fgn (LC)																
Diovan Fgn (with Fx)	488	476	424	457	1,845	389	377	325	300	1,400	250	250	225	225	950	
Diovan/Co-Diovan Total	918	928	835	843	3,524	803	743	435	400	2,380	325	325	275	275	1,200	
Tekturna	68	86	77	59	290	54	54	55	55	220	50	50	45	45	190	
LIK066																
Exforge U.S.	86	93	89	88	356	95	80	60	60	295	50	40	30	20	140	
Exforge Fgn (LC)																
Exforge Fgn (with Fx)	262	284	270	284	1,100	268	290	290	290	1,140	280	315	300	305	1,200	
Exforge Total	348	377	359	372	1,456	363	370	350	350	1,435	330	355	330	325	1,340	
Lescol	50	50	50	40	190	25	25	25	25	100	15	15	10	10	50	
Lotrel	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Mature CV	274	270	275	275	1,094	275	275	275	275	1,100	250	250	250	250	1,000	
Total Cardiovascular	1,925	2,000	1,912	1,917	7,754	1,828	1,795	1,490	1,470	6,585	1,320	1,365	1,315	1,325	5,325	
% Change	-12%	-12%	-5%	-6%	-90%	-5%	-10%	-22%	-23%	-15%	-28%	-24%	-12%	-10%	-19%	

Source: Company data, Cowen and Company estimates

Novartis Quarterly Product Sales Buildup 2013-15 (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Oncology															
Gleevec U.S.	404	507	472	556	1,939	420	541	500	580	2,040	450	570	530	610	2,160
Glivec Fgn (LC)								610	620		625	605	570	565	
Glivec Fgn (with Fx)	739	683	661	671	2,754	677	658	625	620	2,580	620	600	570	565	2,355
Gleevec/Glivec Total	1,143	1,190	1,133	1,227	4,693	1,097	1,199	1,125	1,200	4,620	1,070	1,170	1,100	1,175	4,515
Tasigna U.S.	96	106	111	115	428	116	131	130	135	510	145	155	160	165	625
Tasigna Fgn. (LC)								250	280		270	315	315	340	
Tasigna Fgn. (with Fx)	188	209	204	237	838	221	242	255	280	1,000	270	315	315	340	1,240
Tasigna Total	284	315	315	352	1,266	337	373	385	415	1,510	415	470	475	505	1,865
Afinitor U.S.	168	160	182	181	691	175	194	195	205	770	215	225	235	245	920
Afinitor Fgn. (LC)								195	220		215	225	235	255	
Afinitor Fgn. (with Fx)	135	148	155	180	618	182	190	200	220	790	215	225	235	255	930
Afinitor Total	303	308	337	361	1,309	357	384	395	425	1,560	430	450	470	500	1,850
Votrient/Patorma U.S.													100	110	210
Votrient/Patorma Fgn. (LC)													150	160	
Votrient/Patorma Fgn. (with Fx)													150	160	310
Votrient/Patorma													250	270	520
Jakavi	35	33	48	47	163	57	69	80	90	295	100	110	120	130	460
Sandostatin U.S.	164	176	185	185	710	162	185	185	185	715	155	175	175	175	680
Sandostatin Fgn (LC)								225	240		200	235	220	230	
Sandostatin Fgn (with Fx)	204	228	216	231	879	222	232	230	240	925	200	235	220	230	885
Sandostatin Franchise Total	368	404	401	416	1,589	384	417	415	425	1,640	355	410	395	405	1,565
LEE011													75	85	160
Tafinlar															
Mekinist													65	75	140

Source: Company data, Cowen and Company estimates

Novartis Quarterly Product Sales Buildup 2013-15 (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Oncology - Cont'd															
Promacta U.S.														40	50
Promacta Fgn. (LC)														75	75
Promacta Fgn. (with Fx)														75	75
Promacta														115	125
Signifor		5	5	5	15	10	15	20	15	60	35	35	40	40	150
Exjade U.S.	59	67	68	71	265	68	74	75	75	290	70	80	80	80	310
Exjade Fgn. (LC)								150	180		145	185	160	185	
Exjade Fgn. (with Fx)	144	167	144	173	628	140	170	155	180	645	145	185	160	185	675
Exjade Total	203	234	212	244	893	208	244	230	255	935	215	265	240	265	985
Tykerb U.S.														25	25
Tykerb Fgn. (LC)														75	75
Tykerb Fgn. (with Fx)														75	75
Tykerb														100	100
Arzerra U.S.														35	35
Arzerra Fgn. (LC)														20	20
Arzerra Fgn. (with Fx)														20	20
Arzerra														55	55
CTL019															
LBH 589														10	20
Zykadia								5	10	15	10	10	10	10	40
LDE225														10	10
PKC412															
MEK162															
TKI 258															

Source: Company data, Cowen and Company estimates

Novartis Quarterly Product Sales Buildup 2013-15 (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Oncology - Cont'd															
2110183															
LGX818															
BKM120															
AUY922															
BYL719															
LJM716															
HSC835															
BGJ398															
Hycamtin U.S.														0	0
Hycamtin Fgn. (LC)													15	30	-
Hycamtin Fgn. (with Fx)													15	30	45
Hycamtin													15	30	45
Zometa U.S.	76	25	10	4	115	5	5	5	5	20	5	5	5	-	15
Zometa Fgn (LC)								55	50		40	30	20	10	
Zometa Fgn (with Fx)	166	135	94	90	485	69	71	55	50	245	40	30	20	10	100
Zometa Total	242	160	104	94	600	74	76	60	55	265	45	35	25	10	115
Femara U.S.	5	4	5	5	19	5	4	5	0	15	5	0	5	0	10
Femara Fgn. (LC)								80	80		75	75	75	70	
Femara Fgn. (with Fx)	92	93	85	95	365	89	87	80	80	335	75	75	75	70	295
Femara Total	97	97	90	100	384	94	91	85	80	350	80	75	80	70	305
Other Oncology	30	72	70	70	242	85	85	80	80	330	85	85	85	85	340
Total Oncology	2,705	2,818	2,715	2,916	11,154	2,703	2,953	2,880	3,050	11,585	2,870	3,155	3,765	3,995	13,785
% Change	7%	5%	3%	2%	4%	0%	5%	6%	5%	4%	6%	7%	NM	NM	19%

Source: Company data, Cowen and Company estimates

Novartis Quarterly Product Sales Buildup 2013-15 (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Neuroscience And Ophthalmics															
Gilenya U.S.	243	255	273	252	1,023	260	284	290	300	1,135	310	320	330	340	1,300
Gilenya Fgn. (LC)								340	360		370	380	390	400	
Gilenya Fgn. (with Fx)	178	213	245	275	911	292	322	350	360	1,325	365	375	390	400	1,530
Gilenya Total	421	468	518	527	1,934	552	606	640	660	2,460	675	695	720	740	2,830
Secukinumab											20	30	40	60	150
Lucentis	596	576	581	630	2,383	620	619	625	650	2,515	640	640	645	670	2,595
Extavia	41	42	39	37	159	45	44	40	40	170	45	50	45	45	185
Fanapt	15	15	20	20	70	20	20	25	25	90	25	25	30	30	110
Tegretol (CR/XR)	83	86	83	90	342	80	96	75	80	330	75	80	70	75	300
Trileptal	59	66	63	69	257	63	72	55	60	250	55	55	55	55	220
CAD106 BAF312															
Exelon/Patch U.S.	112	121	117	107	457	126	108	125	115	475	135	145	100	65	445
Exelon/Patch Fgn.(LC)								130	125		125	130	125	115	
Exelon/Patch Fgn. (with Fx)	154	142	136	143	575	136	138	135	125	535	125	130	125	115	495
Exelon/Patch Total	266	263	253	250	1,032	262	246	260	240	1,010	260	275	225	180	940
Comtan Group U.S.	10	4	10	9	33	8	5	5	5	25	5	5	5	-	15
Comtan Group Fgn. (LC)								85	85		80	80	75	75	
Comtan Group Fgn. (with Fx)	90	93	91	94	368	89	87	85	85	345	80	80	75	75	310
Comtan Group Total	100	97	101	103	401	97	92	90	90	370	85	85	80	75	325
Ritalin Group U.S.	111	106	100	118	435	74	88	70	60	290	50	40	35	35	160
Ritalin Group Fgn. (LC)								35	35		30	30	25	25	
Ritalin Group Fgn. (with Fx)	35	40	41	43	159	36	44	35	35	150	30	30	25	25	110
Ritalin Group Total	146	146	141	161	594	110	132	105	95	440	80	70	60	60	270
Other Neuroscience	23	21	20	20	84	20	20	20	20	80	20	20	20	20	80
Mature Neuroscience	85	80	85	85	335	75	75	75	75	300	65	65	70	70	270
Total Neuroscience	1,835	1,860	1,904	1,992	7,591	1,944	2,022	2,010	2,035	8,010	2,045	2,090	2,060	2,080	8,275
% Change	8%	6%	9%	8%	8%	6%	9%	6%	2%	6%	5%	3%	2%	2%	3%

Source: Company data, Cowen and Company estimates

Novartis Quarterly Product Sales Buildup 2013-15 (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Respiratory															
Xolair	141	148	151	173	613	173	197	200	205	775	185	210	210	215	820
Ultibro (QVA149)				6	6	14	22	30	40	105	50	60	70	80	260
TMB100 (TIP)	35	40	75	83	233	86	90	90	95	360	100	105	105	110	420
Onbrez (QAB149)	43	47	49	53	192	53	56	60	65	235	70	75	80	85	310
Seebri	15	12	15	25	67	30	37	40	45	150	50	55	60	65	230
QMF149															
QAW039															
QAX576															
BCT197															
QGE031															
Foradil	56	46	48	55	205	47	49	45	45	185	40	40	35	35	150
Tobi	83	67	34	5	189										
Other Respiratory	7	7	10	10	34	5	10	10	10	35	10	10	10	10	40
Mature Respiratory	20	18	20	20	78	20	20	15	15	70	15	15	15	15	60
Total Respiratory	400	385	402	430	1,617	428	481	490	520	1,920	520	570	585	615	2,290
% Change	22%	13%	20%	17%	18%	7%	25%	22%	21%	19%	21%	19%	19%	18%	19%
Immunology & Infectious Disease															
Myfortic U.S.	62	63	70	75	270	43	36	35	30	145	30	25	25	20	100
Myfortic Fgn. (LC)								90	85		95	90	95	90	
Myfortic Fgn. (with Fx)	87	107	89	84	367	90	87	90	85	350	95	90	95	90	370
Myfortic Total	149	170	159	159	637	133	123	125	115	495	125	115	120	110	470
Neoral/Sandimmun U.S.	14	15	14	13	56	14	12	10	10	45	10	10	5	5	30
Neoral/Sandimmun Fgn. (LC)								150	170		145	165	150	160	
Neoral/Sandimmun Fgn. (with Fx.)	168	179	165	182	694	154	167	155	170	645	145	165	150	160	620
Neoral/Sandimmun Total	182	194	179	195	750	168	179	165	180	690	155	175	155	165	650
Certican	58	62	66	63	249	75	81	80	80	315	85	85	90	90	350
Ilaris	24	27	31	37	119	42	47	50	50	190	50	50	55	55	210
Cubicin	25	30	25	30	110	30	30	35	35	130	35	35	40	40	150

Source: Company data, Cowen and Company estimates

Novartis Quarterly Product Sales Buildup 2013-15 (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Immunology & Infectious Disease - cont'd.															
LCI699															
ACZ885															
DEB025															
Aclasta U.S.	54	27	10	20	111	5	5	5	5	20	10	5	5	5	25
Aclasta Fgn. (LC)															
Aclasta Fgn. (with Fx)	58	65	40	40	203										
Aclasta	112	92	50	60	314	5	5	5	5	20	10	5	5	5	25
Others IID	25	25	25	25	100	20	20	20	20	80	15	15	15	15	60
Mature IID	110	110	115	135	470	125	164	125	145	560	115	155	115	135	520
Total IID	685	710	650	704	2,749	598	649	605	630	2,480	590	635	595	615	2,435
% Change	-3%	-15%	-10%	-15%	-11%	-13%	-9%	-7%	-11%	-10%	-1%	-2%	-2%	-2%	-2%
Other Products															
Voltaren Total	155	177	167	176	675	148	161	155	165	630	135	155	145	155	590
Everolimus to stent manf	80	81	40	46	247	65	43	45	45	200	70	50	50	50	220
BYM338															
Enablex/Emselex	5	5	5	5	20	5	5	5	5	20	5	5	5	5	20
Other products	87	85	98	137	407	88	90	100	140	420	85	85	95	135	400
Mature OGU															
Total Other	327	348	310	364	1,349	306	299	305	355	1,265	295	295	295	345	1,230
% Change	-11%	-5%	-6%	9%	-3%	-6%	-14%	-2%	-2%	-6%	-4%	-1%	-3%	-3%	-3%
Total Pharma Sales	7,877	8,121	7,893	8,323	32,214	7,807	8,199	7,780	8,060	31,845	7,640	8,110	8,615	8,975	33,340
% Change	1%	-2%	1%	1%	0%	-1%	1%	-1%	-3%	-1%	-2%	-1%	11%	11%	5%

Source: Company data, Cowen and Company estimates

Novartis Quarterly Product Sales Buildup 2013-15 (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
US	63	89	250	189	591	30	66	250	200	545	50	75	150	150	425
ROW -LC								250	350		200	275	100	100	
ROW (Incl'd Fx)	127	188	202	314	831	185	174	255	350	965	200	275	100	100	675
Vaccines	190	277	452	503	1,422	215	240	505	550	1,510	250	350	250	250	1,100
% Change	NM	NM	NM	NM	NM	13%	-13%	12%	9%	6%	16%	46%	NM	NM	NM
US	696	670	718	737	2,821	717	717	760	795	2,990	750	750	790	825	3,115
ROW -LC								1,600	1,750		1,700	1,725	1,710	1,850	
ROW (Incl'd Fx)	1,563	1,546	1,555	1,674	6,338	1,601	1,614	1,645	1,750	6,610	1,690	1,710	1,710	1,850	6,960
Sandoz	2,259	2,216	2,273	2,411	9,159	2,318	2,331	2,405	2,545	9,600	2,440	2,460	2,500	2,675	10,075
% Change	6%	3%	11%	1%	5%	3%	5%	6%	6%	5%	5%	6%	4%	5%	5%
US	196	219	222	210	847	221	225	230	245	920	260	215			475
ROW -LC								865	875		840	735			
ROW (Incl'd Fx)	791	785	817	824	3,217	819	825	890	875	3,410	835	730			1,565
Consumer Health	987	1,004	1,039	1,034	4,064	1,040	1,050	1,120	1,120	4,330	1,095	945			2,040
% Change	6%	11%	11%	8%	9%	5%	5%	8%	8%	7%	5%	NM			
US	1,000	1,114	1,037	1,028	4,179	1,021	1,159	1,125	1,125	4,430	1,125	1,250	1,225	1,225	4,825
ROW -LC								1,550	1,675		1,650	1,750	1,650	1,775	
ROW (Incl'd Fx)	1,566	1,622	1,502	1,627	6,317	1,621	1,658	1,590	1,675	6,545	1,640	1,735	1,650	1,775	6,800
Alcon	2,566	2,736	2,539	2,655	10,496	2,642	2,817	2,715	2,800	10,975	2,765	2,985	2,875	3,000	11,625
% Change	1%	3%	3%	3%	3%	3%	3%	7%	5%	5%	5%	6%	6%	7%	6%
Total Novartis Sales	13,879	14,354	14,196	14,926	57,355	14,022	14,637	14,525	15,075	58,260	14,190	14,850	14,240	14,900	58,180
% Change	1%	0%	3%	1%	1%	1%	2%	2%	1%	2%	1%	1%	-2%	-1%	0%

Source: Company data, Cowen and Company estimates

Novartis Annual Product Sales Buildup 2013-20 (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CAGR	2013-20 CAGR
Cardiology										
LCZ696				500	1,000	2,000	3,000	4,000	NM	NM - ARB/NEP inhib; PARADIGM-HF trial in HFrEF stopped early, NDA Q4:14 (US), '15 (EU); hypertension NDA 2013 (Japan); PIII for CHF + preserved EF NDA 2017+
Galvus	1,200	1,350	1,515	1,650	1,800	1,950	2,100	2,250	9%	9% - DPP-IV inhibitor; launched ex-U.S., Japan 1/10; U.S. filing delayed indefinitely
Serelaxin						100	200	300	NM	NM - Relaxin; approval denied on RELAX-acute heart failure trial; RELAX-AHF-2 interim results in 2015, final results in H2:16, mortality endpoint
LCQ908			30	50	75	100	125	150	NM	NM - DGAT1 inhibitor; familial chylomicronemia syndrome; Phase III; NDA 2014
Diovan U.S.	1,679	980	250	200	150	100	75	50	-39%	-39% - ARB; generic plain form and HCTZ combo generic launched; Ranbaxy + Sandoz plain generic assumed end Q2:14
Diovan Fgn (LC) Diovan Fgn (with Fx)	1,845	1,400	950	750	500	250	100	50	-43%	-40% - Pat exp 2/11 Spain, Portugal, Brazil; 11/11 other EU; Japan 9/14 (\$1B+); NVS guided to \$2B+ ex-U.S. sales in >2014 for valsartan franchise
Diovan/Co-Diovan Total	3,524	2,380	1,200	950	650	350	175	100	-41%	-40% - Japan 20% of sales; patent expiration 2013; expect less dramatic erosion
Tekturna	290	220	190	170	150	125	100	75	-16%	-18% - Early stoppage of ALTITUDE for safety substantially tarnished prospects; HF NDA 2016
LIK066								50	NM	NM - Type II diabetes; Phase II; NDA 2018+
Exforge U.S. Exforge Fgn (LC) Exforge Fgn (with Fx)	356	295	140	100	75	50	25	10		- Declines with Diovan exp in U.S.; combo patent exp 12/2017
Exforge Total	1,100	1,140	1,200	1,250	1,300	500	250	100		- EU data exclusivity thru 2017 and 75% of sales are ex U.S.
Lescol	1,456	1,435	1,340	1,350	1,375	550	275	110	-35%	-31% - Diovan+amlodipine
Lotrel	190	100	50	25	15	5	5	5	-39%	-41% - Fluvastatin; XL 75% of sales; 2/3rds sales ex-U.S.; simvastatin generics eroding share
Mature CV	1,094	1,100	1,000	900	800	700	600	500	-12%	-11% - Includes off patent compounds
Total Cardiovascular	7,754	6,585	5,325	5,595	5,865	5,880	6,580	7,540	2%	0%
% Change	-9%	-15%	-19%	5%	5%	0%	12%	15%		

Source: Company data, Cowen and Company estimates

Novartis Annual Product Sales Buildup 2013-20 (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CAGR	2013-20 CAGR
Oncology										
Gleevec U.S.	1,939	2,040	2,160	400	150	50	25	10	-59%	-53% - CML, GIST; alpha crystal pat. exp. 7/15 (includes pedi), beta crystal patent exp. 2019; settlement with Sun allows launch on Feb 1, 2016
Glivec Fgn (LC)										
Glivec Fgn (with Fx)	2,754	2,580	2,355	2,000	1,000	500	250	100	-42%	-38% - Greater incidence ex-US; positive opinion for 36 months in GIST; pat exp 6/16+6 months exclusivity, to 12/16; beta crystal form patent exp. 7/18
Gleevec/Glivec Total	4,693	4,620	4,515	2,400	1,150	550	275	110	-46%	-42% Japan patent expiration 2014
Tasigna U.S.	428	510	625	750	875	1,000	1,125	1,250		Off treatment trials fully enrolled, data available in 2 years
Tasigna Fgn. (LC)										
Tasigna Fgn. (with Fx)	838	1,000	1,240	1,450	1,650	1,850	2,050	2,250		
Tasigna Total	1,266	1,510	1,865	2,200	2,525	2,850	3,175	3,500	15%	16% - Nilotinib; 1st and 2nd line CML; cKIT melanoma 2012; GIST study discontinued
Afinitor U.S.	691	770	920	1,050	1,150	1,250	1,350	1,450		
Afinitor Fgn. (LC)										
Afinitor Fgn. (with Fx)	618	790	930	1,075	1,275	1,475	1,675	1,875		
Afinitor Total	1,309	1,560	1,850	2,125	2,425	2,725	3,025	3,325	13%	14% - Everolimus; mRCC, SEGA, NET, TSC AML, ER+/HER2- brca approved; HER2+ 1st, 2nd, 3rd line filing 2014; GI/lung NET 2015
Votrient/Patorma U.S.			210	500	600	700	800	900	NM	Advanced RCC and advanced soft tissue sarcoma
Votrient/Patorma Fgn. (LC)										
Votrient/Patorma Fgn. (with Fx)			310	750	900	1,000	1,100	1,200	NM	Advanced RCC and advanced soft tissue sarcoma
Votrient/Patorma			520	1,250	1,500	1,700	1,900	2,100	NM	Pazopanib; VEGFR 2 tyrosine kinase inhibitor; ovarian no longer pursued
Jakavi	163	295	460	650	850	1,050	1,250	1,400	30%	36% - JAK2 from Incyte; marketed for myelofibrosis and myeloproliferative; Japan reg. decision H2:14; polycythemia vera 2014
Sandostatin U.S.	710	715	680	625	575	525	475	425		
Sandostatin Fgn (LC)										
Sandostatin Fgn (with Fx)	879	925	885	800	750	700	650	600		
Sandostatin Franchise Total	1,589	1,640	1,565	1,425	1,325	1,225	1,125	1,025	-8%	-6% - Octreotide; formulation patent E.U. exp. 2010 but no impact, U.S. 2014-15; 85% of sales from LAR, two-thirds ex U.S.
LEE011				50	100	250	500	1,000	NM	CDK 4/6 inhibitor; breast cancer NDA 2016, solid tumors 2018; 150
Tafinlar				160	420	550	675	800	NM	Dabrafenib; BRAF inhibitor; metastatic melanoma; approved for mono and combo in US (V600E mutations); mono in E.U.
Mekinist				140	375	500	625	750	NM	Trametinib; Mek (1/2) inhibitor; metastatic melanoma; approved for mono in US (V600E and K mutations); positive opinion in E.U.

Source: Company data, Cowen and Company estimates

Novartis Annual Product Sales Buildup 2013-20 (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CAGR	2013-20 CAGR	
Oncology - Cont'd											
Promacta U.S.		90	200	225	250	275	300	NM	NM	Approved for ITP, anemia assoc. with HCV tx; submitted for severe aplastic anemia	
Promacta Fgn. (LC)		150	335	385	435	485	535	NM	NM	Approved for ITP, anemia assoc. with HCV tx; submitted for severe aplastic anemia	
Promacta Fgn. (with Fx)											
Promacta		240	535	610	685	760	835	NM	NM	Eltrombopag; treatment of low platelet count; FDA approved with restrictive label; MDS and AML Phase II	
Signifor	15	60	150	250	350	450	550	650	49%	NM - Pasireotide; oral 2nd gen. Sandostatin; approved for Cushing's; resistant carcinoid; acromegaly PDUFA H2:14; NET in Phase III	
Exjade U.S.	265	290	310	330	350	200	100	50			
Exjade Fgn. (LC)		628	645	675	695	715	650	550	-10%	-8% - Oral tablet for iron overload; label expansion into myelodysplastic syndrome; patent expiration 2017	
Exjade Fgn. (with Fx)											
Exjade Total	893	935	985	1,025	1,065	850	650	500			
Tykerb U.S.		50	100	100	100	100	100	NM	NM	HER2+ mBC; failed in adjuvant	
Tykerb Fgn. (LC)		150	310	330	345	360	375	NM	NM	HER2+ mBC	
Tykerb Fgn. (with Fx)											
Tykerb		200	410	430	445	460	475	NM	NM	Lapatinib	
Arzerra U.S.		70	175	185	195	205	215	NM	NM	CLL approved for refractory and first line	
Arzerra Fgn. (LC)		40	75	100	125	150	175	NM	NM	CLL approved for refractory; positive opinion for first line	
Arzerra Fgn. (with Fx)											
Arzerra		110	250	285	320	355	390	NM	NM	Ofatumumab/HuMax-CD20; fully human Mab	
CTL019					100	250	500	NM	NM	- Leukemia (CLL and B-ALL); pivotal trials to start in 2014; NDA 2016	
LBH 589		100	150	200	250	300	350	NM	NM	- Panobinostat; oral deacetylase inhibitor; multiple myeloma WW NDA 2014 (delayed due to event rate); hematological tumors >2015	
Zykadia	15	40	75	100	150	200	250	NM	NM	- ALK+ advanced NSCLC; approved 4/14 for first therapy after PFE's crizotinib	
LDE225		40	60	80	100	120	140	NM	NM	- Gorlin's syndrome NDA 2012; basal cell carcinoma NDA 2014; solid tumors PI and medulloblastoma PIII NDA 2018+	
PKC412				25	50	75	100	125	NM	NM - Aggressive systemic mastocytosis NDA 2015; acute myeloid leukemia NDA 2015	
MEK162				20	40	60	80	100	NM	NM - NRAS mutant melanoma PIII, NDA 2015; low grade serious ovarian cancer PIII, NDA 2016; solid tumors PII, NDA 2018+	
TKI 258							25	50	NM	NM - Solid tumors Phase II, NDA 2017	

Source: Company data, Cowen and Company estimates

Novartis Annual Product Sales Buildup 2013-20 (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CAGR	2013-20 CAGR
Oncology - Cont'd										
2110183						25		50	NM	NM - AKT protein kinase inhibitor; multiple myeloma, ovarian cancer, Phase II
LGX818								50	NM	NM - BRAF mutant melanoma PIII, NDA 2016; solid tumors NDA 2018+
BKM120								50	NM	NM - Breast cancer NDA 2015; solid tumors NDA 2018+
AUY922								50	NM	NM - Solid tumors, Phase II; NDA >2018
BYL719								50	NM	NM - Solid tumors, Phase II; NDA >2018
LJM716								50	NM	NM - Solid tumors, Phase II; NDA >2018
HSC835								50	NM	NM - Stem cell transplant, Phase II; NDA >2018
BGJ398								50	NM	NM - Solid tumors, Phase II; NDA >2018
Hycamtin U.S.		-	-	-	-	-	-	-	NM	NM
Hycamtin Fgn. (LC)										
Hycamtin Fgn. (with Fx)		45	100	115	130	145	160		NM	NM
Hycamtin		45	100	115	130	145	160		NM	NM - Oral topotecan for refractory SCLC; first line ovarian
Zometa U.S.	115	20	15	10	5	5	5	5		
Zometa Fgn (LC)										
Zometa Fgn (with Fx)		485	245	100	75	50	25	10	5	
Zometa Total	600	265	115	85	55	30	15	10	-42%	-47% - U.S. patent expired 03/13
Femara U.S.	19	15	10	5	5	5	5	5		
Femara Fgn. (LC)										
Femara Fgn. (with Fx)		365	335	295	100	50	25	5	5	
Femara Total	384	350	305	105	55	30	10	10	-45%	-36% - Aromatase inhibitor; exp. 12/10; U.S. generics June 2011; EU generics May 2011
Other Oncology	242	330	340	360	380	400	420	440	5%	22%
Total Oncology	11,154	11,585	13,785	14,345	14,740	15,725	17,265	19,645	9%	7%
% Change	4%	4%	19%	4%	3%	7%	10%	14%		

Source: Company data, Cowen and Company estimates

Novartis Annual Product Sales Buildup 2013-20 (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CAGR	2013-20 CAGR
Neuroscience And Ophthalmics										
Gilenya U.S.	1,023	1,135	1,300	1,450	1,600	1,750	1,900	2,050		- PPMS Phase III, NDA 2015; CIDP Phase III, NDA 2016
Gilenya Fgn. (LC)										
Gilenya Fgn. (with Fx)	911	1,325	1,530	1,650	1,750	1,850	2,000	2,150		12% - MS; marketed in U.S. and E.U.; labels reflect adverse events; BIB's Tecfidera a significant competitive risk
Gilenya Total	1,934	2,460	2,830	3,100	3,350	3,600	3,900	4,200	9%	
Secukinumab				150	300	600	800	1,000	1,200	NM - IL-17; psoriasis PDUFA 1/15, CHMP decision H2:14; PsA 2014, RA/AS 2015
Lucentis	2,383	2,515	2,595	2,700	2,800	2,000	1,750	1,500	-8%	-6% - AMD; Ex-U.S./Japan rights; pat exp. 3/18; E.U. off-label Avastin use small; DME approved 2012; RVO approved 2011; Eylea a competitive challenge
Extavia	159	170	185	200	215	230	245	260	7%	7% - NVF233; interferon-b1 for MS/ Betaseron under agreement with Bayer; launched in E.U. and U.S.
Fanapt	70	90	110	130	150	170	190	210	15%	17% - Undifferentiated anti-psychotic; subQ formulation in development
Tegretol (CR/XR)	342	330	300	280	260	240	220	200	-8%	-7% - Off patent but patients unlikely to be switched
Trileptal	257	250	220	200	180	160	140	120	-12%	-10% - Oxcarbazepine; composition patent expired 2006; generics launched Q4:07
CAD106								50	NM	NM - SubQ A-beta mAb for Alzheimer's disease Phase II; NDA 2018+
BAF312								50	NM	NM - Phase II, RRMS; NDA >2018
Exelon/Patch U.S.	457	475	445	200	150	100	50	25		- U.S. oral patent exp. 08/12 settled w/Sun; higher strength patch supports till 8/15
Exelon/Patch Fgn.(LC)										
Exelon/Patch Fgn. (with Fx)	575	535	495	450	400	350	300	250		
Exelon/Patch Total	1,032	1,010	940	650	550	450	350	275	-19%	-17% - Patch driving growth, 60% of franchise; Aricept generics 11/10 clip oral sales
Comtan Group U.S.	33	25	15	10	5	5	5	5		
Comtan Group Fgn. (LC)										
Comtan Group Fgn. (with Fx)	368	345	310	280	250	220	190	160		
Comtan Group Total	401	370	325	290	255	225	195	165	-13%	-12% - Includes Stalevo for PD; from Orion; Stalevo Paragraph IV filing in 8/07 (Teva and Sun); Comtan exp 8/12 -10/13
Ritalin Group U.S.	435	290	160	75	50	35	25	15		
Ritalin Group Fgn. (LC)										
Ritalin Group Fgn. (with Fx)	159	150	110	80	60	40	20	10		
Ritalin Group Total	594	440	270	155	110	75	45	25	-38%	-36% - Includes Ritalin LA and Focalin XR; Focalin exclusivity expired 5/08; patent exp 12/15 but generics could have entered in 12/12
Other Neuroscience	84	80	80	80	80	80	80	80	0%	-1%
Mature Neuroscience	335	300	270	240	210	180	150	120	-14%	-14% - Includes Clozaril
Total Neuroscience	7,591	8,010	8,275	8,325	8,760	8,210	8,265	8,455	1%	2%
% Change	8%	6%	3%	1%	5%	-6%	1%	2%		

Source: Company data, Cowen and Company estimates

Novartis Annual Product Sales Buildup 2013-20 (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CAGR	2013-20 CAGR
Respiratory										
Xolair	613	775	820	875	925	975	1,025	1,075	6%	8% - Severe asthma; with Roche; chronic spontaneous urticaria NDA 7/13
Ultibro (QVA149)	6	105	260	400	500	600	700	800	NM	NM - QD FDC indacaterol/glycopyrronium bromide; COPD; launched in Germany, Netherlands, Japan; ROW NDA filed October 2012, U.S. Q4:14
TMB100 (TIP)	233	360	420	475	525	575	625	675	11%	16% - 2nd genTOBI, 3 min vs 18 min inhalation; E.U. filing Q4:09; U.S. approval in 3/13, Gilead's aztreonam complimentary
Onbrez (QAB149)	192	235	310	400	450	500	550	600	17%	18% - Once-daily LABA (Indacaterol) for COPD; approved E.U. and U.S.
Seebri	67	150	230	300	350	400	450	500	22%	NM - NVA237; QD LAMA, glycopyrronium, for COPD; approved in E.U. 10/1/12 and Japan 9/28/12, U.S. filing Q4:14; licensed from Vectura
QMF149				50	100	150	200	250	NM	NM - LABA/steroid combination; COPD Phase II, NDA 2015; asthma Phase II, NDA 2015, both ex-U.S.
QAW039								50	NM	NM - Asthma, Phase II; filing >2018
QAX576								50	NM	NM - Allergic diseases, Phase II; filing >2018
BCT197								50	NM	NM - COPD, Phase II; filing >2018
QGE031								50	NM	NM - Allergic diseases; NDA 2018+; Phase II study in peanut allergy commenced H2:11
Foradil	205	185	150	125	100	75	50	25	-28%	-26% - Formoterol (LABA); clipped by QAB149
Tobi	189								NM	NM - Inhaled tobramycin for cystic fibrosis; assume replaced by TIP in Q4:10 in E.U. and 2012 in U.S.; generics
Other Respiratory	34	35	40	45	50	55	60	65	11%	10%
Mature Respiratory	78	70	60	50	40	30	20	10	-28%	-25%
Total Respiratory	1,617	1,920	2,290	2,720	3,040	3,360	3,680	4,200	14%	15%
% Change	18%	19%	19%	19%	12%	11%	10%	14%		
Immunology & Infectious Disease										
Myfortic U.S.	270	145	100	75	50	25	10	5		- Generics
Myfortic Fgn. (LC)										
Myfortic Fgn. (with Fx)	367	350	370	390	410	430	450	470	-1%	-4% - Oral transplant agent
Myfortic Total	637	495	470	465	460	455	460	475		
Neoral/Sandimmun U.S.	56	45	30	20	10	5	5	5		
Neoral/Sandimmun Fgn. (LC)										
Neoral/Sandimmun Fgn. (with Fx)	694	645	620	575	525	475	425	375	-9%	-9% - Cyclosporine; ROW majority of sales; generic but substitution minimal
Neoral/Sandimmun Total	750	690	650	595	535	480	430	380		
Certican	249	315	350	390	430	470	510	550	10%	12% - Everolimus; launched ex-U.S.; U.S. approval 4/10 for renal transplant; refile heart-transplant 2010; liver 2011
Ilaris	0	119	190	210	230	250	270	290	310	9%
										15% - Canakinumab; anti-IL 1 beta mAb; CAPS approved; refractory gout BLA 2/11 but CR, E.U. approval in 3/13; SJIA approval in U.S. in 5/13; type 2DM '12
Cubicin	110	130	150	170	190	210	230	250	12%	12% - I.V. MRSA antifective; European rights only

Source: Company data, Cowen and Company estimates

Novartis Annual Product Sales Buildup 2013-20 (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CAGR	2013-20 CAGR
Immunology & Infectious Disease - cont'd.										
LCI699					25	50	75	NM	NM - Cushing's NDA 2017	
ACZ885					25	50	75	NM	NM - Hereditary periodic fevers NDA 2016; sec prev CV events 2017	
DEB025							25	NM	NM - HCV; alisporivir; cyclophilin inhibitor; Phase III study in untx genotype 1 HCV patients; NDA 2017	
Aclasta U.S.	111	20	25	15	10	5	5	5	-21%	-45% - I.V. zoledronate; Paget's & OP; generics clip
Aclasta Fgn. (LC)										
Aclasta Fgn. (with Fx)	203									
Aclasta	314	20	25	15	10	5	5	5	-21%	-45% - I.V. zoledronate; Paget's & OP; generics clip
Others IID	100	80	60	40	20	10	5	5	-37%	-35% - Simulect (basiliximab) transplant; Tyzeka (HBV)
Mature IID	470	560	520	450	400	350	300	250	-13%	-9%
Total IID	2,748	2,480	2,435	2,355	2,295	2,300	2,330	2,400	-1%	-2%
% Change	-11%	-10%	-2%	-3%	-3%	0%	1%	3%		
Other Products										
Voltaren Total	675	630	590	550	500	450	400	350	-9%	-9% - Older NSAID; still growing ex-U.S.
Everolimus to stent manf	247	200	220	240	260	280	300	320	8%	4% - Sales to Abbott
BYM338						25	50	75	NM	NM - SIB myositis filing 2016; hip fracture, Phase II, filing 2018+
Enablex/Emselex	20	20	20	20	20	20	20	20	0%	0% - Overactive bladder; U.S. rights sold to Warner Chilcott
Other products	407	420	400	375	350	325	300	275	-7%	-5%
Mature OGU										
Total Other	1,349	1,265	1,230	1,185	1,130	1,100	1,070	1,040	-3%	-4%
% Change	-3%	-6%	-3%	-4%	-5%	-3%	-3%	-3%		
Total Pharma Sales	32,214	31,845	33,340	34,525	35,830	36,575	39,190	43,280	5%	4%
% Change	0%	-1%	5%	4%	4%	2%	7%	10%		

Source: Company data, Cowen and Company estimates

Novartis Annual Product Sales Buildup 2013-20 (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CAGR	2013-20 CAGR	
US	591	545	425	330	360	390	420	450	-3%	-4%	- Flu sales were \$500MM in 2013, 30MM of 50MM doses in U.S.
ROW -LC ROW (Incl'd Fx)	831	965	675	220	240	260	280	300	-18%	-14%	- Sales process underway for flu business Blood dx sales eliminated in 2013; fgn assumed to be 60% of sales
Vaccines	1,422	1,510	1,100	550	600	650	700	750	-11%	-9%	Divested blood transfusion dx unit 1/9/14; divested vaccines ex flu as of end Q2:15 to GSK for \$5.25B + \$1.8B in milestones
% Change	NM	6%	NM	NM	9%	8%	8%	7%			
US	2,821	2,990	3,115	3,200	3,400	3,600	3,800	4,000	5%	5%	- Fougera Pharma added sales of \$430MM growing at double digit; 6 biosimilars in development including Humira, Enbrel, Rituxan, EPO
ROW -LC ROW (Incl'd Fx)	6,338	6,610	6,960	7,300	7,600	7,900	8,200	8,550	4%	4%	- Omnitrope biologic; Binocrit, EPO, AirFluSal (generic Advair)
Sandoz	9,159	9,800	10,075	10,500	11,000	11,500	12,000	12,550	5%	5%	Includes Falcon generic ophthalmics
% Change	5%	5%	5%	4%	5%	5%	4%	5%			
US ROW -LC ROW (Incl'd Fx)	847	920	475						NM	NM	-
Consumer Health	3,217	3,410	1,565						NM	NM	
	4,064	4,330	2,040						NM	NM	- Excludes animal health as of end Q1:15, sold to LLY for \$5.4B; excludes consumer as of end Q2:15; JV with GSK, income to associates line
% Change	9%	7%									
US ROW -LC ROW (Incl'd Fx)	4,179	4,430	4,825	5,200	5,600	6,000	6,400	6,800	7%	7%	
Alcon	6,317	6,545	6,800	7,250	7,550	7,800	8,050	8,350	4%	4%	
% Change	3%	5%	6%	7%	6%	5%	5%	5%			- Includes Ciba Geigy Vision; Vigamox patent exp. 2014
Total Novartis Sales	57,355	58,260	58,180	58,025	60,580	62,525	66,340	71,730	4%	3%	
% Change	1%	2%	0%	0%	4%	3%	6%	8%			

Source: Company data, Cowen and Company estimates

Novartis Estimated 2013-20 Summary Balance Sheet (\$MM)

	2013A	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Assets								
Property, plant & equipment net	\$18,197	\$16,600	\$16,550	\$16,450	\$17,200	\$17,750	\$18,850	\$20,350
Intangible assets	58,867	55,000	54,800	54,600	54,400	54,200	54,000	53,800
Investment in associated companies	9,225	9,500	9,500	9,500	9,500	9,500	9,500	9,500
Deferred taxes	7,375	7,500	7,500	7,500	7,500	7,500	7,500	7,500
Financial and other non-current assets	2,048	2,000	2,000	2,000	2,000	2,000	2,000	2,000
Total non-current assets	95,712	90,600	90,350	90,050	90,600	90,950	91,850	93,150
Inventories	7,267	6,900	6,700	6,100	6,250	6,250	6,400	6,650
Trade accounts receivable	9,902	9,400	9,400	9,350	9,750	10,050	10,500	11,250
Marketable securities	2,535	2,500	2,500	2,500	2,500	2,000	2,000	2,000
Cash and cash equivalents	6,687	8,715	13,377	18,947	25,628	33,233	42,382	53,457
Other current assets	4,151	3,550	3,550	3,550	3,600	3,700	3,900	4,100
Total current assets	30,542	31,065	35,527	40,447	47,728	55,233	65,182	77,457
Total assets	126,254	121,665	125,877	130,497	138,328	146,183	157,032	170,607
Liabilities								
Financial debt	\$11,242	\$13,000	\$12,750	\$12,500	\$12,250	\$12,000	\$11,750	\$11,500
Deferred taxes	6,904	7,500	7,500	7,500	7,500	7,500	7,500	7,500
Other non-current liabilities	7,268	7,000	7,000	7,000	7,000	7,000	7,000	7,000
Total non-current liabilities	25,414	27,500	27,250	27,000	26,750	26,500	26,250	26,000
Trade accounts payable	6,148	5,200	5,000	4,700	4,800	4,750	4,950	5,250
Financial debts and derivatives	6,776	7,500	7,500	7,500	7,500	7,500	7,500	7,500
Current income tax liabilities	2,459	2,500	2,500	2,500	2,500	2,500	2,500	2,500
Other current liabilities	10,985	10,320	10,100	9,445	9,660	9,820	10,105	10,700
Total current liabilities	26,368	25,520	25,100	24,145	24,460	24,570	25,055	25,950
Total liabilities	51,782	53,020	52,350	51,145	51,210	51,070	51,305	51,950
Net Equity	\$ 74,472	\$ 68,645	\$ 73,527	\$ 79,352	\$ 87,118	\$ 95,113	\$ 105,727	\$ 118,657

Source: Company data, Cowen and Company

Novartis Estimated 2013-20 Working Capital Analysis (\$MM)

	2013A	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Inventories	7,267	6,900	6,700	6,100	6,250	6,250	6,400	6,650
COGS	16,291	\$17,200	\$16,450	15,380	15,735	15,840	16,195	16,875
Inventory Turns	2.2	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Months	5.4	4.8	4.9	4.7	4.8	4.7	4.7	4.7
Accounts Receivable	9,902	9,400	9,400	9,350	9,750	10,050	10,500	11,250
Sales	\$58,054	\$59,209	\$59,070	\$58,795	\$61,395	\$63,385	\$67,245	\$72,680
Receivables Days	62.3	58.0	58.0	58.0	58.0	58.0	57.0	56.5
Other Current Assets	4,151	3,550	3,550	3,550	3,600	3,700	3,900	4,100
% of Sales	7.2%	6.0%	6.0%	6.0%	5.9%	5.9%	5.8%	5.7%
Accounts Payable	6,148	5,200	5,000	4,700	4,800	4,750	4,950	5,250
COGS	16,291	17,200	16,450	15,380	15,735	15,840	16,195	16,875
Payables Days	137.7	110.0	111.0	111.0	111.0	110.0	112.0	113.5
Other Current Liabilities	10,985	10,320	10,100	9,443	9,661	9,821	10,106	10,699
% of COGS	67%	60%	61%	61%	61%	62%	62%	63%
Net Working Capital (Ex. Cash, Debt)	\$4,187	\$4,330	\$4,550	\$4,857	\$5,139	\$5,429	\$5,744	\$6,051

Source: Company data, Cowen and Company

Novartis Estimated 2013-20 Cash Flow Analysis (\$MM)

	2013A	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Net Income (continuing operations)	\$12,352	\$12,647	\$14,165	\$15,645	\$17,113	\$18,459	\$20,532	\$23,095
Depreciation, amortization, and impairments	4,990	5,000	5,050	5,050	5,100	5,100	5,150	5,150
Net financial income	775	900	900	900	900	900	900	900
Other	(1,566)	(1,500)	(1,500)	(1,500)	(1,500)	(1,500)	(1,500)	(1,500)
Taxes paid	(2,024)	(2,082)	(2,335)	(2,585)	(2,832)	(3,056)	(3,418)	(3,870)
Restructuring	(1,015)	0	0	0	0	0	0	0
Change in working capital	(338)	(143)	(220)	(307)	(282)	(290)	(315)	(307)
Operating activities	13,174	14,821	16,060	17,202	18,499	19,613	21,349	23,469
Capital expenditure (net)	(3,064)	(3,100)	(3,100)	(3,200)	(3,250)	(3,300)	(3,350)	(3,400)
Intangible assets (net)	(711)	0	0	0	0	0	0	0
Acquisitions and divestments (net)	504	(500)	(500)	(500)	(500)	(500)	(500)	(500)
Net investments	(81)	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0
Investing activities	(3,352)	(3,600)	(3,600)	(3,700)	(3,750)	(3,800)	(3,850)	(3,900)
Dividends	(6,100)	(6,443)	(6,548)	(6,682)	(6,819)	(6,958)	(7,100)	(7,245)
Treasury shares	(1,237)	(2,000)	(500)	(500)	(500)	(500)	(500)	(500)
Change in short and long-term debt	(1,333)	(750)	(750)	(750)	(750)	(750)	(750)	(750)
Other	(99)	0	0	0	0	0	0	0
Financing activities	(8,769)	(9,193)	(7,798)	(7,932)	(8,069)	(8,208)	(8,350)	(8,495)
Others including Fx adjustment	82							
Net change in cash and cash equivalents	1,135	2,028	4,662	5,570	6,681	7,605	9,150	11,074
Cash at the beginning of the year	5,552	6,687	8,715	13,377	18,947	25,628	33,233	42,382
Cash at year end	6,687	8,715	13,377	18,947	25,628	33,233	42,382	53,457

Source: Company data, Cowen and Company

NVS DCF Analysis

9/26/2014														
Assumptions:														
		Output												
Share Price	\$93	Equity Value	\$230,750											
		Estimated Share Price	\$95											
Discount Rate	9.6%	Net Cash	(8,796)											
Shares Outstanding (000)	2,430	Enterprise Value	\$239,546											
NVS DCF														
	2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021P	2022P	2023P	2024P	2025P	Terminal
Total Revenues	\$58,054	\$59,209	\$59,070	\$58,795	\$61,395	\$63,385	\$67,245	\$72,680	\$77,041	\$80,893	\$84,937	\$88,335	\$91,868	
% Change	+1%	+2%	-0%	-0%	+4%	+3%	+6%	+8%	+6%	+5%	+5%	+4%	+4%	
Cost of Goods	\$16,291	\$17,200	\$16,450	\$15,380	\$15,735	\$15,840	\$16,195	\$16,875	\$18,105	\$19,010	\$19,960	\$20,759	\$21,589	
Gross Profit	\$41,763	\$42,009	\$42,620	\$43,415	\$45,660	\$47,545	\$51,050	\$55,805	\$58,936	\$61,883	\$64,977	\$67,576	\$70,279	
Gross Margin - Total	71.9%	71.0%	72.2%	73.8%	74.4%	75.0%	75.9%	76.8%	76.5%	76.5%	76.5%	76.5%	76.5%	
SG&A	\$17,491	\$17,445	\$16,930	\$16,445	\$17,045	\$17,450	\$18,240	\$19,430	\$20,570	\$21,598	\$22,933	\$23,850	\$24,804	
% of Revs	30.1%	29.5%	28.7%	28.0%	27.8%	27.5%	27.1%	26.7%	26.7%	26.7%	27.0%	27.0%	27.0%	
R&D	\$9,613	\$9,635	\$9,635	\$9,385	\$9,520	\$9,655	\$10,115	\$10,835	\$11,556	\$12,134	\$12,741	\$13,250	\$13,780	
% of Revs	16.6%	16.3%	16.3%	16.0%	15.5%	15.2%	15.0%	14.9%	15.0%	15.0%	15.0%	15.0%	15.0%	
Operating Expenses	\$27,104	\$27,080	\$26,565	\$25,830	\$26,565	\$27,105	\$28,355	\$30,265	\$32,126	\$33,732	\$35,674	\$37,101	\$38,585	
% of Revenues	46.7%	45.7%	45.0%	43.9%	43.3%	42.8%	42.2%	41.6%	41.7%	41.7%	42.0%	42.0%	42.0%	
Operating Income	\$14,659	\$14,929	\$16,055	\$17,585	\$19,095	\$20,440	\$22,695	\$25,540	\$26,810	\$28,151	\$29,303	\$30,476	\$31,695	
% Operating Margin	25.3%	25.2%	27.2%	29.9%	31.1%	32.2%	33.7%	35.1%	34.8%	34.8%	34.5%	34.5%	34.5%	
Non-operating income	361	450	1,035	1,170	1,325	1,500	1,630	1,750	1,775	1,800	1,825	1,850	1,850	
EBIT	\$15,020	\$15,379	\$17,090	\$18,755	\$20,420	\$21,940	\$24,325	\$27,290	\$28,585	\$29,951	\$31,128	\$32,326	\$33,545	
% of Revs	25.9%	26.0%	28.9%	31.9%	33.3%	34.6%	36.2%	37.5%	37.1%	37.0%	36.6%	36.6%	36.5%	
D&A	\$4,990	\$5,000	\$5,050	\$5,050	\$5,100	\$5,100	\$5,150	\$5,150	\$5,200	\$5,250	\$5,250	\$5,250	\$5,250	
EBITDA	\$20,010	\$20,379	\$22,140	\$23,805	\$25,520	\$27,040	\$29,475	\$32,440	\$33,785	\$35,201	\$36,378	\$37,576	\$38,795	
% of Revs	34.5%	34.4%	37.5%	40.5%	41.6%	42.7%	43.8%	44.6%	43.9%	43.5%	42.8%	42.5%	42.2%	
Net Interest Income (Expense)	(\$683)	(\$650)	(\$590)	(\$525)	(\$475)	(\$425)	(\$375)	(\$325)	(\$300)	(\$275)	(\$250)	(\$250)	(\$250)	
Pre-Tax Income	\$14,337	\$14,729	\$16,500	\$18,230	\$19,945	\$21,515	\$23,950	\$26,965	\$28,285	\$29,676	\$30,878	\$32,076	\$33,295	
Taxes	\$1,985	\$2,082	\$2,335	\$2,585	\$2,832	\$3,056	\$3,418	\$3,870	\$4,031	\$4,223	\$4,389	\$4,558	\$4,730	
Income Tax Rate	13.8%	14.1%	14.2%	13.8%	13.9%	13.9%	14.1%	14.2%	14.1%	14.1%	14.1%	14.1%	14.1%	
Minority Interest	\$117	\$100	\$125	\$150	\$175	\$190	\$210	\$230	\$240	\$250	\$260	\$270	\$275	
Net Income	\$12,235	\$12,547	\$14,040	\$15,495	\$16,938	\$18,269	\$20,322	\$22,865	\$24,015	\$25,203	\$26,229	\$27,248	\$28,290	
% of Revs	21.1%	21.2%	23.8%	26.4%	27.6%	28.8%	30.2%	31.5%	31.2%	31.2%	30.9%	30.8%	30.8%	
% Change	-4%	+3%	+12%	+10%	+9%	+8%	+11%	+13%	+5%	+5%	+4%	+4%	+4%	
NOPAT	\$13,035	\$13,297	\$14,755	\$16,170	\$17,588	\$18,884	\$20,907	\$23,420	\$24,555	\$25,728	\$26,739	\$27,768	\$28,815	
<u>Adjustments:</u>														
Capex	(\$3,064)	(\$3,100)	(\$3,100)	(\$3,200)	(\$3,250)	(\$3,300)	(\$3,350)	(\$3,400)	(\$3,450)	(\$3,500)	(\$3,550)	(\$3,600)	(\$3,650)	
Depreciation & Amortization	\$4,990	\$5,000	\$5,050	\$5,050	\$5,100	\$5,100	\$5,150	\$5,150	\$5,200	\$5,250	\$5,250	\$5,250	\$5,250	
Change In Working Capital	(\$338)	(\$143)	(\$220)	(\$307)	(\$282)	(\$290)	(\$315)	(\$307)	(\$250)	(\$200)	(\$150)	(\$100)		
Operating Free Cash Flow	\$18,823	\$14,304	\$15,770	\$17,038	\$18,508	\$18,779	\$21,807	\$24,308	\$25,515	\$26,753	\$27,729	\$28,748	\$29,790	\$310,310

Source: Cowen and Company.

Novartis Key Upcoming Events

Time Frame	Event Type	Product	Event
2014 Clinical		Gilenya PKC 412	Phase III data in PPMS; data possible H2:14 but communication/publication might be 2015 FLT3+ AML 1st line data possible
Regulatory		Afinitor Jakavi LBH589 LCQ908 LCZ696 Secukinumab Secukinumab Seebri/Ultibro Signifor	2014 filings for HER2+ BC 1st line; HER2+ BC 2nd/3rd line; U.S., EU H2:14 filing for polycythemia vera in Japan Filed; U.S. approval for multiple myeloma 2014 filing for familial chylomicronemia syndrome Complete U.S. rolling submission for heart failure (reduced ejection fraction) by December CHMP opinion in psoriasis FDA AdCom meeting October 20th; severe plaque psoriasis U.S. filing Q4:14 Approval in U.S.; CHMP opinion H2:14; acromegaly

Source: Company data

Novartis Patent Vulnerability

Company	Drug	Territory	Patent Exp. Date	U.S. Sales		Estimated U.S. Sales (\$MM)*	Non-U.S. Sales As % Of Total Sales	Estimated Non-U.S. Sales (\$MM)*	% Total Sales	% Total EPS (#)	
				Estimated WW Sales (\$MM)	As % Of Total Sales					EPS	EPS
NVS	Sandostatin LAR	U.S.	Jan-14	\$1,589	44%	\$705			1%	\$0.07	1%
	Gleevec	U.S.	Jul-15	4,620	45%	2,085			4%	0.22	4%
	Focalin XR	U.S.	Dec-15	440	67%	293			1%	0.03	1%
	Glivec	E.U.	2016	4,515			55%	2,478	4%	0.26	4%
	Lescol XL	E.U.	2017	25			78%	20	0%	0.00	0%
	Lotrel	U.S.	Dec-17	0	100%	0			0%	0.00	0%
	Myfortic	U.S.	Apr-17	465	29%	136			0%	0.01	0%
	Xolair	E.U.	2017	875			100%	875	1%	0.09	1%
	Lucentis	E.U.	2018	2,800			100%	2,800	4%	0.29	4%
	Tekturna/Rasilez	U.S.	2018	150	38%	57			0%	0.01	0%
	Trileptal	U.S.	2018	180	100%	180			0%	0.02	0%
	Xolair	U.S.	2018	925	0%	0			0%	0.00	0%
	Afinitor/Certican	E.U.	2018	2,425			49%	1,200	2%	0.12	2%
	Gilenya	E.U.	2018	3,350			53%	1,780	3%	0.18	2%
	Gilenya	U.S.	2019	3,600	47%	1,687			3%	0.17	2%
	Exjade	U.S.	2019	850	30%	258			0%	0.03	0%
	Exforge	U.S.	2019	550	26%	144			0%	0.01	0%
	Exforge	E.U.	2019	550			74%	406	1%	0.04	0%
	Exelon Patch	E.U.	2019	450			56%	252	0%	0.03	0%
	Exelon Patch	U.S.	2019	450	44%	198			0%	0.02	0%
	Afinitor/Certican	U.S.	2020	3,025	51%	1,528			2%	0.16	2%

*Estimated sales in year prior to patent expiration

**Estimated sales in the year generic competition is expected

#Assumes 25% net margin

Source: Cowen and Company; Thomson Pharma; Company data; FDA Orange Book

NOVARTIS R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Arthritis/Inflammation							
AIN457				.	Q4:2013		Filed for psoriasis, FDA AdCom scheduled for October 20, 2014 ; PIII for RA, ankylosing spondylitis, psoriatic arthritis PIII data met its primary and secondary endpoints; data to be presented at ACR 2014
Blood and Blood Products							
Exjade FCT					May-14		Iron overload; film-coated tablets
Cancer/Oncology/Hematology							
LBH589				⇒	3/1/2014		Relapsed or relapsed-and-refractory multiple myeloma; filed in EU and U.S. (priority review status); PIII trial in combo with bortezomib and dexamethasone met primary endpoint
Arzerra				.	Oct-13		Ofatumumab; high affinity; filed October 2013 for first line CLL in EU; relapsed CLL, maintenance CLL and diffuse large B cell lymphoma, follicular lymphoma; filed for RCC in Japan
Signifor LAR				.	Q4:2013		Long-acting formulation; filed in U.S. and EU for acromegaly, PIII Cushing's
Tykerb				.	Feb-12		Lapatinib; Erb-B2 and EGFR dual kinase inhibitor; filed in EU for metastatic breast cancer; PIII for adjuvant breast cancer; metastatic breast cancer - dual blockade
Votrient				.	Aug-13		Pazopanib; VEGF 2 tyrosine kinase inhibitor; filed in EU, ovarian cancer; PIII adjuvant and metastatic (dual blockade) breast cancer; renal cell carcinoma
Zykadia (LDK378)				.	Q2:14		ALK-positive advanced NSCLC, filed in EU, approved in U.S.; PIII chemo and crizotinib naïve; 1st-line, treatment naïve
LDE225		.	.	.	2014->2018		Sonidegib; filed in EU for advanced basal cell carcinoma, PIII in U.S.; treatment of medulloblastoma (PIII); solid tumors (PI)
Trametinib (1120212)		.	.	.			Mitogen-activated protein kinase inhibitor cancer (MEK1/2); PII for NSCLC; EU filing for combo with dabrafenib in metastatic melanoma withdrawn 3/2014
Afinitor		.	.	.	2014-2017		2014-17 filings for HER2+ breast cancer (1st/2nd/3rd lines); non-functioning GI/lung NET; TSC seizure; diffuse large B cell lymphoma; PIII BOLERO-2 trial in HR+/HER2- breast cancer did not meet secondary survival endpoint
Jakavi (ruxolitinib)		.	.	.	2014		Polycythemia vera; PIII study met primary endpoint; filed in EU Q2:14
MEK162+LGX818		.	.	.	2016		Combo therapy for BRAF mutant melanoma
LGX818		.	.	.	2016->2018		BRAF mutant melanoma in combo with MEK162 (PIII); solid tumors (PII)
MEK162		.	.	.	2015->2018		Oral MEK inhibitor; PIII for NRAS mutant melanoma, low-grade serious ovarian cancer; PII solid tumors
PKC412		.	.	.	2015		Tyrosine protein C kinase inhibitor; first positive results from pilot trial in advanced phase AML; PII aggressive systemic mastocytosis (ASM)
BKM120		.	.	.	2015->2018		Oral PI3K inhibitor; PIII mBC ER+ AI resistant mTOR naïve; mBC ER+ post AI and mTOR inhibitor; PI solid tumors
LEE011		.	.	.	2016->2018		Oral CDK4/6 inhibitor; PIII breast cancer; PI solid tumors

NOVARTIS R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
AUY922			.		>2018		IV non-geldanamycin-based HSP90 inhibitor; solid tumors
BEZ235			.		>2018		Oral PI3K/mTOR inhibitor; solid tumors
BGJ398			.		>2018		Oral FGFR inhibitor; solid tumors
LCI699			.		2017		Cushing's disease
Promacta/Revolade			.				Eltrombopag; PII for oncology-related thrombocytopenia
Tasigna			.		2016		CML treatment-free remission
TKI258			.		2017		Solid tumors
Afuresertib		.					2110183; AKT protein kinase inhibitor; multiple myeloma, ovarian cancer
BYL719		.			>2018		Solid tumors
LJM716		.			>2018		Solid tumors
Cardiovascular							
Serelaxin (RLX030)					Dec-12		Acute heart failure; RELAX2 registration study ongoing in U.S., EU; RELAX-ASIA registration study ongoing; FDA requested additional data on efficacy
Aliskiren			.		2016		Phase III (ATMOSPHERE) trial for both aliskiren monotherapy and aliskiren/enalapril combination therapy in CHF patients; failure of ALTITUDE puts franchise at risk
Ilaris			.		2016-17		Secondary prevention of cardiovascular events; hereditary periodic fevers
LCZ696		.	.		2014->2018		PIII chronic heart failure with reduced ejection fraction; PII CHF with preserved ejection fraction; PIII PARADIGM-HF trial ended early due to efficacy; FDA granted Fast Track designation
Central Nervous System							
BAF312			.		>2018		Secondary progressive multiple sclerosis
Gilenya			.		2015-2016		Chronic inflammatory demyelinating polyradiculoneuropathy; primary progressive multiple sclerosis
BYM338		.	.		2016->2018		Sporadic inclusion body myositis FDA breakthrough therapy designation Q3:13; hip fracture (PII)
AQW051		.					Cognitive impairment associated with schizophrenia
BGG492		.					Epilepsy
CAD106		.			>2018		Alzheimer's disease
ATI355		.					Spinal cord injury
Diabetes							
LCQ908			.		2014		DGAT inhibitor; familial chylomicronemia syndrome; PIII study recruitment completed
LIK066		.			>2018		Type 2 diabetes
Endocrine/Metabolic/Hormones							
BGS649		.			>2018		Obese hypogonadotropic hypogonadism
Gene Therapy							
CTL019		.			2016		Chimeric antigen receptor (CAR); relapsed/refractory acute lymphoblastic leukemia; granted Breakthrough Therapy status by FDA in July, 2014; from UPENN
FCR001		.			>2018		Renal transplant
HSC835		.			>2018		Stem cell transplantation
Infectious Disease							
DEB025		.			2017		Hepatitis C; PII met its primary endpoint; clinical development resumed
KAE609		.			2017		Malaria
LFF571		.			2017		Clostridium difficile GI infections
Ophthalmology							
EXE844					Apr-14		Otic Infections

NOVARTIS R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Simbrinza					2013		Brinzolamide/Brimonidine; glaucoma; Timolol-free fixed combination; approved in U.S., filed in EU; favorable CHMP opinion
Fovista				.	2016		Wet AMD
Pataday (new formulation)				.	2014E		Ocular allergy
Lucentis			.	.	2016->2018		Ranibizumab; with DNA, rights outside North America; PIII for choroidal neovascularization and macular edema secondary to conditions other than AMD, DME, RVO and myopic CNV; PII for retinopathy of prematurity
Respiratory							
Seebri Breezhaler		.			2017		COPD (U.S. filing Q4:14E); asthma
Ultibro Breezhaler			.				COPD; approved in EU; U.S. filing expected Q4:14
BCT197		.			>2018		Bronchodilator; COPD
QAW039		.			>2018		Asthma
QAX576		.			>2018		Allergic diseases
QGE031		.			>2018		Allergic diseases; PII study in patients with peanut allergy
QMF149		.			>2018		Once-daily fixed dose combination of QAB149 and mometasone; asthma and COPD; ex-US
Vaccines							
Fluad			.		2014		Influenza; PIII in U.S., pediatric indication
Flucelvax			.				Approved for influenza prevention age 18+; pii FOR AGE 4+
Quadrivalent Influenza Vaccine (QIV)			.		>2015		Seasonal influenza
Group B streptococcus		.			>2015		Prevention of group B streptococcus
MenABCWY		.	.		>2015		Prevention of meningococcal disease (serogroups A, B, C, Y and W-135)
Staphylococcus aureus					>2015		Prevention of staphylococcus aureus
TdP					>2015		Prevention of tetanus, diphtheria, pertussis
Total Drugs In Development	0	6	26	24	11		67

Progress since last update in bold; movement marked by arrow

U.S. Investor Relations Contacts: Stephen Rubino 862 778 8301



Price: \$29.57 (09/30/2014)
Price Target: \$34.00

MARKET PERFORM (2)

Steve Scala, R.Ph., CFA

617.946.3923
steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA

617.946.3857
kathy.miner@cowen.com

Jean Perreault

617.946.3967
jean.perreault@cowen.com

Key Data

Symbol	NYSE: PFE
52-Week Range:	\$32.96 - 27.87
Market Cap (MM):	\$187,499.3
Net Debt (MM):	\$4,081.0
Cash/Share:	\$5.06
Dil. Shares Out (MM):	6,340.9
Enterprise Value (MM):	\$191,627.3
ROIC:	NA
ROE (LTM):	NA
BV/Share:	\$12.08
Dividend:	\$1.04
Yield:	3.52%

FY (Dec)	2013A	2014E	2015E
Earnings Per Share			
Q1	\$0.51	\$0.57A	\$0.58
Prior Q1	-	-	\$0.57
Q2	\$0.56	\$0.58A	\$0.58
Prior Q2	-	-	\$0.59
Q3	\$0.58	\$0.54	\$0.59
Prior Q3	-	-	-
Q4	\$0.56	\$0.51	\$0.55
Prior Q4	-	-	-
Year	\$2.22	\$2.20	\$2.30
P/E	13.3x	13.4x	12.9x
Adjusted diluted earnings per share (EPS) are defined as reported diluted EPS excluding purchase-accounting adjustments, merger related costs, discontinued operations, and certain significant items.			
Consensus EPS	\$2.22	\$2.25	\$2.24
Consensus source: Thomson Reuters			

Revenue (MM)

Year	\$51,453.0	\$48,750.0	\$47,555.0
Prior Year	-	\$48,585.0	\$47,145.0
EV/S	3.7x	3.9x	4.0x

Pfizer

Solid Outlook But Upside Unlikely

The Cowen Insight

Expectations for a potential corporate breakup and success of palbociclib appear reflected in the stock's valuation.

We rate Pfizer stock Market Perform given our view that it appears fairly valued on a SoTP basis; segment P&Ls suggest a mixed outlook (GIP and GEP more profitable than expected, VOC less profitable); palbociclib has big potential, but approval on Phase II data is uncertain; and the pipeline has a limited number of opportunities of similar magnitude. Furthermore, we think there is a better than 50/50 chance Pfizer attempts to acquire AZN post the mandatory six-month waiting period.

Modest EPS Decline In 2014, With Growth Re-Starting In 2015

We look for a 1% decline in EPS in 2014, clipped by the Lyrica patent expiration in the E.U.; wind-down of Spiriva alliance revenue; lapse of participation in Enbrel NA economics, which ceased in November 2013; and Celebrex generics in the U.S. as of December 2014, reflecting recent settlements. We forecast 5% EPS growth in 2015 on a 2% decline in sales. The outlook strengthens thereafter, assuming success of late-stage pipeline candidates, and one in four earlier stage targets contributes \$400MM in 2020.

Expectations For Key Stock Drivers Appear Fully Reflected In Valuation

Investors were enthusiastic about the prospects for a breakup of Pfizer in 2016-17, but the greater individual business transparency shows the innovative businesses (VOC, GIP) having lower-than-expected margins, and GEP higher than expected. As stand-alone entities, GEP would likely have a lower multiple and VOC and GIP higher multiples. Palbociclib Phase II PFS data presented at AACR showed unprecedented PFS, but final data was less impressive than interim data, potentially compelling the FDA to seek at least interim Phase III results. We peg palbociclib sales at \$3B in 2020. The favorable August ACIP recommendation for use of Prevnar-13 in addition to MRK's Pneumovax boosted our 2020E Prevnar-13 sales by \$1.2B to \$7.06B, although reimbursement/timing issues and a re-look in 2018 bear watching.

Possible AZN Acquisition May Overshadow Fundamentals Near Term

While AZN rebuffed Pfizer's initial offer, we think there is a better than 50% chance that Pfizer revisits its acquisition plans when the mandatory waiting period expires in late November. The likelihood of a revised offer may keep the stock in a trading range.

Pfizer's Interest In AstraZeneca Could Be Rekindled

In late April 2014, Pfizer confirmed that it was seeking to acquire AstraZeneca. In mid-May Pfizer made a final offer of \$92.53 per share (55% stock, 45% cash) which AZN rejected and the offer expired on May 26. Per British takeover rules, discussions could have re-started in late August if AZN expressed interest, which does not appear to have occurred. As such, Pfizer must now wait six months (to the end of November) to make a new offer. Pfizer has cited complementary pipelines, operational synergies, and a lower tax rate as the reasons for the transaction. Critically, the combined entity would be a U.K. company. Pfizer has indicated that any deal must be accretive in the first year. Risks include: 1) whether or not AZN shareholders will accept such a large amount of PFE stock; 2) upcoming data on AZN's pipeline; and 3) resistance from U.S. constituencies regarding Pfizer becoming a U.K. company.

Pipeline Complementarity – Pfizer noted complementarity on a number of fronts, most notably oncology. We do agree that AZN has a full and compelling pipeline, but validation of key assets has yet to be delivered, creating risk for Pfizer.

Operational Synergies – PFE noted that the Wyeth transaction (announced 1/26/09) allowed for \$4B in savings over time, one-half from SG&A and one-half from R&D and COGS. We assume PFE delivers \$1B in savings in the acquisition of AZN in 2015. PFE has said that the acquisition will be accretive in the first year; our analysis suggests accretion is quite achievable in 2015.

U.K. Domicile Results In Lower Tax Rate – PFE noted that the U.K. tax system offers several advantages: 1) a statutory tax rate that will be 20% in 2015, 2) a favorable U.K. territorial tax system, 3) a permanent R&D tax credit, and 4) patent box legislation. We assume a PFE+AZN tax rate of 20% in 2015. We anticipate that various U.S. constituencies will put up considerable resistance to PFE becoming a U.K. company.

Deal Terms: 50/50 Appears To Be The Break Point For Stock And Cash – In order to gain the benefits of “tax inversion”, the target company must hold at least a 20% stake in the combined entity. At a ratio of 50% cash and 50% PFE stock, AZN shareholders would appear to own just about 20% of the combined entity. However, PFE might wish to build in more cushion, and completing the deal at a ratio of 70% PFE stock and 30% cash (proposed split according to AZN press release) would afford them that cushion. In a 70/30 stock/cash transaction, AZN shareholders will own 27% of the combined entity. At 30% cash, PFE could use predominantly existing cash to fund the cash portion of the transaction (at YE 2013, PFE's balance sheet showed \$2B in cash, \$30B in short term investments, and \$16B in long term investments). Whether or not AZN shareholders are willing to accept such a large amount of PFE stock is unclear.

A Price Of \$99 Per AZN Share Would Achieve Necessary Hurdles – There are two hurdles that the deal must cross: 1) AZN shareholders must own at least 20% of the new entity to gain U.K. tax status, and 2) PFE has said that the deal would be accretive in the first year. A price of \$99, assuming 55% stock and 45% cash, would achieve both criteria. At a price of \$99, the new entity's 2015 EPS is forecast to be \$2.42 (versus our estimate of PFE stand-alone EPS of \$2.30), assuming \$1B in cost savings in 2015 and a tax rate of 20%. The various scenarios are detailed on the next page.

PFE + AZN 2015 EPS Scenarios

	PFE	AZN = \$92.53*	AZN = \$100	AZN = \$110
2015E EPS	\$2.30	\$2.44	\$2.37	\$2.29
Transaction value (\$B)		\$118,809	\$128,400	\$141,240

Assumptions:

Deal terms: 55% stock, 45% cash
 \$1B cost savings in 2015
 Tax rate 20% (UK rate)
 Use \$25B cash (out of \$49B total on PFE balance sheet)); interest rate on borrowings of 4%
 AZN shares 26-29% of total shares post deal in all scenarios
 PFE share buybacks continue
 PFE price \$30.15 (July 8, 2014)

* PFE final offer price (May 19, 2014)

Source: Cowen and Company

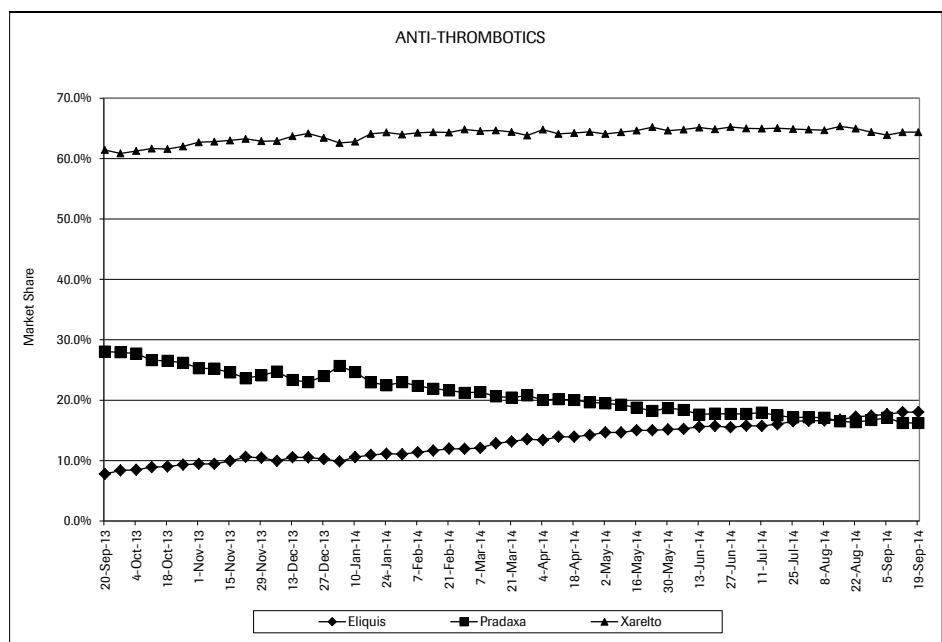
GIP - Cardiovascular

Eliquis Rollout Gaining Momentum

In late 2012, FDA and EMA approved Eliquis (apixaban) for stroke prevention in atrial fibrillation with strong labels that accurately reflect data from the ARISTOTLE and AVERROES trials. Eliquis is a selective, oral direct Factor Xa inhibitor that offers good oral bioavailability, no food effect, a half-life of 12 hours with a low peak to trough ratio, and no organ toxicity or raised LFTs seen in animal toxicity studies. Apixaban is excreted predominantly via the liver but also by the kidney (25%), may not require monitoring, and has a superior bleeding profile when compared to warfarin.

Additional indications that have been approved include: DVT prevention - FDA approved in March 2014 and EU approved May 2011; DVT and PE treatment and prevention of recurrent DVT and PE following initial therapy - EU approved July 2014, US approved August 2014. Eliquis continues to build momentum with 20.4% share as of August 2014, and continues to show monthly improvement. JNJ's Xarelto continues to perform well, likely due to its once-daily dosing format, multiple indications, and second to market position. However, we believe superior data ultimately will make Eliquis the leader among the newer agents. BMY/PFE initiated DTC advertising in the U.S. in Q3:13, and has launched Eliquis in 15+ markets including Japan and all major E.U. markets. We estimate Pfizer's share of Eliquis sales to be \$340MM in 2014, \$540MM in 2015, \$700MM in 2016, \$950MM in 2018, and \$1.2B in 2020.

ANTI-THROMBOTICS



Source: IMS America

European SPAF Labeling As Expected

In November 2012, the EMA approved Eliquis for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors (prior stroke/TIA, age \geq 75 years, hypertension, diabetes, NYHA Class \geq 2 HF). The label reflects the data from ARISTOTLE and AVERROES, defining Eliquis as providing superior efficacy, superior safety (bleeding), and improved mortality relative to warfarin. The label does not contain a black box warning for bleeding risk. Eliquis is recommended for use in patients with normal renal function and mild-to-moderate renal impairment, but is not recommended for use in patients with SCr <15 mL/min (Xarelto dose adjusted for SCr <50 mL/min). The label does not contain any reference to an increase in events when stopping therapy (this is a boxed warning for Xarelto).

U.S SPAF Labeling Is Best In Class

On December 28, 2012, FDA approved Eliquis to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Eliquis was approved with a strong label, including superiority to warfarin for stroke prevention, bleeding, and all cause death. The label includes a box black warning citing a higher incidence of thromboembolic events in patients who discontinue Eliquis (Xarelto's label also has a black box warning). In the event that a patient discontinues Eliquis for a reason other than pathological bleeding, coverage with another anticoagulant is recommended. Eliquis is priced at \$8.85 per day, at parity to Pradaxa (Bd; \$8.85 per day) and Xarelto (JNJ; \$8.85 per day). Bristol/Pfizer launched Eliquis in Q1:13.

Eliquis Offers Superior Clinical Profile Relative To Competition At Similar Price

Both Eliquis and Pradaxa have demonstrated superiority to warfarin in reducing strokes in patients with nonvalvular atrial fibrillation; Xarelto demonstrated non-inferiority. Eliquis is the only novel anticoagulant to demonstrate a reduction in major and clinically relevant non-major bleeding relative to warfarin and is the only novel

anticoagulant to improve overall mortality. Given the superior clinical profile of and pricing of Eliquis, we believe there is no compelling reason to prescribe any other anticoagulant for SPAF.

Comparison Of Novel Anticoagulants

	Eliquis (BMY/PFE)	Pradaxa (BI)	Xarelto (JNJ)
FDA Indication	SPAF	SPAF	SPAF, DVT treatment and prevention
Superiority to warfarin (SPAF)	Yes	Yes	No
Superior bleeding to warfarin	Yes	No	No
Mortality benefit	Yes	No	No
Black box warning	Increased event rate in patients discontinuing Eliquis	NA	Increased event rate in patients discontinuing Xarelto; increased risk of spinal/epidural hematoma with spinal puncture
Price	\$8.85/day	\$8.85/day	\$8.85/day

Source: Product labels, PriceRx.com

SPAF:

Two studies in stroke prevention in atrial fibrillation (SPAF) were initiated: ARISTOTLE and AVERROES. ARISTOTLE enrolled 18,183 patients to evaluate Apixaban in SPAF; data was presented at ESC 2011. Absolute and relative risk reductions for apixaban in ARISTOTLE were in line with our expectations. Consistent with previously released top-line data, apixaban demonstrated superiority over warfarin for stroke prevention with an improved bleeding profile. Apixaban also met its secondary all-cause mortality endpoint versus warfarin, although the magnitude of the mortality benefit in ARISTOTLE was similar to what has been observed in trials for other novel anticoagulants. Nonetheless, ARISTOTLE is the first trial to demonstrate a statistically significant mortality benefit. AVERROES was stopped early because a predefined interim analysis by the independent Data Monitoring Committee revealed clear evidence of a clinically important reduction in stroke and systemic embolism. This interim analysis also demonstrated an acceptable safety profile for Apixaban compared to aspirin. The AVERROES study included 5,600 patients with atrial fibrillation at risk for stroke who were considered intolerant of or unsuitable for therapy with a vitamin K antagonist such as warfarin; as many as 40% of patients enrolled in AVERROES had previously failed therapy with a vitamin K antagonist. Patients were randomized to receive either Apixaban 5mg twice daily or aspirin 81mg to 324mg once daily. In February 2011 the complete results from AVERROES were published in the NEJM. 51 patients on apixaban (1.6% per year) experienced a stroke during the course of the study versus 113 patients (3.7% per year) on aspirin (HR 0.45, CI 0.32-0.62, p<0.001). Rates of death were 3.5% per year with apixaban versus 4.4% in the aspirin group (HR 0.79, CI 0.74-1.02, p=0.07). There were 44 major bleeds in the apixaban group (11 intracranial) compared to 39 on aspirin (13 intracranial) (HR=1.13, CI 0.74-1.75, p=0.57). Apixaban also significantly reduced the risk for hospitalization in these patients. No differences were noted between important patient subgroups.

VTE Prevention:

Data from the Phase III U.S. VTE prevention study, ADVANCE-1, released in August 2008 revealed that it had missed the primary endpoint. BMY/PFE filed VTE prevention in mid-2013, and plans to file for VTE treatment later this year. The data from the Phase III, European DVT prevention study in knee surgery appear robust, with superior efficacy and less bleeding than Lovenox. The full data were presented at ISTRH 2009. Bristol submitted the VTE filing in March 2010 in the E.U. based on the positive results of ADVANCE-2 and -3. On March 20, 2011, apixaban was approved in the E.U. for the

prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery.

ACS:

In March 2009, Bristol and Pfizer initiated the 10,848 patient ACS study, APPRAISE-2. However in November 2010, APPRAISE-2 was stopped early due to excessive bleeding in patients on apixaban plus dual antiplatelet therapy. Bristol has stated that the opportunity for the orthopedic indications is 5% of the potential market, with the ACS and atrial fibrillation indications making up the remainder.

Apixaban Phase III Program

Study	Clinical Setting	Apixaban Dose	Comparator	Number of Patients	Status
Surgical VTE Prophylaxis					
ADVANCE-1	Knee replacement surgery	2.5mg BID	Lovenox 30mg BID	3,200	Failed to show non-inferiority
ADVANCE-2	Knee replacement surgery	2.5mg BID	Lovenox 40mg QD	3,100	Superior results in major VTE and clinically relevant bleeding AEs
ADVANCE-3	Hip replacement surgery	2.5mg BID	Lovenox 40mg QD	5,400	Superior to enoxaparin in prevention of symptomatic/asymptomatic DVT, PE, and all-cause death. No difference in bleeding or clinically relevant bleeding compared to enoxaparin alone
Medical Prophylaxis					
AVERROES	Stroke prevention in atrial fibrillation	5mg BID; 2.5mg BID in selected patients	Aspirin in warfarin ineligible patients	5,600	Stopped early for efficacy
ARISTOTLE	Stroke prevention in atrial fibrillation who VKA ineligible	5mg BID	Warfarin	18,183	Superior efficacy and bleeding profile compared to warfarin. Statistically significant mortality benefit demonstrated
ADOPT	Acute medical illness	2.5mg BID	Lovenox 40mg QD	6,524	Did not show differentiation from Lovenox
APPRAISE-2	Prevent MACE in recent ACS	5mg BID	Placebo	10,848	Stopped for safety; no path forward
VTE Treatment					
AMPLIFY	Acute DVT/PE	10mg BID for 7 days; 5mg BID for 6 months	Lovenox + warfarin	5,395	Non-inferior to standard of care
AMPLIFY-EXT	Long-term treatment of VTE/PE	2.5mg or 5mg BID	Placebo	2,486	Superiority vs. placebo in reduction of recurrent VTE/all cause death

Source: Company data; clinicaltrials.gov

Anti-PCSK9 Bococizumab Now In Phase III

In October 2013, Pfizer initiated a Phase III program for its anti-PCSK9 bococizumab (RN316) which includes multiple lipid-reduction studies and two CV outcomes studies enrolling over 22,000 patients. One of the outcome studies (SPIRE-2) will evaluate high-risk patients with an LDL >100mg/dl despite statin treatment. The other outcome study (SPIRE-1) will evaluate whether lowering LDL well below guidelines will improve CV event profile. A Phase IIb study in 354 statin treated patients with high cholesterol presented at March 2014 ACC showed that bococizumab met its primary endpoint of significantly lowering LDL-C across all doses (50mg, 100mg, 150mg twice/month or 250mg, 300mg once a month). The Phase III program will use 150mg twice monthly as the starting dose.

At this point, it is unclear what impact the recently revised cholesterol treatment guidelines will have on the bococizumab development program. The movement away

from targeted blood cholesterol levels could alter a trial design. However, Pfizer's CV outcome studies will have greater importance and likely be a key component to future regulatory approvals.

Pfizer is also evaluating a once-monthly dosing formulation of bococizumab which may include Halozyme's technology. Pfizer has an exclusive license with Halozyme for the PCSK9 class. We estimate bococizumab sales at \$100MM in 2017, \$200MM in 2018, and \$400MM in 2020.

Viagra's Patent Settlement Delays Generics Until 2017

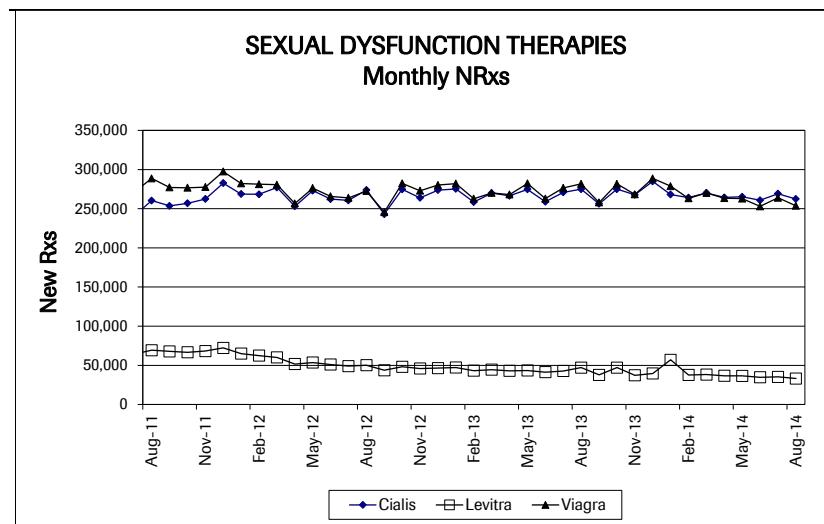
Viagra (sildenafil) remains the leading PDE5 inhibitor, holding 46.6% (-7% Y/Y) prescription share of the U.S. market in May 2014. Viagra's share has been clipped by Lilly's Cialis. We expect reimbursement pressures and lackluster prescription growth to hold the PDE5 inhibitor class roughly flat overall. We estimate U.S. Viagra sales of \$1.125B (-1%) in 2014, \$1.1B in 2015-17, \$250MM in 2018, and \$50MM in 2020. Note that only U.S. sales are included in GIP reporting; ROW sales are part of GEP.

Pfizer prevailed in the Viagra erectile dysfunction use patent infringement case against Teva. The ruling from the U.S. District Court for the Eastern District of Virginia prevented Teva from receiving approval for a generic Viagra in the U.S. until October 2019. Teva filed an appeal against this ruling, and subsequently the companies entered into an agreement to settle the use patent litigation. Via settlement, Teva may launch a generic in December 2017 (or earlier under certain unspecified circumstances). Teva will pay Pfizer a royalty for a license to produce its generic version. Litigation against the same patent remains pending against other generic companies, although no trials have been scheduled for these cases. Viagra's E.U. exclusivity expired in June 2013.

Generic Revatio Has Not Provided Substantial Competition

Despite preservation of the Viagra use patent, the composition of matter patent for sildenafil, which covers both Revatio (PAH indication) and Viagra, expired in March 2012, allowing for generic Revatio to be prescribed for erectile dysfunction. However, Revatio is provided in 20mg tablets compared to Viagra's 25mg, 50mg, and 100mg tablets, making precise dose matching a challenge. Dr. Reddy's launched a 20mg generic Revatio in November 2012.

Sexual Dysfunction Therapies



Source: IMS America

Comparison Of PDE5 Inhibitors Currently On The Market

Attribute	Cialis	Levitra	Viagra	Comment
Time to onset of action	16 min.	NA	11 min.	Likely to be relatively similar for all drugs
t ½ (h)	16-20	4	4	Cialis' longer half-life could increase dosing convenience
Food Interaction	No	Yes	Yes	Impacts drug absorption
Duration of action (intercourse >1 in 24h period)	Yes	NA	NA	Longer half-life provides for larger window of effect
IC ₅₀ (nM) for PDE5*	1	0.7	6	Target enzyme in corpus cavernosum muscle of penis
IC ₅₀ (nM) for PDE6*	780	157	10	PDE isoform in retina
IC ₅₀ (nM) for PDE1*	>10,000	180	80	PDE isoform believed to mediate flushing
Most common side effects	Headache/dyspepsia	Headache/flushing	Headache/flushing	Differential selectivity causes different side effect profile
Nitrate interaction	Yes	NA	Yes	Inhibition of other PDEs potentiates effects of nitrates

*Low numbers imply greater affinity for enzyme

Source: Company data, Cowen and Company

GIP - Incontinence

Modest Toviaz Growth Expected

Pfizer licensed worldwide rights to Toviaz (fesoterodine) from Schwarz Pharma in April 2006. The licensing deal settled ongoing litigation between the two companies over Toviaz. Toviaz is a M2 selective antagonist. In January 2013, Pfizer announced the results of a Phase IV study suggesting that the 8mg dose of Toviaz is superior to the 4mg dose in reducing the mean number of urge urinary incontinence episodes per 24 hours from baseline to week 12. Our physician consultants are underwhelmed by Toviaz, in part due to its once-daily two-dose formulation compared to Detrol LA's one-dose-fits-all formulation. We estimate Toviaz sales of \$285MM (+21%) in 2014, \$310MM in 2015, \$330MM in 2016, \$370MM in 2018, and \$410MM in 2020.

Two studies of Toviaz were presented at AUA in May 2012:

- Toviaz Nocturnal Urgency Study (October 2011): Results were positive on both the primary endpoint (mean number of micturition-related nocturnal urgency episodes) and key secondary endpoint (mean number of nocturnal micturations). This represents a unique dataset in this category, as Toviaz is the first antimuscarinic to prospectively demonstrate a significant improvement on OAB-related nocturnal urgency symptoms.
- Toviaz Vulnerable Elderly Study (November 2011): Results were positive on both the primary endpoint (mean number of urge urinary incontinence episodes per 24 hours) and key secondary endpoint (mean number of micturations per 24 hours). Toviaz was well tolerated and showed a comparable safety profile with elderly subjects from other studies. No new safety signal was identified. With the study results from the Vulnerable Elderly Study, Toviaz is the only antimuscarinic agent with data in a medically complex, vulnerable OAB population with UUI.

GIP - CNS

Lyrica Growth Expected Through 2018 In U.S. And ROW Ex EU

Lyrica (pregabalin) was launched in September 2005 in the U.S. for three indications: (1) painful diabetic peripheral neuropathy; (2) postherpetic neuralgia; and (3) adjunctive treatment of partial seizures in adults. In June 2007, Lyrica received FDA approval for the management of fibromyalgia syndrome (FMS). Despite the fact that Lyrica is classified as a Schedule V controlled substance, which increases the complexity of prescribing, and the availability of inexpensive and similar gabapentin generics, Lyrica has been a success. In the E.U., Lyrica is indicated for management of peripheral and central neuropathic pain, treatment of generalized anxiety disorder (GAD), and add-on therapy for partial epilepsy with or without secondary generalization. In the U.S., Lyrica typically is used as first-line monotherapy in patients who present with FMS, but do not have depression or anxiety issues. In addition to helping with FMS-related pain, Lyrica's sedating effects help treat the insomnia FMS patients often experience. Lyrica is also used in combination with Cymbalta or Effexor XR in FMS patients with depression that are poorly controlled on an SNRI alone. Our consultants use gabapentin off-label for the treatment of FMS and indicate that gabapentin and Lyrica have similar efficacy. Lilly's Cymbalta was approved in June 2008 for FMS and Forest's Savella (milnacipran) was approved in January 2009. We believe that Cymbalta's antidepressant capabilities are an important differentiating feature.

In July 2012, Pfizer announced that the U.S. District Court for the District of Delaware had upheld Lyrica's basic composition of matter patent ('819) and method of use patents ('517, seizures and '920, pain). In August 2012 the generic companies appealed. In February 2014, the Federal Circuit affirmed the validity and enforcement of one claim and on the grounds of mootness, did not have to render a decision on any other issues raised on appeal, including with respect to the patent that expires in 2018. As a result, generic companies cannot obtain FDA approval prior to the 2018 patent expiry, subject to the possible filing of a petition for certiorari requesting a review by the U.S. Supreme Court.

We estimate Lyrica sales (all indications) of \$3.48B (+11%) in 2014, \$3.7B in 2015, \$4.015B in 2016, \$4.695B in 2018, and \$1.475B in 2020. All Lyrica sales ex EU are reported in GIP; EU sales are shown in GEP.

Other Indications Under Evaluation But Results Mixed

Post-traumatic peripheral nerve pain/spinal cord injury: At AAN 2010, Lyrica was shown to be effective in patients with post-traumatic peripheral nerve pain. In June 2011, Pfizer announced that Lyrica met its primary endpoint: positive efficacy in reducing central neuropathic pain following spinal cord injury with Lyrica compared to placebo.

Restless Leg Syndrome: In December 2011, Pfizer reported Phase III data for Lyrica in RLS. Study A0081186 was a randomized, double-blind, 12-month trial. It enrolled more than 700 patients, who received either a placebo, Lyrica at 300 mg/day, pramipexole at 0.25 mg/day or pramipexole at 0.5 mg/day. Patients treated with Lyrica experienced a statistically significant improvement compared with placebo in RLS symptom severity as measured by the International Restless Leg Group Rating Scale following 12 weeks of treatment. The Lyrica group also demonstrated a statistically significant improvement following 12 weeks of treatment in the proportion of patients responding to treatment compared with those on placebo as measured by the Clinical Global Impression Improvement scale. In addition, Lyrica treatment resulted in a statistically significant reduction in the rate of augmentation (worsening of RLS symptoms that occur after starting a medication to treat RLS) compared with pramipexole 0.5 mg/day over 12 months.

Diabetic peripheral neuropathy/HIV associated neuropathy: In May 2012, Pfizer reported that Lyrica had failed to meet its primary endpoints in two separate trials in patients with inadequately treated diabetic peripheral neuropathy and HIV-associated neuropathy. In Q1:2014, Pfizer announced that a study evaluating painful diabetic neuropathy (pDPN) as an addition to a NSAID did not meet its primary endpoint of pain reduction. And in August 2014, a Phase III study in China in pDPN also failed to meet its primary endpoint.

Postherpetic neuralgia: A Phase IV study in China, reported in August 2014, in postherpetic neuralgia (pain after shingles) was successful in demonstrating a statistically significant improvement in pain scores after 8 weeks of treatment, compared to placebo. The safety profile was consistent with the known profile.

Partial-onset epileptic seizures: In November 2012, Pfizer reported top-line results from Lyrica's Phase III adjunctive treatment trial in patients with partial onset epileptic seizures. The primary endpoint was the loge-transformed 28 day seizure rate for all partial onset seizures vs. placebo. The analysis of the primary endpoint showed a non-significant result between pregabalin and placebo ($p=0.0907$). Responder rates, defined as the percentage of patients with $\geq 50\%$ reduction in seizure frequency from baseline, were 45.9%, 37.8%, and 35.8% for the CR 330mg, 165mg, and placebo groups, respectively. The responder rates highlight the high placebo response observed in this study, which Pfizer believes contributed to the failed outcome.

In January 2013, Pfizer announced top-line results from a Phase III study that showed Lyrica was as effective as levetiracetam (Keppra) as an adjunctive therapy in adult epilepsy patients experiencing refractory partial onset seizures. The top-line results indicated that the study met its primary endpoint by demonstrating that a comparable proportion of patients on Lyrica achieved at least a 50% reduction in the 28-day seizure rate during the maintenance phase relative to levetiracetam. The adverse event profile in the study was consistent with that known for Lyrica. However in Q1:2014, Pfizer announced that a Lyrica trial in adults with partial-onset seizures did not meet its endpoint of significantly reducing seizure frequency compared to gabapentin over a 28-day period.

Fibromyalgia: In October 2013, Pfizer released top line results from a Phase IIIb fibromyalgia study ($n=197$) which met its primary endpoint of a statistically significant reduction in pain in patients with fibromyalgia and depression (who are taking an antidepressant). Adverse effects were consistent with label. Lyrica is approved in the U.S. for fibromyalgia, but as a large number of patients with fibromyalgia also have depression, this study provides efficacy and safety confirmation for patients being treated with both medications.

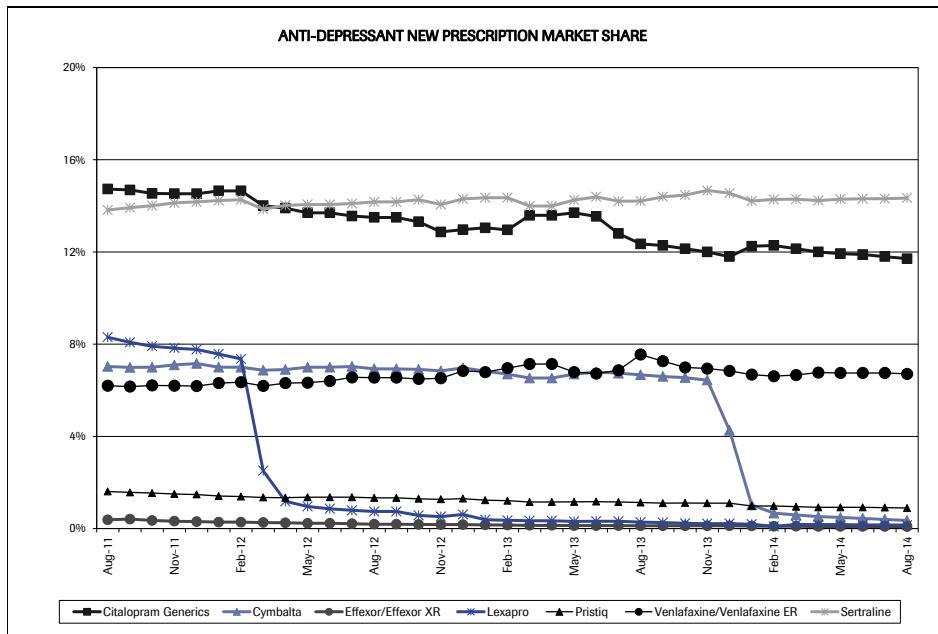
Anti-Epilepsy Drug's Warnings For Suicide Have Not Impacted Use

An FDA analysis of suicidality reports released in January 2008 from placebo-controlled studies of 11 anti-epilepsy drugs shows that patients taking these drugs, including Lyrica, have about twice the risk of suicidal thoughts and behaviors (0.43 percent) compared with patients receiving placebo (0.22 percent). This risk corresponds to an estimated 2.1 per 1,000 more patients in the drug treatment groups who experienced suicidality than in the placebo groups. An FDA Advisory Committee meeting in July 2008 concluded that additional warnings should be added to the labels of anti-epilepsy drugs. In December 2008, FDA issued a release requiring manufacturers of anti-epilepsy drugs, including Lyrica, to add warnings of increased risk of suicidal thoughts and behaviors to the products' prescribing information or labeling. These warnings do not appear to have impacted use.

Discontinuation Symptoms Low Post Withdrawal In GAD

In July 2012, Pfizer announced top-line results from Lyrica's post-authorization safety and efficacy study in generalized anxiety disorder (GAD). The study demonstrated that discontinuation symptoms were low after tapering Lyrica following three- and six-months of treatment. This trial was an EMA requirement to investigate the relationship between dose and duration of treatment on discontinuation symptoms, including rebound anxiety.

Anti-Depressant New Prescription Market Share



Source: IMS America

Chantix Growth Modest, Tempered By Safety Concerns

Chantix (varenicline; Champix in Europe) is an oral, partial agonist of the alpha-4 beta-2 nicotinic receptor. Chantix was launched in the U.S. in August 2006, received final E.U. approval in September 2006 and Japanese approval in January 2008. Chantix initially had a very solid roll-out keyed to: excellent efficacy, with a 44% quit rate at eight weeks, and international launches, particularly Asia. However, in November 2007, FDA notified health care professionals of post-marketing reports of suicidal thoughts and aggressive and erratic behavior, including one death, in patients who have taken Chantix. In January 2008, Pfizer added a warning to Chantix's label that patients who are attempting to quit smoking by taking Chantix should be observed by a physician for neuropsychiatric symptoms. In February 2008, FDA issued an early warning with respect to the November findings. In May 2008, FDA announced that it was convinced that there was a real association between Chantix and the serious neuropsychiatric side effects, which resulted in an additional label change. The updated label advises that patients should stop taking Chantix and contact their health care provider immediately if agitation, depressed mood, or changes in behavior that are not typical for them are observed, or if they develop suicidal thoughts or suicidal behavior.

The agency's review of Chantix was finalized in July 2009 with FDA requiring a boxed warning on Chantix and for Glaxo's Zyban and Wellbutrin as well as for generic Bupropion. The updated label highlights safety information about reports of serious neuropsychiatric events in a boxed warning; updates the warning about reports of neuropsychiatric symptoms and suicidality; adds warnings about reports of allergic reactions and serious skin reactions; and updates precautionary information about driving or operating machinery to include details about reports of accidental injury.

In October 2011, FDA updated its safety communication regarding Chantix. After reviewing two clinical trials and data from more than 700 patients, FDA noted that neither study found a difference in risk of neuropsychiatric hospitalizations between Chantix and nicotine replacement therapy (i.e., NicoDerm patches). However, both studies had a number of design limitations, including only assessing neuropsychiatric events that resulted in hospitalization, and not having large enough samples sizes to detect rare adverse events. Although these studies suggest that Chantix is not associated with neuropsychiatric events that result in hospitalization, they do not rule out other neuropsychiatric events that may occur on drug.

In November 2012, a FDA safety review revealed a potential CV signal for Chantix. A higher occurrence of CV-related death, nonfatal MI, and nonfatal stroke was observed in patients using Chantix compared to placebo. These events were uncommon in both Chantix and placebo groups and the increase in excess risk for Chantix was not statistically significant. While it is difficult to demonstrate causality with these data, the data were analyzed several different ways and consistently showed a higher event rate in patients using Chantix, making it more likely that the increase in risk is due to the drug and is not a chance finding. The FDA Psychopharmacologic Drugs/Drug Safety and Risk Management committee will meet on October 16, 2014 to again discuss Chantix adverse effects. In May 2012, FDA granted tentative approval to Apotex's generic varenicline 0.5mg and 1.0mg tablets. We estimate Chantix sales of \$615MM (-5%) in 2014, \$610MM in 2015, \$615MM in 2016, \$625MM in 2018, and \$650MM in 2020.

Pain Franchise: Remoxy Uncertainty; Embeda Re-Launch Early 2015; ALO In Phase III

Remoxy (tamper-resistant oxycodone ER) received its first CRL in December 2008, and Pfizer responded to FDA in December 2010. Remoxy received its second CRL in June 2011 with FDA citing concerns related to chemistry, manufacturing, and controls; certain lots of Remoxy demonstrated inconsistent release performance during in-vitro testing. Pfizer conducted a Type C meeting with FDA in March 2013 to discuss a regulatory pathway for Remoxy. In October 2013, Pfizer announced that they achieved technical milestones related to manufacturing and will proceed with the additional clinical trials and other actions required to address the CRL. The new studies will include 1) a pivotal bioequivalence study with the modified Remoxy ER formulation to bridge the gap to the data from the original formulation and 2) an abuse-potential study with the modified formulation. The complete response submission is not expected before mid-2015. We forecast Remoxy sales of \$50MM in 2016 and \$400MM in 2020.

In November 2013, FDA approved the prior approval supplement for Embeda (morphine sulfate ER/naltrexone co-formulation) which was submitted in July 2013 for a manufacturing change. The prior approval supplement addressed the stability requirement that led to the voluntary recall of Embeda in March 2011. Re-launch is expected in early 2015. We forecast Embeda sales of \$55MM in 2014, \$150MM in 2015 and \$400MM in 2020.

In January Pfizer announced top-line results from its 12-week, double-blind, randomized Phase III study of ALO-02 (oxycodone and naltrexone ER) in 281 patients with moderate-to-severe chronic low back pain. ALO-02 met the primary endpoint of statistically significant pain improvement vs. placebo (using self-reported NRS-Pain scale). The most common AEs were nausea, vomiting, and diarrhea, but grade of AE or percentage of occurrence are not yet available.

GIP - Arthritis

Enbrel Foreign Sales Solid, But U.S. Alliance Revenue Ended In 2013

Enbrel is a soluble tumor necrosis factor receptor linked to the Fc portion of human IgG₁. First approved in the U.S. in 1998, Enbrel is indicated for the treatment of RA, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and adult plaque psoriasis. Enbrel is poised for continued growth despite stiff competition from other anti-TNF therapies, namely Humira (Abbott). Physicians differentiate Enbrel based on its excellent efficacy (inhibiting clinical and radiographic progression) and safety as well as its weekly subcutaneous dosing regimen. Enbrel may be administered as a 50mg self-injectable, pre-filled syringe versus Humira's once every two weeks or once weekly format. Wyeth had started a dose push-out study in Europe that administers Enbrel less frequently than its current label. Enbrel's label was updated in March 2008 to include a black box for infections and TB reactivation; this update is in line with other TNFs. In June 2008, FDA announced that it was investigating 30 reports of cancer in children and young adults who were on anti-TNFs. FDA requested manufacturers provide it with information on all cases of cancer in children reported with anti-TNF use. All anti-TNFs have a cancer risk in their labels. Also in June 2008, FDA's Dermatologic and Ophthalmic Drugs Advisory Committee voted 8-5 in favoring approval of Enbrel for the treatment of moderate to severe plaque psoriasis in children. Amgen/Wyeth submitted a sBLA for this indication in September 2007, but decided not to pursue this indication post a CRL in 2008 requesting additional clinical trials. Enbrel is approved for severe plaque psoriasis in pediatric patients ages 8 and

over in the E.U., making it the first anti-TNF approved in the E.U. for this indication. Increasing direct (from novel agents and anti-TNFs) and indirect (Roche's Actemra: IL-6 mAb and JNJ's Stelara: IL-12 mAb) competitors could clip Enbrel growth.

Under its agreement with Amgen, across all indications, the two companies had split profits in North America, while Pfizer holds all rest-of-world rights. North American rights reverted to Amgen in November 2013, with Pfizer receiving a declining royalty tail three years post the transfer of U.S. rights. Enbrel's E.U. patent expires in February 2015. Enbrel foreign sales are forecast at \$3.84B (+2%) in 2014, \$3.955B in 2015, \$4.09B in 2016, \$4.33B in 2018, and \$4.57B in 2020.

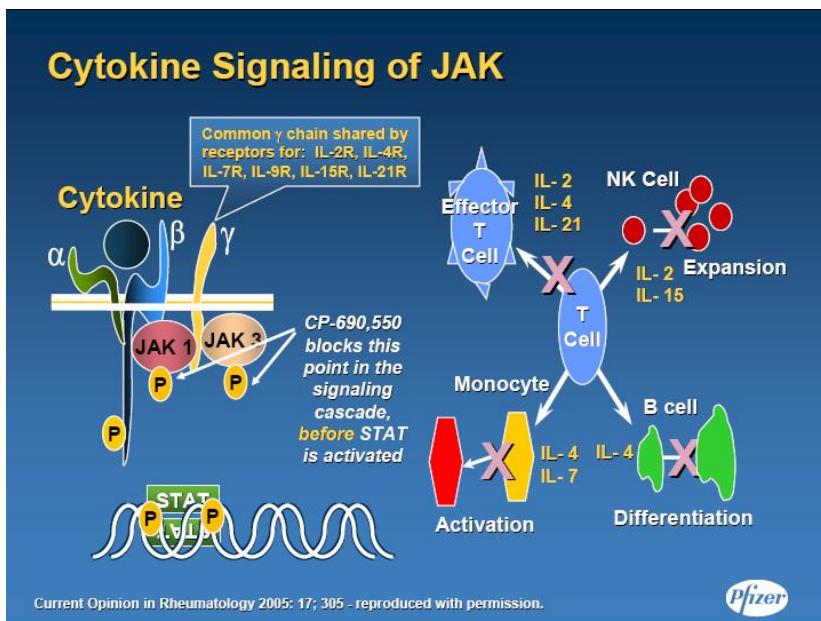
Xeljanz Enjoying Moderate Rollout

In November 2012, FDA approved the 5mg dose of Xeljanz (tofacitinib) for the treatment of moderate-to-severe rheumatoid arthritis (RA) in patients who have failed methotrexate. Xeljanz was approved with a REMS, which consists of a medication safety guide and a plan to communicate Xeljanz-associated safety issues to healthcare providers. Pfizer has committed to conducting a post-marketing study to evaluate the long-term effects of Xeljanz on heart disease, cancer, and serious infections.

Xeljanz is priced at \$2,197 for a 30-day supply or approximately \$26,300 per year. This represents a 7% discount to Humira (ABT) and Enbrel (AMGN/PFE). In June 2013, Pfizer began DTC advertising. Xeljanz has been unable to garner CHMP approval, and it was turned down by the MAA for a second time in July 2013 due to safety concerns. Pfizer believes the necessary additional clinical data needed for approval will require several years to complete. Pfizer is working on a once-daily version of Xeljanz for the U.S. RA market. The company indicated that the FDA will not require a Phase III study so they anticipate filing an NDA in H1:15. We estimate Xeljanz sales of \$290MM in 2014, \$460MM in 2015, \$700MM in 2016, \$1.1B in 2018, and \$1.5B in 2020.

Xeljanz is an oral small molecule that targets JAK 1/3 for autoimmune diseases such as rheumatoid arthritis (RA). JAK 1/3 is important for white blood cell production (T-cells, natural killer cells) and inhibiting this enzyme leads to the inhibition of IL-6, which is produced by a number of cell types including lymphocytes and is an important regulator of hematopoiesis and inflammation. IL-6 plays an active role in the pathogenesis of RA and targeting IL-6 has already been proven to be a valid therapeutic approach as demonstrated by Roche's Actemra. JAK 1/3 inhibition also leads to a decline in IL-8, MMP3, IL-17, and IFN and an increase in IL-10. However, an inhibitor of JAK-3 has the potential to cause immunosuppression.

Cytokine Signaling of JAK



Source: Pfizer

Approval Of 5mg Dose Positive; 10mg Dose Requires Additional Data

Both the 5mg and 10mg doses of tofacitinib met the primary ACR endpoint in ORAL SOLO, SEQUEL, SYNC, STANDARD, and STEP, and the structural progression endpoint in methotrexate naïve patients in ORAL START; however, only the 10mg dose demonstrated a statistically significant improvement in structural progression in ORAL SCAN. Pfizer will continue to generate additional clinical data for the 10mg dose and work with FDA to understand what additional data may be required.

Label As Expected; Safety Warnings Prominent, Structural Progression Claims Not Included

Tofacitinib's label includes a black box warning for serious infections leading to hospitalizations or death including TB and bacterial, invasive fungal, viral, and other opportunistic infections and a warning against lymphoma and other malignancies. The label recommends monitoring for potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids. In February 2014, FDA approved labeling for delay in progression of structural damage.

Potential New Indications Bolster Outlook

Xeljanz is in five Phase III trials (OPT program) for moderate to severe chronic plaque psoriasis evaluating over 3,600 patients in 36 countries. Top-line data from first two trials (OPT Compare and OPT Retreatment) were released in October 2013 and top-line results from the two pivotal trials (OPT Pivotal #1 and Pivotal #2) were announced in April 2014. All four trials met their primary endpoints. A long-term extension study (OPT Extend) is ongoing. These five studies will be the basis for the filing by early 2015 of Xeljanz 5mg or 10mg twice a day in adults with moderate-to-severe chronic plaque psoriasis.

Pfizer has also initiated a Phase III program in active psoriatic arthritis which includes two pivotal studies and a long-term extension study. Read out on these trials will be in

2015. There is also a Phase III program in UC, and Phase II studies in Crohn's, ankylosing spondylitis, and a topical formulation for psoriasis.

Primary Endpoint Met At 10mg Dose In Trial Vs. Enbrel

The OPT Compare trial is a 12-week non-inferiority trial, which enrolled 1,106 patients with moderate-to-severe chronic plaque psoriasis, and compared safety and efficacy of tofacitinib (Xeljanz) 5mg and 10mg twice-daily to high-dose Enbrel given twice a week (its approved starting dose) and placebo. Xeljanz met the primary endpoint of non-inferiority at the 10mg BID dose, but not at the 5mg BID dose (which is consistent with Phase II dose results).

Primary Endpoint Met In Retreatment Trial

The OPT Retreatment trial, which enrolled 674 patients with moderate-to-severe chronic plaque psoriasis, treated patients initially with Xeljanz 5mg or 10mg twice-daily for 24 weeks, then, in patients who achieved a PASI75 and a clear/almost clear PGA response, were randomized to either placebo or Xeljanz for 16 weeks (or until lost half of PASI score), and then restarted on their original Xeljanz dose until week 56. Xeljanz met the primary efficacy endpoint of demonstrating that a greater proportion of patients continuing on Xeljanz maintained their response during the treatment withdrawal phase. In addition, patients who lost adequate response after withdrawal were shown to recapture response after restart. No new safety signals were reported in either study. Full data will be presented at a future scientific meeting.

Pending data from the pivotal OPT trials, we believe Xeljanz will have a role as an oral treatment option in plaque psoriasis, even though it is less effective than injectable biologics (Enbrel, Humira, Stelara).

Pivotal Trials Also Successful

Pfizer announced top-line results for the Pivotal #1 and #2 trials in April 2014. Xeljanz met its primary endpoint of statistically significant superiority versus placebo in achieving Physician's Global Assessment "clear" or "almost clear" response at week 16 and the proportion of patients achieving at least a 75% reduction in PASI. No new safety data was reported. Full data will be presented at a future scientific meeting.

Phase III ORAL SOLO And Phase II/II SEQUEL Data Positive

ORAL SOLO was a double-blinded, placebo-controlled Phase III randomized clinical trial to evaluate the efficacy of tofacitinib for the treatment of patients with moderate to severe rheumatoid arthritis who have failed at least one disease-modifying antirheumatic drug. Patients were randomized 2:2:1 (n=122:243:245) to 5mg of tofacitinib, 10mg tofacitinib, or placebo given twice daily for 3 months. At the 3-month time point, placebo patients were randomized to either the 5 or 10mg and all patients were followed for an additional 3 months. The primary efficacy endpoints were significant change in ACR20 response rate, and HAQ-DI, and a DAS28-(ESR) < 2.6 at 3 months. Secondary endpoints include ACR50/70 and changes in DAS28 at 3 months.

Tofacitinib showed a dose responsive and significant change in ACR20/50/70 compared to placebo at both doses. Additionally, both doses showed significant improvements in HAQ-DI scores compared to placebo and showed a statistically significant decrease in DAS28-4(ESR); however, while trending favorably from a numerical standpoint, this decrease in DAS28-4(ESR) did not meet the primary endpoint of being less than 2.6.

Tofacitinib Efficacy Overview

Tx Group	ACR20	ACR50	ACR70	HAQ-DI	DAS28<2.6	
	(%)	(%)	(%)	Mean Change	(%)	Mean Change
5mg	59.8*	31.1*	15.4**	-0.50*	6.0	-2.04*
10mg	65.7*	36.8*	20.3*	-0.57*	9.6	-2.26*
Placebo	26.7	12.5	5.8	-0.19	4.4	-1.17

ACR20, HAQ-DI, and DAS28<2.6 are primary endpoints

*p<.0001, **p<.05

Source: Company data

Patients treated with tofacitinib experienced a similar number of adverse events compared to placebo. Among patients treated with tofacitinib, statistically significant differences in several laboratory safety values were observed: statistically significant increases in LDL and HDL cholesterol (no change in LDL/HDL ratios), and a significant decrease in the absolute neutrophil count. No significant changes were noted with regard to serum creatinine or hemoglobin.

Tofacitinib Safety Overview

Tx Group	PBO (n=122) (n=122)	5mg BID n=(243)	10mg BID (n=245)
LS mean change from baseline			
Neutrophil Count	-0.06	-0.83*	-1.35**
Hemoglobin, g/dL	-0.12	0.28	0.03
% LDL (mean increase)	3.35	13.63*	19.05**
% HDL (mean increase)	-0.76	12.24**	14.98**
Serum Cr (mg/dL)	0	0.04	0.05
Incidence, n (n%)	n=103	n=223	n=216
Neutropenia (500-1499 cells/mm ³)	0	1.3	<1.0
Decreased hemoglobin (-1.0 to -3.0 g/dL)	14.6	15.8	14.4

*p<0.001, **p<0.0001 vs. PBO

Source: ACR 2011

ORAL SEQUEL was a Phase 2/3 open-label extension study to evaluate the safety and efficacy of oral tofacitinib in patients with rheumatoid arthritis over the course of 24 months. The primary end points were laboratory AEs and safety reports assessed at 1, 2, and 3 months and each 3 months afterwards. Secondary endpoints were assessed at similar time points and included ACR20/50/70 response rates, DAS28-4(ESR) and HAQ-DI scores. In total, 1,070 patients from previous index studies were enrolled and received treatment. Index patients from Phase II studies were started on 5mg bid and Phase III index patients were started on 10mg bid dosing regimens. Dosing was decreased from 10mg to 5mg twice daily or withheld for a period of 2 weeks from patients who experienced significant adverse effects. Alternatively, dosing was increased from 5mg to 10mg bid if RA symptoms were not adequately controlled at the lower dose. The percentage of patients receiving tofacitinib 5mg and 10mg bid at baseline was 77.5% and 22% respectively; at month 6, 93.5% and 3.9%; at month 12, 92.8% and 3.3%; and at month 24, 91.2% and 6.2% respectively.

In total, 2,611 AEs were reported with the most treatment-emergent AEs being infections, gastrointestinal disorders, and musculoskeletal and connective tissue disorders. The most common infections were upper respiratory tract infections,

nasopharyngitis, and bronchitis. The most frequent class of SAEs was infections, which occurred at an incidence rate of 2.62/100 patient years.

Several laboratory safety parameters were negatively influenced by both acute and chronic tofacitinib treatment, notably total cholesterol, LDL, serum creatinine, AST, ALT, and a decrease in the absolute neutrophil count. Approximate changes from baseline at 12 weeks are as follows: total cholesterol 195 to 230; LDL from 112 to 130; SCr from 0.74 to 0.80; AST from 21 to 25; ALT from 21 to 25, and a neutrophil count from 5.55 to 4.55 at 12 weeks. These changes at 12 weeks were maintained and did not progress throughout the 24-month treatment period.

Tofacitinib 10mg Showed Increase In LDL, Decrease In Neutrophil Compared To 5mg Dose

Tofacitinib 10mg has demonstrated a statistically significant increase in LDL and significant decrease in absolute neutrophil count compared to the 5mg dose. Given that the 5mg dose was not effective in reducing mTSS in ORAL Scan, physicians and FDA will have to carefully weigh the risk:benefit ratio of the 5mg and 10mg doses. Our rheumatology consultants are not concerned with the general safety profile of tofacitinib, but note that the incidence of infection will be a key component of approval and adoption.

ORAL SYNC Supports SOLO And SEQUEL, Meets Primary Endpoints...

ORAL SYNC enrolled 792 patients with moderate-to-severe active RA who had a previous inadequate response to a traditional or biologic DMARD. Patients were randomized 2:2:1 to receive tofacitinib 5 mg or 10 mg twice a day or placebo added to background traditional DMARD(s), including methotrexate (MTX). At month 3, non-responder placebo patients were advanced to tofacitinib 5 or 10 mg BID. At month 6, all remaining placebo patients were advanced to tofacitinib.

ORAL SYNC met its primary efficacy endpoints by showing statistically significant changes versus placebo in ACR20 at six month and statistically significant improvements in mean HAQ-DI at three month and DAS 28-4(ESR) <2.6 at six months.

ORAL Sync Endpoints

Treatment Group	ACR20 (%) #	ACR50 (%)	ACR70 (%)	HAQ-DI mean change from baseline#	DAS28-4 (ESR)<2.6 (%)	DAS28-4 (ESR) mean change from baseline
5mg	52.7***	33.8***	13.2***	-0.46***	11.0**	-2.2***
10mg	58.3***	36.6***	16.2***	-0.56***	14.8***	-2.5***
Placebo	31.2	12.7	3.2	-0.21	2.7	-1.6

#Primary endpoint; **p<0.001; ***p<0.0001

All endpoints 6 months; HAQ-DI month 3

Source: Company data

...But Concerns About AEs And Infections Linger

Comparable rates of AE/SAEs were observed between tofacitinib and placebo arms from 0-3 months with a numerical increase in the frequency of AE/SAEs from 3-6 months in the tofacitinib groups compared to placebo. Additionally, there was a higher rate of discontinuation from 0-6 months in patients receiving tofacitinib compared to placebo. The most frequently reported classes of AEs throughout the study were infections and infestations. Serious infectious events were reported for two (5 mg BID)

and four (10 mg BID) patients in months 0-3 and one patient each in the placebo-to-5 mg BID and placebo-to-10 mg BID groups during months 3-6. There were four deaths, one of which was assessed by the investigator as study drug related, and four opportunistic infections in the study all of which occurred in the tofacitinib arms. Of the four deaths, two occurred after discontinuation of drug. The deaths included: 1) 81 year old male in U.S. with traumatic brain injury after a fall; 2) 37 year old male in China from valvular heart disease (not related); 3) 48 year old male in Russia from RA (not related); 4) 58 year old male in U.S. from respiratory failure (related). Details of the four causality related opportunistic infections were provided. These included: 1) disseminated herpes zoster in a 59-year-old female in Finland; she made a quick recovery; 2) cryptococcal pneumonia in a 68-year-old female in Australia; patient treated with antifungals; 3) pulmonary tuberculosis in a 51-year-old female in Thailand; patient had history of T.B.; and 4) pulmonary tuberculosis in 51-year-old male in China; patient recovered. Among patients treated with tofacitinib, dose-dependent decreases in mean neutrophil counts, increases in mean LDL, HDL and total cholesterol, transaminase increases, and small increases in serum creatinine were observed. Our physician experts are not particularly concerned with alterations in lipid profiles, liver enzymes, or modest changes in renal function.

ORAL Sync Safety

Treatment Group	AEs 0-3 months	SAEs 0-3 months	AEs 3-6 months	SAEs 3-6 months	D/C (AEs) 0-6 months
5mg	166 (52.7)	9 (2.9)	121 (38.4)	5 (1.6)	13 (4.2)
10mg	173 (54.4)	8 (2.5)	124 (39.0)	7 (2.2)	15 (4.7)
Placebo	97 (61.0)	6 (3.8)	21 (25.9)	0	3 (1.9)

Source: Company data

Tofacitinib Comparable To Less-Aggressive TNF Regimen In ORAL-Standard

In ORAL-Standard, 717 patients were randomized 4:4:4:1:1 to tofa 5mg BID: tofa 10mg BID: Humira 40mg SQ Q2W: Placebo advanced to 5mg tofa BID: or placebo advanced to 10mg tofa BID. Placebo patients were advanced to tofacitinib at month 6 or month 3 if non-responders. Both the 5mg and 10mg doses of tofacitinib demonstrated statistically significant improvements in ACR20/50/70, HAQ-DI, and DAS20<2.6 compared to placebo and these improvements were numerically similar to those in the Humira group, although it should be noted that Humira dosed once-weekly has previously been shown to be more effective than the every two week dosing comparator in ORAL-Standard. The frequency of total adverse events from months 0-3 and months 3-6 were similar between all treatment groups with a numerical increase in the number of serious adverse events in both the 5mg and 10mg tofacitinib groups.

Tofacitinib ORAL-Standard Efficacy Data

Efficacy Measure	Time	5mg BID	10mg BID	Humira	PBO
ACR20	6 months	51.5***	52.6***	47.2**	28.3
ACR50	6 months	36.7***	34.7***	27.6**	12.3
ACR70	6 months	19.9***	21.9***	9.1**	1.9
Mean change HAD-DI	3 months	-0.55***	-0.61***	-0.49***	-0.24
DAS28<2.6	6 months	7.3*	12.5***	6.2*	1.1
Mean change DAS28	3 months	-2.0***	-2.0***	-1.9***	-1

*p<0.05

**p<0.001

***p<0.0001 vs PBO

Source: Company data

Tofacitinib ORAL-Standard Safety Data

Safety Measure	Time	5mg BID (%)	10mg BID (%)	Humira (%)	PBO (%)
AE	0-3 months	52.0	46.8	51.5	47.2
SAE	0-3 months	5.9	5.0	2.5	1.9
AE	3-6 months	32.8	30.8	33.3	27.1
SAE	3-6 months	4.9	3.5	2.9	3.4

Source: Company data

ORAL-STEP Confirms Tofacitinib Efficacy In TNF Failures

ORAL-STEP was a six month study evaluating the efficacy of tofacitinib in patients on a stable dose of methotrexate who had failed at least one TNF inhibitor compared to methotrexate alone. Patients were randomized 2:2:1:1 to tofa 5mg BID: tofa 10mg BID: placebo advanced to 5mg tofa BID at 3 months: or placebo advanced to 10mg BID at 3 months. All tofacitinib groups showed statistically significant improvements in ACR/20/50/70, HAQ-DI, and DAS28-4<2.6 compared to placebo without significant changes in the frequency of adverse events compared to placebo.

Tofacitinib ORAL-Step Efficacy Data

Efficacy Measure	Time	5mg BID	10mg BID	PBO
ACR20	3 months	41.7*	48.1***	24.4
ACR20	6 months	51.5***	54.9***	N/A
ACR50	3 months	26.5***	27.8***	8.4
ACR50	6 months	37.1***	30.1***	N/A
ACR70	3 months	13.6***	10.5***	1.5
ACR70	6 months	15.9***	15.8***	N/A
Mean change HAD-DI	3 months	-0.43***	-0.46***	-0.18
Mean change HAD-DI	6 months	-0.51***	-0.50***	N/A
DAS28-4(ESR)<2.6	3 months	6.7*	11.2*	1.7
DAS28-4(ESR)<2.6	6 months	10.7*	15.8*	N/A

*p<0.05

**p<0.001

***p<0.0001 vs. PBO

Source: Company data

Tofacitinib 10mg BID Prevents Structural Disease Progression In ORAL-Scan, 5mg BID Tofacitinib Dose Did Not

ORAL-Scan was a 797 patient trial designed to evaluate the effects of tofacitinib in patients on background methotrexate on structural disease progression in RA. Patients were randomized 4:4:1:1 to 5mg BID: tofa 10mg BID: placebo advance to 5mg tofa: or placebo advance to 10mg tofa. While tofacitinib improved ACR20's at 6 months for both doses compared to placebo, only the 10mg tofacitinib dose improved structural disease progression at 6 months as measured by change from baseline in total sharp score (mTSS). A secondary analysis showed that both the 5mg and 10mg doses of tofacitinib were effective in increasing the proportion of patients without radiographic progression (mTSS change from baseline <0.5) or new erosions (ES change from baseline <0.5). The most frequently reported adverse events in the tofacitinib group were infections, although most were mild to moderate and were distributed similarly across both doses. The rate of serious adverse infections was numerically greater in the tofacitinib groups during the first 3 months of treatment and similar to placebo in months 3-6. There were 6 deaths in the study, 4 on tofacitinib 5mg BID, 1 on tofacitinib 10mg BID, and 1 on placebo. Increases in LDL, HDL, and

serum creatinine and decreases in absolute neutrophil counts were observed in the tofacitinib groups.

Tofacitinib ORAL-Scan Efficacy Data

Efficacy Measure	Time	5mg BID	10mg BID	PBO
ACR20	6 months	51.5***	61.8***	25.3
Mean change mTSS	6 months	0.12	0.06*	0.47
Mean change is ES	6 months	0.06	0.02	0.15
Mean change in JSN	6 months	0.06	0.04	0.31
Mean change HAD-DI	3 months	-0.4	-0.54***	-0.15
DAS28-4(ESR)<2.6	6 months	7.2	18.3***	1.6

*p<0.05

***p<0.0001 vs PBO

Source: Company data

Tofacitinib ORAL-Scan Safety Data

Safety Measure	Time	5mg BID (%)	10mg BID (%)	PBO (%)
AE	0-3 months	48.9	54.1	45.6
SAE	0-3 months	3.7	3.2	3.1
SIE	0-3 months	1.6	0.9	0
AE	3-6 months	45.2	35.1	25.9
SAE	3-6 months	5.3	2.2	6.2
SEI	3-6 months	2.5	0.6	2.5

Source: Company data

Tofacitinib Monotherapy Meets Structural Progression Endpoint In ORAL-Start

In August 2012, Pfizer announced top-line results from tofacitinib's ORAL-Start, a two-year study in methotrexate-naïve patients with moderate-to-severe RA comparing tofacitinib as monotherapy to methotrexate (MTX). Tofacitinib was found to be superior to MTX in inhibiting structural progression (mTSS) and reducing signs and symptoms of RA (ACR70) at 6-months.

Analysis Across Phase III And Long-Term Safety Studies Suggests Increased Risk Of Serious Infections

An analysis of patients across all Phase III studies for tofacitinib and the 36-month long-term extension study was presented at ACR 2011. Tofacitinib demonstrated an increased risk of serious infections compared to placebo and Humira (2.91 per 100 pt. years for all tofa doses vs. 1.48 per 100 pt. years for placebo and 1.68 per 100 pt. years for Humira). Tofacitinib also increased the risk of herpes zoster compared to placebo and Humira (4.36 per 100 pt. years vs. 1.49 per 100 pt. years for placebo and 2.81 per 100 pt. years for Humira). No serious herpes zoster infections were observed in patients on placebo or Humira, while serious herpes zoster infections occurred at a rate of 0.24 per 100 patient years in patients treated with tofacitinib. All cause mortality was similar in patients on tofacitinib compared to those on placebo and Humira (0.57 per 100 pt. years for tofa vs. 0.49 per 100 pt. years for placebo and 0.58 per 100 pt. years for Humira). 1.3% of patients on tofacitinib discontinued treatment within the first 3-months as the result of a serious infection compared to 0% for both placebo and Humira.

Serious infections for tofacitinib were highest in patients over 65 years of age, a trend that also occurred with Humira; however the rate of tofacitinib infections in patients

<65 years old was significantly greater compared to Humira (2.69 per 100 pt. years for tofa 10mg vs. 0.65 per 100 pt. years for Humira). While the infection rates appeared similar across Phase III studies in patients >65 years old for Humira and tofa, the LTE study showed an elevated risk of infection in this patient population (12.39 per 100 pt. years for tofa 10mg in LTE study vs. 7.87 for Humira in Phase III study). Interestingly, males on tofacitinib appeared more susceptible to infection compared to females across all Phase III doses and the long-term extension study (2.47 infections per 100 pt. years in females on 10mg in Phase III vs. 5.67 per 100 pt. years in males in Phase III; 4.25 infections per 100 pt. years in females in LTE study vs. 8.01 per 100 pt. years for males in LTE study).

Safety Concerns In Japanese Studies Consistent With ROW

At the ACR analysts' meeting, in 2011, data was provided for the three studies of tofacitinib in Japanese patients, with a single poster summarizing the Japanese studies and comparing them to global trials. ACR20 responses in the Japanese population were similar-to-improved compared to global studies; lower doses (1-5mg BID) appeared to show superior ACR20 responses in Japanese patients compared to ROW. DAS28 (ESR) and HAQ-DI responses appeared similar in Japanese populations and global cohorts for all doses. The incidence of infections and infestations appeared similar in the Japanese and ROW populations with a dose-dependent increase in infection incidence. In Japanese patients, the dose-dependent increase in neutropenia is numerically greater across all tofacitinib doses compared to the global population (i.e. -2.10 in Japanese vs. -1.41 in the global population for 10mg BID dosing). A potential hypertension signal was also noted in the Japanese population, although Pfizer notes this is a very small population and that an imbalance in CV events across all trials has not been observed. In late July 2013, Xeljanz became commercially available in Japan, co-promoted with Takeda.

Incidence Rates For Serious Infections, Herpes Zoster, And Mortality

	Phase III				LTE
	Tofa 5mg BID (n=1216)	Tofa 10mg BID (n=1214)	All Tofa Doses (n=3030)	Placebo (n=681)	
All Serious Infections					
Unique patients with events (%)	29 (2.4)	27 (2.2)	61 (2.0)	3 (0.4)	3 (1.5)
IR, events/ 100 pt. years (95%CI)	3.22 (2.2, 4.63)	2.97 (2.04, 4.33)	2.91 (2.27, 3.74)	1.48 (0.48, 4.59)	1.68 (0.54, 5.21)
All Herpes Zoster					
Unique patients with events (%)	39 (3.2)	38 (3.1)	90 (3.0)	3 (0.4)	5 (2.5)
IR, events/ 100 pt. years (95%CI)	4.39 (3.21, 6.01)	4.23 (3.08, 5.82)	4.36 (3.54, 5.35)	1.49 (0.48, 4.61)	2.81 (1.17, 6.76)
Serious Herpes Zoster					
Unique patients with events (%)	4 (0.3)	1 (0.1)	5 (0.2)	0	0
IR, events/ 100 pt. years (95%CI)	0.44 (0.17, 1.18)	0.11 (0.02-0.78)	0.24 (0.10, 0.57)	0	0
All cause mortality					
Unique patients with events (%)	5 (0.4)	4 (0.3)	12 (0.4)	1 (0.2)	1 (0.5)
IR, events/ 100 pt. years (95%CI)	0.78 (0.37, 1.63)	0.44 (0.17, 1.17)	0.57 (0.33, 1.01)	0.49 (0.07, 3.51)	0.56 (0.08, 3.97)

Source: Company data, ACR 2011

Source: Company data, ACR 2011

Incidence Rates Of Serious Infections By Demographic Characteristics

Serious Infections (events per 100 pt. Years (95% CI))						LTE	
		Phase III					
		Tofa 5mg BID	Tofa 10mg BID	Placebo	ADA		
Age	<65yrs	2.47 (1.57, 3.67)	2.69 (1.75, 5.36)	1.73 (0.56, 5.36)	0.65 (0.09, 4.63)	Tofa 5mg BID	
	>65yrs	7.63 (4.10, 14.7)	4.71 (2.12, 10.49)	0	7.87 (1.97, 31.47)		
Gender	Male	4.99 (2.38, 10.47)	5.67 (2.84, 11.34)	0	0	Tofa 10mg BID	
	Female	2.89 (1.90, 4.39)	2.47 (1.58, 3.88)	1.81 (0.58, 5.61)	2.13 (0.69, 6.60)		

Source: Company data, ACR 2011

Atorvastatin Improves LDL Without Compromising ACR20

Study A3921109 was a 12-week Phase 2 study that enrolled 111 patients to evaluate the efficacy and safety of atorvastatin treatment versus placebo in reducing LDL-C in RA patients taking tofacitinib. After receiving 10 mg BID tofacitinib open-label for six weeks, patients were randomized to receive atorvastatin 10 mg once daily or placebo plus tofacitinib 10 mg BID for six weeks. The primary endpoint for this study was change in LDL-C from Week 6 to Week 12. The addition of atorvastatin to tofacitinib resulted in a 35% reduction in LDL-C compared to a 5% LDL-C increase in patients receiving tofacitinib plus placebo. HDL-C and apolipoprotein A-1 increased with tofacitinib treatment and continued to trend upward during the last six weeks of the study regardless of treatment group. After six weeks of tofacitinib treatment, 76% of patients achieved ACR20. At Week 12, the atorvastatin group had an ACR20 response rate of 82.6% versus the placebo group with 65.2%.

The side effect profile for tofacitinib appeared consistent with previous trials. Three SAEs were reported during the course of the study, one case each of pneumonia, right hip arthritis aggravation and bacterial pneumonia.

Clinical Trials For Tofacitinib In RA

NCT ID	Trial Design	Dosing	Primary Endpoint	Number Of Patients	Duration	Data
NCT00853385	Background MTX (ORAL Standard)	CP5mg BID, 10mg BID Humira (active comparator) PBO advancing to 5mg BID PBO advancing to 10mg BID	ACR20 HAQ DI Safety	717	12 months	Complete
NCT00856544	Background traditional DMARD (ORAL Sync)	CP5 mg BID, 10mg BID PBO advancing to 5mg BID PBO advancing to 10mg BID	ACR20 HAQ DI Safety	792	6 months	Complete
NCT00847613	Background MTX (ORAL Scan)	CP5 mg BID, 10 mg BID PBO advancing to 5mg BID PBO advancing to 10mg BID	ACR20 Joint damage HAQ DI Safety	750	2 years	Complete
NCT00814307	Monotherapy (ORAL Solo)	CP5 mg BID, 10 mg BID PBO advancing to 5mg BID PBO advancing to 10mg BID	ACR20 HAQ DI	500	3 months	Complete
NCT00960440	TNF failures, on MTX (ORAL Step)	CP5 mg BID, 10 mg BID PBO advancing to 5mg BID PBO advancing to 10mg BID	ACR20 HAQ DI Safety	400	6 months	Complete
NCT01039688	MTX Naïve Patients (ORAL Start)	CP5 mg BID, 10 mg BID MTX (active comparator)	ACR70 X-Rays Physical Exam Safety	900	2 years	Complete
NCT00413699	Open Label Extension (ORAL Sequel)	CP5 mg BID, 10 mg BID	Safety	4000		Mid:15

Source: Clinicaltrials.gov, Cowen and Company

Tanezumab Moving Forward, Although Path Unclear

Tanezumab (intravenous delivery, administered once every 12 weeks) is a humanized IgG₂ monoclonal antibody that blocks nerve growth factor (NGF). An Fc mutation limits antibody-dependent cell-mediated toxicity and complement activation. Tanezumab is being developed for chronic lower back pain, osteoarthritis of the hip and knee, arthritis pain, cancer pain, endometriosis, and pain associated with abacterial prostatitis. Pfizer is also developing a subcutaneous formulation and refrigerated RTU liquid formulation.

The development program is currently in a partial clinical hold pending submission of non-clinical data which Pfizer expects to submit to the FDA by H1:15. Pfizer reached an agreement with the FDA in April 2013 on the path required to remove the clinical hold. In October 2013, Pfizer entered into an agreement with Lilly to jointly develop and globally commercialize tanezumab. Pfizer received a \$200MM up-front fee and

assuming the collaboration continues post FDA response, Lilly will pay Pfizer \$350MM in regulatory-based milestone payments and \$1.23B in sales-based milestones. Pfizer and Lilly will equally share development expenses, potential revenues and certain product costs. We forecast tanezumab sales of \$25MM in 2017, \$50MM in 2018, and \$100MM in 2020.

Several Trials Suspended In 2010 And All NGFs Put On Hold In Late 2012

In 2009, tanezumab was being evaluated in a very large Phase III pain program comparing it to placebo, other NSAIDs and a narcotic, in a wide variety of pain indications, including osteoarthritis of the hip and knee, cancer pain, interstitial cystitis, chronic low back pain, and painful diabetic peripheral neuropathy. In addition, Pfizer was testing tanezumab's benefit as an add-on to NSAIDs. However, in June 2010, Pfizer announced that it had suspended the osteoarthritis trials, at the request of the FDA, due to reports of tanezumab patients' arthritic condition worsening, leading to joint replacement. Then, in July 2010, Pfizer also suspended the chronic lower back pain and painful diabetic neuropathy segments of the Phase III program, following further consideration by the FDA of the AEs from the osteoarthritis segments. In March 2012, an FDA Advisory Panel voted 21-0 that anti-NGF based therapies should continue to be developed to treat OA pain. Because of the joint destruction observed in tanezumab trials, FDA recommended that OA trials continue if the use of concomitant NSAIDs was excluded and additional safeguards are put in place (measuring biomarkers of joint destruction, MRIs, etc.). However, in December 2012, the FDA placed a partial clinical hold on the development of all NGF inhibitors based on peripheral nervous system effects seen in animal studies conducted by other companies.

Phase II Data Promising

Phase II data presented at the World Congress of Pain in August 2008 demonstrated that patients treated with tanezumab experienced significantly less knee pain on walking. The mean change in walking pain in the affected knee from baseline to week 16 was a decrease of 15.5% in the placebo group and a decrease of 32.1% in the group given tanezumab 10 mcg/kg ($p < 0.001$). Headache, upper respiratory tract infection, and parathesias were the three most commonly reported adverse effects associated with tanezumab use, reported by 8.9%, 7.3%, and 6.8% of patients, respectively.

A 450-patient Phase II study presented at ACR 2008 demonstrated that tanezumab once every eight weeks resulted in a significant benefit for patients with painful knee OA, as assessed by OMERACT-OARSI responder index and WOMAC physical function, pain and stiffness score. Phase II data demonstrated that tanezumab affects the peripheral nervous system, albeit at a low frequency (10%). The most frequently reported abnormalities include parathesias, hypoesthesia, and hyperesthesia. According to Pfizer, these are not associated with any structural damage and are transient. There have been no reports of anti-tanezumab antibodies. Based on the Phase II data, Pfizer believes that tanezumab can be dosed six times a year as a fixed dose.

Tanezumab has also successfully treated low back pain. Specifically, tanezumab was tested in a randomized, double blind Phase II trial in patients with low back pain for at least three months. Patients (217 included in the ITT analysis) were administered either tanezumab, placebo, or naproxen 500mg twice daily for twelve weeks. Tanezumab statistically significantly improved physical function versus placebo and reduced pain and improved physical function during the majority of time points throughout the study versus naproxen (see next page). In terms of safety, of note were

tanezumab-related peripheral sensation abnormalities (12.5%, vs. 3.4% for naproxen and 2.4% for placebo), which were described as mild-to-moderate except for two cases of severe hyperesthesia. No patients discontinued from the study due to this neurological abnormality. At the conclusion of the study, all cases of peripheral sensation abnormalities had resolved except in two patients who received tanezumab (1 case of mild paresthesia and 1 case of mild dysesthesia).

Phase II Chronic Low Back Pain Efficacy (Left) And Safety (Right) Data

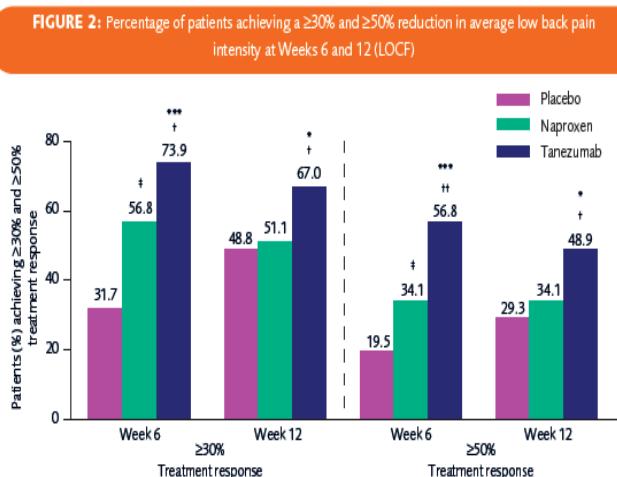


TABLE 2: Summary of adverse events

	Placebo (N = 41)	Tanezumab 200 µg/kg (N = 88)	Naproxen 500 mg BID (N = 88)
Patients n (%) reporting:			
Any adverse event	27 (65.9)	49 (55.7)	53 (60.2)
Treatment-related adverse event	9 (22.0)	27 (30.7)	16 (18.2)
Serious adverse event*	0	0	2 (2.3)
Discontinued due to adverse event	2 (4.9)	4 (4.5)	3 (3.4)
Most common adverse events†			
Arthralgia	0	12 (13.6)	6 (6.8)
Headache	8 (19.5)	10 (11.4)	5 (5.7)
Myalgia	2 (4.9)	7 (8.0)	0
Patients n (%) reporting ≥1 adverse events of abnormal peripheral sensation			
Adverse events of abnormal peripheral sensation	1 (2.4)	11 (12.5)	3 (3.4)
Hyperesthesia	0	6 (6.8)	0
Paresthesia	0	4 (4.5)	1 (1.1)
Dysesthesia	0	2 (2.3)	0
Neuralgia	0	1 (1.1)	0
Peripheral neuropathy	0	1 (1.1)	0
Pallanesthesia	0	0	2 (2.3)
Hypoesthesia	1 (2.4)	0	0

*Non-treatment related

†Occurring in ≥8% of patients in any treatment group

Tanezumab vs. placebo: *P<0.05; **P<0.01; ***P<0.001. Tanezumab vs. naproxen: †P<0.05; ‡P<0.01. Naproxen vs. placebo: †P<0.05.

Source: Pfizer

GIP - Women's Health

Duavee (Aprela) An Option For Menopausal Symptoms And Osteoporosis

Duavee, formerly Aprela, is a tissue selective estrogen complex (conjugated estrogens/bazedoxifene) used to treat menopausal symptoms and osteoporosis. It was approved by the FDA on October 3, 2013 and launched in February 2014, with full promotional efforts rolled out in April. Pricing has not been disclosed but will likely be on par with other HRTs. Pfizer has a proprietary position on conjugated estrogens so a SERM/conjugated estrogen combination would be unique. Our physician consultants are mixed on the value offered by such a treatment regimen for either menopausal symptoms or osteoporosis prevention. Some cite that each agent may have competing functions at the same receptor. Others believe that the estrogen component should negate the adverse effects of the SERM. Wyeth claimed that Viviant's (bazedoxifene) tissue selectivity may provide some key advantages to the combination. Both principal doses studied in the trial (20mg BZA/0.625mg CE and 20mg BZA/0.45mg CE) provided efficacy for bone protection and relief of vasomotor symptoms. Data from the SMART-1 (a pivotal Phase III study) demonstrated both endometrial safety and efficacy. In a second trial presented at the 13th World Congress of Gynecological Endocrinology in Florence, Italy –SMART-4– endometrial safety was demonstrated at the lower dose, but there was a higher incidence of endometrial hyperplasia at the higher dose. Wyeth stated that this higher incidence likely resulted from the relatively low bioavailability of Viviant in one of the formulations used in the SMART-4 trial as compared to the formulation used in SMART-1. We forecast Duavee sales of \$15MM in 2014, \$90MM in 2015, \$150MM in 2016, \$250MM in 2018, and \$350MM in 2020.

Duavee Phase III Data Demonstrate Benefit

Phase III Duavee data were presented at NAMS, 2007. The VMS study evaluated 332 symptomatic postmenopausal women who, at baseline, experienced seven or more moderate to severe hot flashes per day or 50 or more hot flashes per week compared with placebo. Duavee significantly reduced the number and severity of hot flashes. Furthermore, the incidences of breast pain and bleeding were less than 5% and did not differ from placebo. The most commonly reported adverse events were headache and joint pain. Data from the Phase III study, which evaluated 601 postmenopausal women with moderate to severe vulvar and vaginal atrophy, demonstrated that Duavee improved symptoms of vulvar and vaginal atrophy, including dryness. Duavee improved vaginal lubrication, sexual function, and menopause-related quality of life, compared with placebo. The incidences of breast pain and bleeding were less than 5% and did not differ from placebo. There were no differences among groups in the incidences of adverse events and discontinuation rates.

Pfizer And GlaxoSmithKline HIV Joint Venture Delivering Tepid Results Thus Far

In November 2009, Pfizer and GlaxoSmithKline formed a JV focused solely on research, development, and commercialization of HIV medicines. The new company, called ViiV, has a product portfolio with 11 marketed products, including Combivir and Kivexa (GSK) and Selzentry/Celsentri (PFE). ViiV has a pipeline of six medicines, including four compounds in Phase II. ViiV contracts R&D and manufacturing services directly from GSK and Pfizer and entered into a new research alliance agreement with GSK and Pfizer. ViiV invests in Pfizer and GSK's programs for discovery research and development into HIV medicines. ViiV has exclusive rights of first negotiation in relation to any new HIV-related medicines developed by either GSK or Pfizer. Pfizer initially held a 15% equity interest in the new company, and GSK an 85% equity interest. The equity interests are adjusted in the event that specified sales and regulatory milestones are achieved. Pfizer's equity interest in the new company is approximately 13.5%, and GSK's equity interest in the new company is approximately 76.5%. In November, ViiV Healthcare acquired the exclusive global rights to the Shionogi integrase portfolio through an equity transaction by which Shionogi became a 10% shareholder in ViiV. Each company may also be entitled to preferential dividend payments to the extent that specific sales thresholds are met in respect of the marketed products and pipeline assets originally contributed. Pfizer accounts for its share of ViiV as an equity method investment. We estimate sales of the JV to be £1,265MM (+10%) in 2014, £1,415MM in 2015, £1,685MM in 2016, £2,230MM in 2018, and £2,825MM in 2020. We estimate profits to Pfizer to be \$100MM in 2014, \$113MM in 2015, \$136MM in 2016, \$188MM in 2018, and \$252MM in 2020.

VOC - Oncology

Palbociclib May Have Blockbuster Potential, Although Approval May Still Require Phase III Data

Our physician experts are excited about Pfizer's CDK4/6 inhibitor palbociclib (PD-0332991). However, initial enthusiasm over Phase II results in 1st line ER+/HER2- breast cancer (which represent 55–60% of all breast cancer) was somewhat tempered as full data showed less robust, although still strong, PFS compared to earlier interim looks. As such, it seems less likely that palbociclib will be approved based on the Phase II and that Phase III data will be needed. On August 18, 2014, Pfizer announced that it had completed the submission to the FDA based on the Phase II data (the FDA has 60 days to accept the filing). We estimate palbociclib sales of \$250MM in 2016, \$500MM in 2017, \$1B in 2018, and \$3B in 2020.

PALOMA-1 Full Data In-Line To Disappointing

In February 2014, Pfizer provided its final assessment of primary endpoint data from the Phase II PALOMA-1 trial, previously presented as interim data at IMPAKT in May 2012 and SABCS in December 2012. Number of months of PFS provided at the interim read-out was 26.1 for the palbo arm vs. 7.5 for non-palbo. The number of months of PFS at the final assessment was not provided, only that it was statistically significant and met the primary endpoint.

At AACR (April 2014), PFE presented full PALOMA-1 data. The data was roughly in line with our expectations in that we expected statistically significant PFS, viewed OS as a long shot, and did not expect safety to be a significant risk. The combination of palbociclib plus letrozole showed a median PFS of 20.2 month compared to 10.2 months for letrozole alone ($HR=0.488$; $p=0.0004$). However, this benefit tempered substantially from that at the last interim look, where the combination of palbociclib plus letrozole showed a median PFS of 26.1 month compared to 7.5 months for letrozole. A median OS of 37.5 months was observed in the palbo + letrozole arm versus 33.3 months in the letrozole alone arm, a difference of 4.2 months ($HR = 0.813$). This outcome was not statistically significant.

Our physician experts view the PFS data as less dramatic than expected, although still very much positive. For overall survival, they expected there would be a trend that was not statistically significant. However, the survival data are less favorable than anticipated.

Pfizer believes there is a path forward to approval, given the compelling PFS data generated, and that all drugs in this setting have been approved on PFS data. While PFE has interim looks built into its Phase III studies of palbo, PFE stressed that these studies are designed to run to completion, so it does not appear that the filing of palbo could be supplemented by interim looks at Phase III. However, given the narrowing of PFS benefit in the final data, and a lukewarm appraisal by the discussant at the conference, it would appear less likely that palbo will be approved on Phase II data.

Phase III Trials Ongoing With Expanded Access Added

Two Phase III studies are in progress: PALOMA-2 is similar to the PALOMA-1 and evaluates palbociclib + letrozole vs. letrozole + placebo as 1st-line treatment in post-menopausal ER+/HER2- advanced breast cancer patients ($n=450$); PALOMA-3 is in HR+/HER2- patients with metastatic breast cancer that has progressed after endocrine therapy and compares fulvestrant plus palbo to fulvestrant plus placebo. In August 2014, Pfizer announced that recruitment was complete in both trials and that an open-label, expanded access program (EAP) was initiated, enabling additional eligible women (with HR+, HER2- advanced breast cancer) access to the treatment. The Phase III trials are expected to be complete in December 2015.

Pfizer is also enrolling patients in another Phase III trial (PENELOPE-B) that evaluates palbo plus standard endocrine therapy vs. standard endocrine therapy plus placebo in early-stage HR+/HER2- patients who also are deemed at risk for recurrence post pre-op chemo and surgery.)

Sutent Is First-Line Agent Of Choice For mRCC But Having A Tough Time Showing A Benefit In Other Indications

Sutent (sunitinib), an oral tyrosine kinase inhibitor that inhibits signaling through platelet-derived growth factor receptor (PDGFR), KIT, FLT3, and VEGFR, is indicated

for the treatment of advanced renal cell carcinoma (RCC) and GI stromal tumors in patients intolerant of, or refractory to, Gleevec. Sutent has been launched in all major markets including Japan. Our consultants have a clear preference for Sutent as their first-line agent for mRCC. They use Sutent in 75-80% of their first-line Stage III/IV renal patients, and reserve Bayer's Nexavar for the 20% of patients that have the best prognosis. Most physicians believe that the data clearly suggest that Sutent is the more potent agent. Moreover, the physicians believe that while Nexavar prevents further tumor growth, it is not a cytoreductant (does not cause tumor shrinkage), while Sutent is capable of shrinking tumors. Since the sheer tumor burden of metastases at certain sites can cause severe morbidities, for example in bone where marrow destruction leads to low blood hemoglobin levels, Sutent is their preferred agent when tumor burden has led to poor prognostic indicators, and when a reduction in tumor mass would be beneficial. Sutent has not been negatively impacted by Novartis' Afinitor which is approved in second-line mRCC, but this could change if physicians begin to use Afinitor upstream. GSK's Votrient has not negatively impacted Sutent but may ultimately become a solid competitor. Sutent has failed to show a benefit in several other tumor types including breast, colon, liver, and advanced prostate cancer. We estimate sales for Sutent at \$1.185B (-2%) in 2014, \$1.265B in 2015, \$1.36B in 2016, \$1.53B in 2018, and \$1.7B in 2020.

Sutent Approved For PNET...

Pfizer submitted a NDA for Sutent for the treatment of unresectable pancreatic neuroendocrine tumors (PNET) in December 2009 based on positive PFS data from the Phase III A6181111 trial comparing Sutent to placebo in 171 subjects with locally advanced or metastatic well-differentiated PNET. In December 2010 FDA issued a complete response letter citing concerns that the study was terminated for efficacy after only 31% of planned PFS events. Additionally, FDA stated concerns regarding unbinding during the trial and the implications on the magnitude of effect on PFS. Given these concerns, FDA requested: (1) a *post-hoc* blinded independent central radiologic review of PFS events for all 171 subjects enrolled in the Phase III trial, and (2) a recalculation of investigator determined PFS applying strict RECIST criteria and appropriate censoring for missing data.

Reanalysis of PFS rates by a blinded independent central radiologic board applying strict RECIST criteria to the data yielded similar results.

Sutent PFS Data – Independent Reanalysis

PFS Analysis Group	Number of Events	Number Censored	Difference in Median PFS	HR
Investigator (PFE)	81	90	5.9 months	0.42
Central Radiology	61	110	6.8 months	0.32
FDA	82	89	4.8 months	0.43

Source: FDA briefing documents

Source: FDA briefing documents

While the study was not powered to demonstrate OS and low event rates and high cross-over make OS data difficult to interpret, Sutent demonstrated an OS benefit in the 171 patients examined (HR 0.735, 95% CI 0.465-1.168). Patients did not report improvement on a symptoms questionnaire and experienced a worsening in diarrhea on Sutent. In December 2010, Sutent received European approval for treatment of

progressive pancreatic NET. In April 2011, ODAC voted 8-2 in favor of approval of Sutent and FDA approved the pNET indication in May 2011.

...But Sutent Discontinued In mHCC...

In April 2010, Pfizer announced the discontinuation of the SUN 1170 Phase III open-label study of Sutent in advanced hepatocellular carcinoma. Following a review by the independent Data Monitoring Committee (DMC), the study was discontinued based on a higher incidence of serious adverse events in the Sutent arm compared to the Nexavar arm and the fact that Sutent did not meet the criteria to demonstrate that it was either superior or non-inferior to Nexavar in the survival of patients with advanced hepatocellular cancer. At ASCO 2011, Pfizer presented data from a Phase III open-label trial comparing the safety and efficacy of Sutent to sorafenib in advanced hepatocellular carcinoma. Sutent failed to meet its primary OS endpoint, and PFS and TTP were similar between Sutent and sorafenib. In a Hep-B patient subgroup, no significant difference in OS was detected between groups and sunitinib was associated with more frequent toxicities.

...And In Breast Cancer...

In June 2009, Pfizer announced that it was discontinuing the SUN1094 trial of Sutent plus paclitaxel in advanced breast cancer as the DMC found that the combination would be unable to meet the primary endpoint of superior PFS compared to Avastin and paclitaxel. Enrollment in the Phase III study (SUN1107) with Sutent versus Xeloda in taxane and anthracycline failures was discontinued based on a statistical assessment for futility. The independent Data Monitoring Committee found that the trial would be unable to demonstrate a statistically significant improvement in the primary endpoint of progression-free survival. In March 2010, Pfizer announced that two Phase III studies of Sutent in advanced breast cancer did not meet their primary endpoints. The SUN 1064 Phase III study of Sutent + docetaxel for the first-line treatment of patients with advanced HER-2 negative breast cancer did not show a statistically significant improvement in progression-free survival compared with docetaxel alone. In addition, the SUN 1099 Phase III study of Sutent + Xeloda, in previously treated advanced breast cancer patients, did not show a statistically significant improvement in progression-free survival compared with Xeloda alone.

...And In mCRC

In June 2009, Pfizer announced that it was discontinuing the SUN 1122 Phase III in 1st line mCRC as the DMC found that the addition of sunitinib to the chemotherapy regimen FOLFIRI would be unable to demonstrate a statistically significant improvement in the primary endpoint of progression-free survival (PFS) compared to FOLFIRI alone.

Sutent Failed In NSCLC...

In August 2010, Pfizer announced that the SUN 1087 trial of Sutent (sunitinib) in combination with Roche/OSI's Tarceva (erlotinib) versus erlotinib demonstrated a statistically significant improvement in Progression-Free but not in Overall Survival in patients with previously treated advanced non-small cell lung cancer (NSCLC). Overall survival was the primary endpoint of the study and Progression-Free Survival was a secondary endpoint of the study. No new or unexpected types of adverse events were observed in the study.

...And Discontinued In HRPCA

In September 2010, Pfizer announced the discontinuation of the SUN 1120 Phase III trial evaluating Sutent in combination with prednisone for men with advanced

castration-resistant prostate cancer that had progressed despite treatment with docetaxel. During a scheduled interim analysis, DMC found that the combination of sunitinib with prednisone was unlikely to improve overall survival when compared to prednisone alone. No new or unexpected safety issues were identified.

Phase III Data Solidify Sutent's Position As A Preferred First-Line Agent For mRCC

The Phase III trial enrolled 750 patients with untreated clear-cell metastatic renal cell cancer. Patients were randomized to receive either Sutent (50mg orally once per day for four weeks, followed by two weeks off, every six weeks) or alpha-interferon (9MU via subcutaneous injection three times per week). The primary endpoint of the trial was progression-free survival, and secondary endpoints included response, survival, and safety. In the trial's primary endpoint, Sutent produced a median progression-free survival of 11 months, versus progression-free survival of five months for IFN, $p<0.000001$. The hazard ratio for progression was 0.415 in favor of Sutent. By independent review, and according to RECIST criteria, Sutent produced a 31% partial response rate, versus a 6% partial response rate for alpha-interferon, $p<0.00001$. Median overall survival had not been reached in the trial, as there had been only 114 "survival events." Nonetheless, the survival hazard ratio was 0.65 in favor of Sutent ($p=0.0219$). While this did not meet the prespecified criteria for statistical significance, it was a strong trend.

Sutent's toxicity is manageable. More patients withdrew from the study in the interferon arm (13%) than the Sutent arm (8%) for an adverse event. The major laboratory abnormality was neutropenia (12% of Sutent patients vs. 7% of interferon patients had grade 3/4 neutropenia). Fatigue, a side effect that has been associated with Sutent in the past, was lower in the Sutent arm (7% grade 3/4 vs. 11% for Interferon). Grade 3/4 diarrhea was modestly higher in the Sutent arm (5%) than the interferon arm (0%).

Two-Year Survival Analysis Misses P-Value But Unlikely To Change Use

The final survival analysis was presented at ASCO 2008. The results demonstrated a median overall survival of 26.4 months for patients in the Sutent group, compared to 21.8 months in those patients taking IFN- α ($p=0.051$, Log-rank). The median overall survival for patients who did not crossover from IFN- α to Sutent was 26.4 months with Sutent, versus 20 months with IFN- α ($p=0.0362$, Log-rank). The median overall survival for patients who received protocol therapy only, and no subsequent therapies, was 28.1 months with Sutent versus 14.1 months with IFN- α ($p=0.0033$, Log-rank). Sutent was associated with a significant improvement in objective response rate (ORR), a measurable response in tumor size, compared with IFN- α (47% vs. 12%). Our consultants do not believe that these data will change their use of Sutent as a first-line therapy, and suggest the data are largely of academic interest.

Sutent Final Survival Analysis

	Pre-Specified Analyses		Exploratory Analyses
	Unstratified	Stratified	Crossover pts. censored
Median OS (mos.)	26.4 vs. 21.8	26.4 vs. 21.8	26.4 vs. 20.0
HR (95% CI)	0.821 (0.673, 1.001)	0.818 (0.669, 0.999)	0.808 (0.661, 0.987)
P-value (Log-rank)	0.0510	0.0491	0.0362
P-value (Wilcoxon)	0.0128	0.0132	0.0081

Source: Pfizer, ASCO 2008

Xalkori Approved In NSCLC; ALK Testing Catching Fire

In August 2011, FDA gave accelerated approved to Xalkori (crizotinib) for the treatment of ALK-positive NSCLC. Regular approval was gained in 2013 based on the Phase III PROFILE 1007 study. Results from the Phase III PROFILE 1014 were reported in March 2014 demonstrating that Xalkori significantly improved PFS in treatment-naïve advanced NSCLC compared to platinum based chemotherapy. Xalkori is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer that is ALK+ as detected by an FDA-approved test. Xalkori is a first-in-class, selective, ATP-competitive small molecule dual inhibitor of mesenchymal epithelial transition growth factor (c-Met or hepatocyte growth factor) and ALK tyrosine kinases. Both are implicated in the progression of several cancers, including NSCLC. A subset of NSCLC patients have been identified whose tumors carry a unique mutation in which the echinoderm microtubule-associated protein-like 4 (EML4) gene is fused to ALK, also known as an EML4-ALK translocation. This fusion/translocation has been reported in 2-4 percent of all NSCLC patients, with the incidence increasing to 4-8 percent among NSCLC patients with adenocarcinoma histology and those who have a never-to-light smoking history. Worldwide, it is estimated that approximately 45,000 newly diagnosed NSCLC patients per year are ALK positive. The label warns against pneumonitis, as severe/fatal, treatment-related pneumonitis has been observed with Xalkori. Additionally, concurrent elevations in ALK and total bilirubin have been observed, which warrant monthly liver function monitoring in all patients. Periodic monitoring is also recommended for patients with a history of QTc prolongation. The drug was approved in tandem with its companion diagnostic, a break-up FISH test, and is priced at \$9,600 per month.

Our consultants use Xalkori in virtually all identified ALK+ NSCLC patients as first line therapy. The physicians estimate that the average time to progression for ALK+ patients on Xalkori is about 9 months. The physicians may leave some ALK+ patients on Xalkori even after the initial progression. This is the case particularly if the initial progression is localized, for example to the CNS, as the physicians will treat the local progression with other modalities, and continue the Xalkori. Our consultants suggest that in such circumstances Xalkori can maintain control of the disease for 18 months – 2 years.

In June 2013, Germany's IQWiG revised its assessment on Xalkori to state that Xalkori showed a "hint of considerable added benefit in symptoms and in quality of life

compared to chemo". The prior preliminary assessment was that Xalkori showed "no additional benefit." We forecast Xalkori sales of \$450MM (+60%) in 2014, \$620MM in 2015, \$700MM in 2016, \$900MM in 2018, and \$1,100MM in 2020.

Pfizer And Merck To Evaluate Xalkori + Pembrolizumab In Lung

In August 2014, Pfizer entered into an agreement with Merck to evaluate Xalkori + pembrolizumab (PD-1) in a Phase Ib study in ALK+ advanced/metastatic NSCLC. The study, which will be conducted by Pfizer, is expected to start in 2015. Terms of the agreement were not provided.

This agreement adds to the existing plans to study Inlyta with pembrolizumab in RCC and pembrolizumab + IO agent PF-2566 (4-1BB) in multiple cancer types. These studies are expected to begin enrollment later in 2014.

Novel Companion Diagnostic A Recent Trend In Targeted Drug Therapy

The break-apart FISH diagnostic (ABT) provides a clinically validated FISH based assay for the detection of ALK-fusion events. Physicians have previously expressed concern with FISH based assays for detection of ALK+ NSCLC, stating that the amount of tissue required for the assay was often unobtainable after having surveyed for other more common mutations. Because the identification of EML4-ALK translocations is required for a patient to be eligible for Xalkori, tissue supply and/or a physician's willingness to re-biopsy a tumor could be barriers to adoption. However, our consultants suggest all NSCLC patients receive a test to determine ALK status, and that the results are typically available within about 2 weeks.

Targeted Approach Accelerated Approval

At ASCO 2010, Pfizer presented data from a Phase II study. Patients with NSCLC harboring an ALK fusion were recruited into an expanded cohort at the recommended Phase II dose within the first-in-patient monotherapy trial of PF-1066. Patients with ALK fusions, as determined by FISH using a break-apart probe to ALK, were enrolled into the expanded cohort irrespective of prior therapy. Treated brain metastases were allowed. Xalkori was given orally at a dose of 250 mg BID. Responses were determined using RECIST with radiographic studies repeated every 8 weeks. The disease control rate (DCR) was determined based on the frequency of patients with RECIST CR, PR and stable disease at 8 weeks. At the time of submission of the data, 76 ALK+ NSCLC patients had been treated. The median number of prior treatments was 3 (range, 0-7). Most patients had adenocarcinoma histology and were never or former smokers. Mean plasma Ctrough was 292 ng/mL, which was above the predicted efficacious concentration from preclinical models (120 ng/mL). The median t_{1/2} was ~53 hours. Fifty patients were evaluable for response; ORR is 64% and DCR 90%. The median progression-free survival was not yet mature. The median duration of treatment was 25.5+ weeks. Radiological responses typically were observed at the first or second restaging CT scan. Gastrointestinal toxicities, including nausea (55%) and vomiting (39%), were the most frequent adverse events.

At ASCO 2011, Phase I/II data was retrospectively compared to a group of ALK-positive Xalkori naïve controls. In this trial, ALK-positive, Xalkori-naïve patients experienced a trend towards lower survival compared to WT controls (ALK-positive 1-year survival, 44%; 2-year survival, 12%; OS of 6 months vs. WT 1-year survival, 47%; 2-year survival, 32%; OS of 11 months) with a hazard ratio of 1.42 (p=0.18). Xalkori (at maximum tolerated dose of 250mg BID) demonstrated a significant survival benefit when compared to ALK-positive Xalkori-naïve controls (Xalkori 1-year survival, 70%;

2-year survival, 55%; OS not yet reached vs. ALK-positive control 1-year survival, 44%, 2-year survival 12%; OS of 6 months) with a HR of 0.36 ($p=0.004$).

Inlyta Rolling Out For RCC

Inlyta (axitinib), a potent inhibitor of VEGF receptors 1, 2, and 3, was compared to sorafenib in second line therapy in 723 patients with mRCC who had progressed on either sunitinib, bevacizumab, temsirolimus, or a cytokine-based regimen in the Phase III AXIS trial. Patients were randomized to either axitinib (titrated to 10mg/kg BID) or sorafenib (400mg BID). The primary endpoint for the study was PFS as measured by independent radiographic review. In this study, axitinib demonstrated an overall PFS benefit compared to sorafenib (6.7 months for axitinib vs. 4.7 months for sorafenib, HR=0.665, $p<0.0001$). The PFS benefit for axitinib was maintained regardless of whether patients had been previously treated with cytokines or sunitinib. While several other therapies are available for mRCC, up to 33% of patients will experience a recurrence and global five-year survival rates for advanced disease remain near 20% with 13,000 deaths from mRCC anticipated in 2012. FDA approved Inlyta for use as second-line therapy in mRCC in January 2012. The EMA approved marketing authorization for Inlyta in September 2012. However, in December 2012, NICE issued draft guidance suggesting that Inlyta should not be recommended for the treatment of advanced renal cell cancer after failure of prior treatment with Sutent or a cytokine. We forecast Inlyta sales of \$420MM (+32%) in 2014, \$530MM in 2015, \$625MM in 2016, \$775MM in 2018, and \$925MM in 2020.

In Q1:2014, Pfizer announced a collaboration with Merck to combine its PD-1 antibody pembrolizumab with Inlyta. A Phase I/II study in RCC will be conducted. To date, there is no further collaboration in place post this study completion.

A Phase III head-to head superiority study vs. Nexavar as a second-line agent (Sutent failures) enrolled 540 patients with a primary endpoint of PFS and secondary endpoints of OS, CR, and safety. There were no significant difference in mortality between the two drugs, but Inlyta had fewer side effects compared to Nexavar. Inlyta's improved tolerability formed the basis for a positive IQWiG opinion in January 2013.

At ASCO 2012, Pfizer presented Phase II data for axitinib in the first-line setting for the treatment of mRCC. Patients with treatment naïve mRCC received axitinib 5mg BID for a 4-week lead-in period followed by randomization to two-doses of axitinib or placebo. As of July 1, 2011, the ORR rate was 40.2% (95% CI 31.0-49.9%). Median PFS was 13.7 months. Patients with drug exposure above therapeutic threshold had a longer mPFS and higher ORR than those with sub-therapeutic exposure. Increases in dBp >15mmHg were also associated with improved ORR.

In January 2009, Pfizer terminated a Phase III trial of Axitinib in pancreatic cancer after review of the interim data suggested it was unlikely that Axitinib would be superior to standard of care.

Bosulif (bosutinib) Approved As Salvage Therapy In CML

Bosulif (bosutinib), an orally bioavailable dual Src/Abl kinase inhibitor with minimal activity against PDGFR and c-Kit, is approved for the treatment of accelerated or blast phase Ph+ CML (approved 9/4/12) and is in Phase II for glioblastoma and polycystic kidney disease. It has demonstrated activity against most imatinib-resistant mutants of Bcr-Abl, with the exception of T315I and V299L. Data presented at EHA 2008 demonstrated that, in imatinib-resistant patients with chronic-phase CML,

hematologic complete response was observed in 47 of 59 (80%) patients. Overall, 40% of 77 patients had a major cytogenetic response, and 26% had a complete cytogenetic response. A major molecular response was observed in 20 of 57 (35%) patients and a complete molecular response was noted in 10 of 57 (18%) patients. Patients received bosutinib treatment for a mean duration of 6.54 months. Transient dose interruptions were required in 41% of patients, and 26% required permanent dose reductions. The most common any-grade adverse events were diarrhea (72%), nausea (40%), rash (36%), and vomiting (33%). Grade 3/4 adverse events were observed in less than 10% of patients for each adverse event. In chronic-phase patients, thrombocytopenia was reported by 19%, neutropenia by 10%, and anemia by 6%. In patients with more advanced disease (n = 98), the rates were 70% for thrombocytopenia, 49% for neutropenia, and 38% for anemia.

Data from the **Bosutinib Efficacy and safety in chronic myeloid LeukemiA** study (BELA) showed bosutinib missed the primary complete cytogenic response (CCyR) superiority endpoint when compared to imatinib/Gleevec (70% vs. 68%, p=0.601); however, those who responded to bosutinib achieved CCyR faster than those achieving CCyR on Gleevec (p<0.001). Bosutinib showed significant improvement over Gleevec with regard to major molecular response (MMR) (39% vs. 26%, p<0.002). Bosutinib patients experienced significantly more adverse side effects compared to those on Gleevec (25.4% vs. 13.5%) and were more likely to discontinue therapy as a result (19.4% vs. 5.6%).

Several other compounds for first-line and refractory treatment of CML appear to be superior to Gleevec, including Tasigna (NVS) and Sprycel (BMY). Both Tasigna and Sprycel have shown superior CCyRs compared to Gleevec and have equivalent to superior safety profiles. Positive PACE data for Ariad's panotanib in Tasigna/Sprycel failures likely will limit any opportunity for bosutinib in 3rd line. We estimate Bosulif sales of \$75MM in 2014, \$110MM in 2015, \$130MM in 2016, \$170MM in 2018, and \$210MM in 2020.

Torisel Failure In Second-Line mRCC Limits Potential

Torisel (CCI-779), a selective mTOR inhibitor, is indicated for advanced renal cell carcinoma (RCC) in the U.S. and in the E.U. Results presented at ASCO 2006 from a Phase III study in 662 severely refractory RCC patients demonstrated statistically significantly improved overall median survival with Torisel (10.9 months) vs. Torisel + alpha-interferon (8.4 months) or alpha interferon alone (7.2 months). Torisel also resulted in statistically superior progression-free survival vs. IFN alone. Rash, peripheral edema, hyperglycemia, and hyperlipidemia were more common in the Torisel group, whereas asthenia was more common in the interferon group. There were fewer patients with serious adverse events in the Torisel group than in the interferon group (P=0.02).

In May 2008, Wyeth announced the initiation of a Phase IIIb open-label study (INTORACT) comparing Torisel plus Avastin versus Avastin plus interferon in first-line treatment of advanced RCC. In Q1:09 Novartis' oral mTOR, Afinitor was approved in 2nd line metastatic renal cell carcinoma, a downstream approval to Torisel. Novartis does not intend to study Afinitor in first-line mRCC. Torisel has been studied in numerous other tumor types with clinical responses observed in glioblastoma (36% PR as a single agent).

In May 2012, Pfizer announced that the Phase III INTORSECT trial, evaluating Torisel in patients with advanced RCC whose disease had progressed on or after Sutent, did not

meet its primary PFS survival endpoint when compared to sorafenib. Overall survival, a secondary endpoint in the study, showed statistical significance favoring patients randomized to the sorafenib arm.

Results from a Phase III trial in relapsed and/or refractory mantle cell lymphoma (MCL) demonstrated a statistical significant improvement in median PFS compared to single agent therapy (4.8 months versus 1.9 months p=0.0009). There was a non-significant trend to overall survival. MCL accounts for 6% of non-Hodgkin's lymphoma cases. In August 2009, Pfizer won final E.U. approval to sell Torisel for patients with relapsed and refractory mantle cell lymphoma. Pfizer has not filed the mantle cell lymphoma claim in the U.S. The Phase III HORIZON breast cancer study of Femara +/- Torisel was stopped in March 2006 due to lack of efficacy. Pfizer will continue to pursue Torisel in RCC and has initiated several Phase I/II MCL studies. We forecast Torisel sales of \$135MM (+2%) in 2014, \$150MM in 2015, \$165MM in 2016, \$185MM in 2018, and \$205MM in 2020. Torisel's patent expires in October 2014 (includes a 6 month pedi extension) in the U.S. and will expire in April 2020 in the E.U.

Dacomitinib Misses Primary Endpoint In Two Phase III NSCLC Studies

Dacomitinib (PF-299804) is an oral irreversible small molecule inhibitor of the HER-1, -2, and -4 tyrosine kinases. In November 2008, a Phase II trial for HNC was initiated in Canada. In May 2010, a Phase I/II trial for mouth cancer also was initiated in Canada. Phase II data presented at ASCO 2009 and 2010 confirmed activity in second line NSCLC and in first line in patients with EGFR-mutant NSCLC, respectively. At ASCO 2011, dacomitinib demonstrated a PFS benefit in Phase II compared to erlotinib in 2nd/3rd line post-chemotherapy NSCLC. However, in January 2014, top-line data from two Phase III trials in previously treated patients with advanced NSCLC showed that dacomitinib missed its primary endpoint in both trials. In the BR.26 trial, with dacomitinib in patients with advanced NSCLC who have progressed on chemotherapy and EGFR therapy, the endpoint of improved OS vs. placebo was not met. In ARCHER 1009, dacomitinib was compared to erlotinib in 2nd or 3rd line previously treated NSCLC patients, and did not meet the endpoint of improved PFS.

There is an ongoing third Phase III trial, ARCHER 1050, which is evaluating dacomitinib vs. gefitinib in treatment-naïve patients with EGFR-mutant advanced NSCLC. Results are expected in 2015.

At ASCO 2012, Pfizer presented data for dacomitinib in the first-line setting in patients with stage IIIB/IV adenocarcinoma, no prior systemic therapy, had smoked <10 pack years, or had known EGFR mutations. Patients received dacomitinib orally once daily at 45mg or 30mg with the option to escalate to 45mg; evaluation was every 28 days. Endpoints included PFS rate at 4-months and partial response (PR) rate. Preliminary PFS at 4-months was 96% (95% CI 84-99%), preliminary PFS rate at 1 year was 77% (95% CI 61-87%), and preliminary median PFS was 17-months (95% CI 13-24 months). The most common adverse events were dermatitis acneiform (17%) and diarrhea (14%).

We estimate dacomitinib sales of \$25MM in 2017, \$50MM in 2018, and \$100MM in 2020.

Open-Label Phase II First Line Study In EGFR-Mutant Asian Patients Demonstrates Benefit

A Phase II open-label study in 1st line NSCLC patients was presented at ASCO 2010. The patient population with advanced NSCLC was molecularly selected or clinically

enriched for EGFR mutations. Patients with advanced adenocarcinoma of lung and no prior systemic therapy were eligible if they were non/light smokers or known to have EGFR mutations. Tissue was requested from all patients. Patients received PF299 45mg continuously once daily and were assessed every 28 days. The endpoints include: progression-free survival at 4 months (PFS4m; primary), tumor response, safety, serial pharmacokinetics, and tissue- and blood-based biomarkers, including T790M mu. The planned enrollment is ~80 patients, including more than 30 each of Asian and of non-Asian ethnicity. At the time of submission, 39 patients had enrolled (23 female; 23 Asian). Of 29 evaluable patients, 1 had a complete response, 6 a partial response, and 16 stable disease ≥ 6 weeks. Preliminary PFS rates at 3, 4, and 6 months were 90%, 79%, and 79%, respectively. Mutation status was obtained in 31/39 patients. All evaluable patients with known EGFR-mutant NSCLC (n = 14) showed tumor shrinkage. Common treatment-related adverse event (AEs) were diarrhea (79%; grade 3; 9%), dermatitis acneiform (49%; 9%), stomatitis (42%; 6%), acne (24%; 0%), rash (21%; 0%), and anorexia (18%; 0%). One patient discontinued due to an AE; 10 required dose reduction while remaining on study.

Second-Line Data Encouraging

Phase II data in patients with NSCLC (KRAS wild-type) who have progressive disease after at least one prior chemotherapy regimen and after Tykerb presented at ASCO 2009 demonstrated that, of 20 (of 34) response-evaluable patients, stable disease (SD) was observed in 9/18 patients in one arm and 1/2 patients in the second arm: median duration of SD: 11.5 weeks [range 6+, 32+ weeks]. The most common treatment-related adverse events were skin and gastrointestinal disorders, with grade 3 adverse events in 19% and 13% of patients, respectively. Two patients experienced grade 4 pulmonary embolus/dyspnea deemed possibly treatment-related, both in the setting of progressive disease.

Collaboration In CAR-T

In June 2014, Pfizer entered into a collaboration with Cellectis to develop Chimeric Antigen Receptor T-cell (CAR-T) immunotherapies. Pfizer will pay Cellectis \$80MM upfront and acquire 10% of Cellectis equity. Pfizer will also fund development costs for selected products, pay milestones of up to \$185MM per product, and royalties on future sales. Pfizer receives exclusive rights to 15 targets.

VOC - Vaccines

Prevnar-13 Meets CAPiTAL Endpoints, And Garners ACIP Recommendation In 65+

Pfizer's 13-valent pneumococcal vaccine (Prevnar-13) has replaced the 7-valent Prevnar vaccine and is poised to expand into the adult market, which alone has an estimated \$1B+ potential. Prevnar 13 was approved for adult use in both the U.S. and E.U. in late 2011, but has primarily been used in at-risk populations. In October 2013, the E.U. approved an expanded label for Prevnar 13 to include preterm infants, children with sickle cell disease, and adults with HIV. In Q2:14, Prevnar-13 was approved in Japan for adults 65 years and older. Positive CAPiTAL data were released in March 2014 demonstrating efficacy in adults. In August 2014, ACIP recommended that Prevnar-13 be given in addition to Merck's Pneumovax in adults 65yo+, although reimbursement issues and a re-look in 2018 (to assess disease prevalence, given the view that it may decline further due to herd immunity) may temper penetration. We estimate Prevnar-13 sales of \$4.255B (+9%) in 2014, \$4.745B in 2015, \$5.195B in 2016, \$6.035B in 2018, and \$7.06B in 2020.

CAPiTAT Study A Success

Full results of Prevnar-13's CAPiTAT study were presented in March 2014 at the International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD). CAPiTAT, a study of 84,496 subjects 65+ years, achieved its primary and both secondary outcomes.

- The primary outcome was to demonstrate efficacy against a first episode of vaccine-type community-acquired pneumonia (CAP). 49 patients in the treatment group met this endpoint vs. 90 in the control group (VE % reduction of 45.56%, p = 0.0006).
- One secondary outcome was efficacy against a first episode of non-bacteremic/non-invasive vaccine-type CAP. 33 patients in the treatment group met this endpoint vs. 60 in the control group (VE % reduction of 45%, p = 0.0067).
- The other was first episode of vaccine-type invasive pneumococcal disease (IPD). 7 patients in the treatment group met this endpoint vs. 28 in the control group (VE reduction of 75%, p = 0.0005).

These results were largely as expected, but were encouraging as all clinical endpoints were achieved, including efficacy against IPD which was considered a higher hurdle.

Our physician experts have long maintained that Prevnar-13 likely would be effective in people over 65 years of age but questioned whether the magnitude of the benefit would be important from the public health standpoint. The CAPiTAT data showed powerful statistical significance but the number of people who benefited was small relative to the overall population studied.

ACIP Recommends Prevnar-13 For 65yo +

At a special meeting in mid-August, ACIP voted to recommend the use of Prevnar-13 in the elderly. This special meeting was called as the committee believed that pneumonia-related illness in the elderly could be reduced near-term if the Prevnar-13 vaccine was recommended for the upcoming flu season. The committee voted 13-2 in favor of the following recommendation:

- For people 65yo and older with no prior pneumonia vaccine or unknown vaccine history: Prevnar13 followed by Pneumovax (PPSV23) 6-12 months later
- For people 65yo and older who have received prior Pneumovax vaccine: Prevnar13 at least 1 year after most recent Pneumovax
- Re-evaluate and revise recommendation in 2018

Concerns Raised, But Outweighed By Potential Near-Term Benefits

- **Reimbursement:** This was biggest issue discussed by committee; there is no current Medicare coverage for a second pneumonia vaccination; this would not impact Pneumovax-naïve patients for first dose; any change in Part B coverage for a second pneumonia vaccine dose would likely not be effective until January 2016.
- **Herd effect:** evaluating impact on children and adults very complicated; difficulty in assessing this was part of reason for re-look in 2018.

- **Co-administration with other vaccines:** influenza, TDap, Zostavax, other; no answer provided.
- **Intervals between vaccination:** committee felt these could be adjusted in final guideline – goal for meeting was recommendation proposal; intervals would be fine-tuned.
- **Pneumovax:** No direct comparison in CAPiTA study.

Comparison Of Pneumococcal Vaccines

	Prevnar	Synflorix	Prevnar 13
Company	Pfizer	Glaxo	Pfizer
Approved	WW	Ex-U.S.	WW
Serotypes			
4		1	1
6B		4	<u>3</u>
9V		5	4
14	6B		5
18C		7F	<u>6A</u>
19F		9V	6B
23F	14		7F
	18C		9V
	19F		14
	23F		18C
			<u>19A</u>
			19F
			23F
Carrier protein	CRM197	Non-typeable <i>H. influenza</i>	CRM 197

Bold = additional serotypes vs. Prevnar

Underlined= additional serotypes vs. Prevnar and Synflorix

Source: Company data

Prevnar-13 The Leader In Pediatric Pneumococcal Vaccines

Streptococcus pneumoniae is responsible for more than one million deaths in young children per year. Morbidity associated with *S. pneumonia* is typically manifested as otitis media, but less commonly can result in pneumonia, bacteremia and meningitis. Prevnar, the first generation, 7-valent pneumococcal vaccine, has been a significant success. It is approved in 98 countries worldwide, launched in 93, and is included in 39 national immunization programs (NIPs) with several in line to announce their intention to initiate NIPs.

Prevnar-13 includes six new serotypes (1, 3, 5, 6A, 7F, and 19A) in addition to the seven serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) in Prevnar. The inclusion of the 19A serotype in the U.S. is key. A study conducted by the CDC comparing pneumococcal serogroups and their clonal associates pre and post the introduction of Prevnar in the U.S. found that among children <5 years of age, the incidence of invasive disease due to non-Prevnar serogroups together with serogroup 19A increased ($P < 0.001$). Among the non-Prevnar serogroups, newly emerging clones were uncommon, and a significant expansion of already-established clones occurred for serotypes 3, 7F,

15BCF, 19A, 22F, 33F, and 38. In October 2008, data presented at ICAAC/IDSA demonstrated that Prevnar-13 offered broader coverage than Prevnar.

The U.S. pediatric approval is less critical from a competitive perspective where Prevnar-7 has a monopoly. Prevnar-13 has been approved for use in infants and young children in 62 countries, has launched in 33, and is on 14 pediatric national immunization programs. Further pediatric regulatory filings for Prevnar 13 are in advanced stages of review in various countries spanning six continents.

In March 2010 Pfizer signed a 10-year Provisional Supply Agreement to supply Prevnar 13 for infants and young children in the world's poorest countries under the terms of the Advance Market Commitment (AMC) pilot project against pneumococcal disease. The AMC is a novel public-private approach to public health funding designed to create a sustainable marketplace, ensure a stable supply of pneumococcal vaccines and stimulate the development and expansion of manufacturing capacity of vaccines specifically for the world's poorest countries. Under the terms of the agreement, the price of the pneumococcal conjugate vaccine under the AMC framework is \$7.00 for the first several years. The vaccine price includes a \$3.50 subsidy to be paid by the AMC donor fund, and \$3.50 to be paid by GAVI with a co-financing contribution paid by the developing country governments that introduce the vaccine. Under the current AMC framework, participating vaccine manufacturers must make a binding commitment to supply vaccine for 10 years at a maximum "tail" price of \$3.50 per dose to meet long-term demand and ensure affordability of the vaccine in developing countries even after the donor contributions are exhausted. Pfizer is now committed to supply up to a total of 480MM doses of Prevnar 13 through 2023.

Meningococcal B Vaccine U.S. Filing Accepted

In June 2014, Pfizer filed a BLA for its recombinant meningococcal B vaccine LP2086; the filing was accepted in August and has Priority Review with a PDUFA date of February 14, 2015. The vaccine received Breakthrough Therapy designation in March 2014 and positive Phase II data from two studies in adolescents 11-18 years old was reported in May. In one study, a 2-dose vs 3-dose regimen was evaluated with the 2-dose regimen reporting immunological protection in 69-100% of patients and 86-99% in the three dose regimen. In the other Phase II study, LP2086 was co-administered with dTaP-IPV vaccine; immunological responses were similar suggesting the vaccines could be administered at the same time. The most common side effects on both trials were mild-to-moderate injection site pain, headache and fatigue. A Phase III study began in November 2012. The Phase II/III trials include over 20,000 adolescents with approximately 14,000 receiving the vaccine. Pfizer indicates there are 500,000 cases of meningococcal disease WW each year with 20,000-80,000 cases caused by serotype B; 10-15% of these patients die and 11-19% survive with long-term disabilities. We estimate LP2086 sales of \$150MM in 2015, \$250MM in 2016, \$450MM in 2018, and \$650MM in 2020.

Acquisition Of Baxter Vaccines Broadens Portfolio

In July 2014, Pfizer announced the acquisition of Baxter's vaccine business, including part of a manufacturing facility in Austria, for \$635MM (roughly 2.2x sales). The transaction is expected to close by year end. Pfizer does not expect any impact on its 2014 earnings guidance.

Included in the vaccine portfolio is: NeisVac-C, a single-valent group C meningococcal meningitis vaccine; FSME-IMMUN/TicoVac, an inactivated, purified

whole virus tick-borne encephalitis (TBE) vaccine; Preflucel, a cell-based seasonal influenza vaccine, which had been clipped by competition over the last few years; and Celvapan, a cell-based H1N1 influenza vaccine which sold well during the 2010 H1N1 pandemic, but had fallen off in sales since then. Baxter anticipated total WW Vaccine revenues of approximately \$300M in 2014.

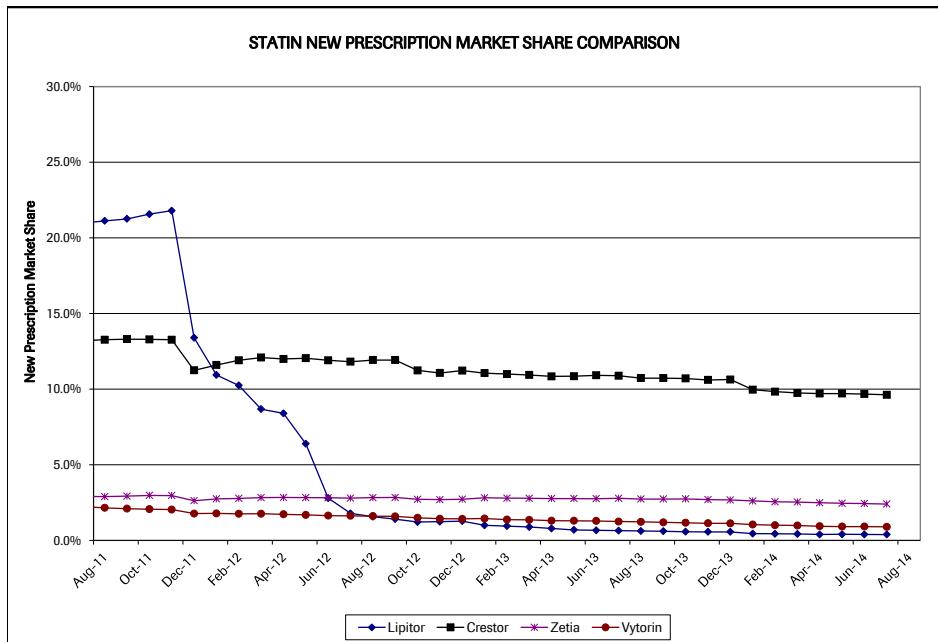
GEP – Cardiovascular

Lipitor Multisource Generics Annualized

Lipitor's worldwide patent expirations began in mid-2011 and have led to a substantial Lipitor sales decline. Multiple companies launched generic Lipitor in May 2012. Pfizer granted Watson the exclusive right to sell the authorized generic version of Lipitor in the U.S. for a period of five years, which commenced in November 2011. However, Watson discontinued the marketing of the AG in January 2013 due to extensive multisource generic competition.

Pfizer does not expect Lipitor revenue in emerging markets to be materially impacted by loss of exclusivity over the next several years. In 2013, emerging market Lipitor revenue was \$1,054MM (+19%). We estimate Lipitor global sales of \$1.925B (-17%) in 2014, \$1.715B in 2015, \$1.7B in 2016, \$1.625B in 2018, and \$1.705B in 2020. Our Lipitor U.S. sales forecasts are \$245MM (-43%) in 2014, \$150MM in 2015, and \$5MM in 2020.

STATIN NEW PRESCRIPTION MARKET SHARE COMPARISON



Source: IMS America

GEP - CNS

Pristiq For MDD A Moderate Contributor

The follow-on compound to Effexor, Pristiq (desvenlafaxine succinate), is marketed for the treatment of major depressive disorder (MDD) in the U.S. In February 2012, Pfizer

discontinued the development of Pristiq for vasomotor symptoms after receiving a CRL from FDA. The MDD label is surprisingly clean, featuring an indication similar to that of Effexor XR and no significantly concerning side effect language. FDA approval was subject to several post-marketing trials including conducting and submitting data from a new long-term maintenance (relapse prevention) study, a sexual dysfunction study, pediatric studies and a study exploring lower doses. FDA also requested an additional non-clinical toxicity study. In January 2013, Pfizer announced top-line results from a Phase VI study supporting the labeling and use of Pristiq 50-100mg/day in MDD. Wyeth launched Pristiq mid-May 2008 at a modest discount to Effexor XR, and subsequently increased Effexor XR's price. Despite what appears to be a solid label, Pristiq still faces commercial risks. In May 2014, Pristiq garnered a 0.9% share of the antidepressant NRx market (-12% Y/Y). Our physician experts do not believe it is distinguished from Effexor and do not prescribe it. Furthermore, Effexor XR generics represent a challenge to Pristiq. In October 2008, Wyeth withdrew its central European Marketing Authorization Application (MAA) for Pristiq for MDD in adults, and has chosen not to pursue the indication. We project Pristiq sales of \$755MM (+8%) in 2014, \$820MM in 2015, \$890MM in 2016, \$1.03B in 2018, and \$1.175B in 2020.

Pristiq Patent Interference Proceeding Settled; Several Claims Revoked

In November 2008, the USPTO declared an interference between Wyeth U.S. Patent No. 7,291,347 (the '347 patent) and a patent application owned by Sepracor. The '347 patent, one of the patents listed in the Orange Book for Pristiq, relates to oral dosage forms containing the active ingredient in Pristiq (O-desmethylvenlafaxine succinate). In February 2009, the PTO declared two additional interferences: the first between Sepracor patent application No. 10/720,134 and Wyeth U.S. Patent No. 6,673,838 B2 (the '838 patent), and the second between Sepracor patent application No. 11/091,518 and the '838 patent. The '838 patent relates to the active ingredient in Pristiq (O-desmethylvenlafaxine succinate) and is also listed in the Orange Book for Pristiq. The hearing at the U.S. PTO took place January 11, 2010. In May 2010, the PTO Board ruled in favor of Wyeth. The Board awarded priority to Sepracor because its constructive reduction to practice predated Wyeth's earliest asserted dates of conception and reduction to practice; however, the Board entered judgment for Wyeth because of a settlement agreement between the parties in which Wyeth becomes owner of the Sepracor involved applications. At the same time, the Board ruled that claims 1-3, 23-34, and 46 of the '838 patent and claims 1-9 of the '347 patent were invalid as a result of additional evaluation.

Aricept Decline Continues Post Patent Expiration

Pfizer/Eisai launched Aricept (donepezil 5 mg and 10 mg) in the U.S. in 1997. In July 2010, the FDA approved a higher-dose (23mg) once-daily tablet formulation of Aricept for the treatment of moderate-to-severe AD. The 23mg tablet has 3 years of data exclusivity in the U.S. The Aricept 23mg QD tablet was approved based on a head-to-head pivotal study of Aricept 23mg versus Aricept 10mg in 1,400 patients with moderate-to-severe AD. Aricept 23mg demonstrated a statistically significant improvement over Aricept 10mg on the Severe Impairment Battery (SIB) cognition endpoint in the study, but did not achieve a statistically significant improvement on the CIBIC+ global function endpoint compared to Aricept 10mg. The most common adverse events in the study were similar to those previously reported for Aricept and included nausea, vomiting, diarrhea, and anorexia. We believe that Aricept will continue to be the acetylcholinesterase inhibitor of choice to treat AD, although its modest efficacy has prompted clinicians to try competitive acetylcholinesterase inhibitors.

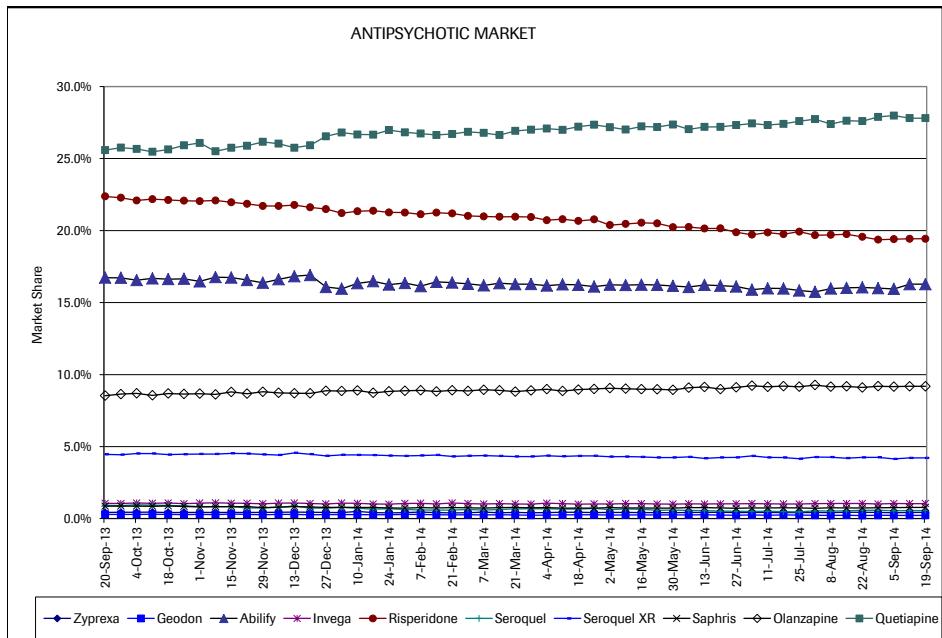
Eisai co-promotes Aricept in the U.S., Western Europe, and Japan. Eisai books 100% of the sales from these regions and pays Pfizer an undisclosed portion of the net profits. Pfizer promotes Aricept in other regions of the world and books 100% of sales from those regions. In September 2009, the companies announced that they had resolved a dispute initiated by Eisai as a result of the Pfizer-Wyeth merger. The companies agreed to continue marketing together in the U.S. and select E.U. markets, while Pfizer will have exclusive rights where it currently markets the drug until 2022. These rights are, however, with the exception of Japan where the rights to Aricept were returned to Eisai in December 2012.

Ranbaxy (first to file) launched generic Aricept in November 2010 with 180-day exclusivity. We forecast Pfizer's profit share of the Aricept JV to be \$50MM in 2014, \$25MM in 2016 and \$0 in 2018. In regions where Pfizer promotes Aricept directly, we forecast sales of \$150MM (-36%) in 2014, \$130MM in 2015, \$105MM in 2016, \$70MM in 2018 and \$50MM in 2020.

Geodon Sales Rapidly Eroding Post Patent Expiration

Geodon is indicated for schizophrenia, acute agitation associated with schizophrenia, bipolar mania, mixed and manic episodes of bipolar disorder, and adjunctive maintenance treatment of bipolar disorder in adults. Geodon's prescription share has eroded significantly since its March 2012 patent expiration. Geodon did not garner pediatric exclusivity, given that pediatric studies were not conducted in a manner consistent with good scientific practices. We estimate Geodon sales of \$150MM (-23%) in 2014, \$155MM in 2015, \$155MM in 2016, \$180MM in 2018 and \$210MM in 2020.

Antipsychotic Market



Source: IMS

GEP – Arthritis

Significant Celebrex Decline Forecast To Begin In 2015

Celebrex's substance patent expired 5/30/2014. In March 2014, the U.S. District Court for the Eastern District of Virginia invalidated the reissue patent covering methods of treating osteoarthritis with Celebrex. The reissue patent expires in December 2015. Pfizer has appealed, but since April, has settled with Teva, Watson/Actavis, and Mylan allowing a December 2014 launch. We forecast a 4% decline in sales in 2014 with at least one generic expected on the market in December 2014. We forecast Celebrex sales of \$2.835B (-3%) in 2014, \$1.3B in 2015, \$1.005B in 2016, \$945MM in 2018 and \$895MM in 2020.

Celebrex Patent Background

After appealing a March 2007 patent challenge, in March 2008, a panel of the Federal Circuit held that the two main Celebrex patents were valid, enforceable, and infringed, but ruled that the secondary patent was invalid. The decision prohibited Teva from marketing its 100, 200, and 400 mg generic celecoxib products before May 2014. Pfizer and Teva requested a panel rehearing and an en banc rehearing by the entire Federal Circuit. In May 2008, the Appeals Court refused to rehear the case. Separately, in April 2008, Teva notified Pfizer that it had filed an amendment to its abbreviated new drug application with the FDA with respect to the 50 mg dose of Celebrex, challenging Pfizer's secondary patent for Celebrex covering use in the treatment of inflammation and seeking to market a 50 mg product containing celecoxib upon the expiration of Pfizer's two main patents in May 2014. Pfizer's action against Teva discussed above involves the 100, 200, and 400 mg doses. In March 2008, Mylan notified Pfizer that it had filed an ANDA with the FDA challenging its secondary patent for Celebrex covering use in the treatment of inflammation and seeking to market a product containing celecoxib upon the expiration of Pfizer's two main patents in May 2014.

In March 2013, Pfizer announced that the USPTO granted a reissue patent (RE44048) covering the methods of treating osteoarthritis and other approved indications for Celebrex. The reissue patent will expire on 12/2/15, which includes 6-months of pediatric exclusivity. Pfizer subsequently filed suit against Teva, Mylan, Watson, Lupin, and Apotex in the U.S. District Court for the Eastern District of Virginia for the infringement of the reissue patent.

Outside the U.S., the Federal Court of Appeal of Canada reversed a lower court ruling that would have permitted Novopharm to launch a Celebrex generic. Celebrex's Canadian and EU composition-of-matter patent expires in November 2014.

Other Indications Under Evaluation

A Phase III trial in acute gouty arthritis has been completed, but Pfizer is not pursuing this indication. In chronic pain, three large studies continue. The 4,400-patient CONDOR (Celecoxib versus Omeprazole aNd Diclofenac for at-risk Osteoarthritis and Rheumatoid arthritis patients) study was initiated in 2006 and is now complete. A 20,000-patient study (PRECISION) is under way to demonstrate Celebrex's relative safety in high-risk heart disease patients versus ibuprofen and naproxen, and is scheduled to report in September, 2015. SCOTSSS (Standard Care versus Celecoxib Outcome Trial) is a 16,000-patient study comparing Celebrex to NSAIDs assessing cardiovascular and gastrointestinal safety. The trial is event-driven and not yet complete.

Dynastat Sold In Many Offshore Markets

Dynastat (parecoxib) is currently marketed in 35 countries outside the U.S., with a label that includes a warning against use post CABG surgery. Pfizer filed parecoxib, an injectable pro-drug formulation of Bextra, for use in treating pain associated with general surgery in the U.S. in December 2004. In September 2005, Pfizer received a non-approvable letter for parecoxib in this indication. This likely stemmed from questions raised by two post-CABG studies which showed elevated cardiovascular risk with parecoxib as well as broad safety concerns with the Cox-2 inhibitor class. We forecast Dynastat sales of \$145MM (+12%) in 2014, \$150MM in 2015, \$160MM in 2016, \$180MM in 2018 and \$200MM in 2020.

GEP – Respiratory

Spiriva Dominates COPD Market But Pfizer's Participation Declines Through 2016

The Pfizer/BI co-promotion of Spiriva in the E.U. ended in 2013, and will terminate in the U.S./Japan in 2014, and in several smaller markets in 2016. We estimate Spiriva revenue on which Pfizer books alliance revenue of \$650MM in 2014, \$500MM in 2015, and \$250MM in 2016. While Pfizer's co-promotion expires in 2012-16, Spiriva is covered by a broad portfolio of formidable patents extending to 2027.

Spiriva, an anticholinergic agent similar to Atrovent (ipratropium) and Combivent (ipratropium plus albuterol), claimed 72.9% prescription share of the anticholinergic market in May 2014, with NRxs up 2% Y/Y. Spiriva is available in most major WW markets. Spiriva's advantage over Atrovent and Combivent is once-daily dosing, while Atrovent and Combivent are dosed 4+ times per day. In May 2008, FDA announced that it was investigating a possible increased incidence of stroke in patients taking Spiriva using the Handihaler device. The UPLIFT data presented at ERS 2008 confirmed that there is no increased risk of stroke in patients taking Spiriva although UPLIFT missed its efficacy endpoint. In December 2009, FDA approved Spiriva for the reduction of exacerbations in COPD. Spiriva is the first steroid-free regimen to achieve such a claim.

In November 2007, Pfizer received E.U. approval for the Respimat device and submitted it for approval to FDA. However, in September 2008, FDA issued a complete response letter for the Respimat submission, seeking additional data. A 17,000+ patient clinical trial to define the safety profile of Respimat reported results in August 2013 and demonstrated Respimat (with Spiriva) to be as safe and effective as the older HandiHaler device (with Spiriva). The risks of death and disease worsening were similar for both inhalers. The study evaluated the inhalers in COPD patients and followed usage for an average of 2.3 years. In clinical studies comparing inhaler devices, patients preferred Respimat. The dose-delivery system of Respimat is unlike dry powder inhalers, where the dose delivered is not dependent on patient's inspiratory flow. However, Respimat is still a single-dose device which is less convenient than Advair's multi-dose inhalers.

In May 2012, Pfizer presented data from a Phase II study of Spiriva in adolescents with symptomatic, moderate persistent asthma. When added to standard of care, Spiriva doses between 1.25ug and 5ug increased lung function parameters (FEV1, FEV1 AUC, and trough FEV1) compared to placebo. Statistically significant improvements were only observed at the 5ug dose. A comprehensive confirmatory Phase III trial (UniTinA-asthma) is ongoing to fully evaluate the potential of Spiriva in the treatment of asthma.

GEP - Infectious Disease

Tygacil Making Inroads Despite Delays In New Indications

Tygacil (tigecycline), a modified tetracycline antibiotic, is approved for the treatment of complicated skin infections and intra-abdominal infections in 100+ countries, and is on over 90% of U.S. hospital formularies. Supply constraints clipped Tygacil's ex-U.S. launch. Tygacil is administered via intravenous infusion twice daily and has a broad spectrum covering gram-positive and -negative infections including MRSA, anaerobes, and atypical infections. The most common side effects are nausea and vomiting. Tygacil has failed to garner additional indications beyond complicated skin and skin structure infections (cSSSI) and complicated intra-abdominal infections (CAI). In April 2008, Wyeth withdrew its regulatory filing in the E.U. for community acquired pneumonia (CAP) based on the opinion of the CHMP that its clinical data were not sufficient to support a positive risk-benefit balance. In response to the CHMP's opinion, Wyeth commenced a Phase II study in HAP in Q4:08 that has been subsequently suspended. In March 2009, FDA finally approved the sNDA for CAP and also approved the addition of pathogens to the cSSSI claim. In July 2009, Wyeth announced that it was discontinuing the development of Tygacil in diabetic foot after the Phase III study failed to meet the primary efficacy endpoints. In September 2013, FDA issued a new box warning discussing increased risk of death with IV Tygacil. Tygacil sales are estimated to be \$350MM (-2%) in 2014, \$380MM in 2015, \$405MM in 2016, \$455MM in 2018, and \$505MM in 2020.

Vfend Facing Generic Competition

Vfend, a broad spectrum antifungal azole, targets the treatment of severe fungal infections, including molds and yeasts, such as systemic aspergillosis and candidiasis respectively. It has convenient oral and IV dosing, and utility in pediatric patients. Vfend had a statistically significant survival benefit compared with amphotericin B in one study and has become the drug-of-choice for primary prophylaxis of fungal infections in high-risk individuals. However, Vfend has limitations that include unpredictable kinetics that make the drug hard to dose consistently, drug interactions, and hepatic and ocular toxicity. Pfizer lost exclusivity on all dosage forms in the U.S. and generics have been launched. We peg Vfend sales at \$815MM (+5%) in 2014, \$825MM in 2015, \$610MM in 2016, \$575MM in 2018, and \$565MM in 2020.

GEP - Incontinence

Detrol LA Generics Launched

The composition of matter patent for tolterodine expired in 3/12 and exclusivity had been set to expire in 9/12; however, in September 2012, Pfizer settled litigation with Mylan that extended U.S. exclusivity for Detrol LA into January 2014. Teva launched a generic on January 3rd, 2014. We estimate worldwide Detrol franchise sales of \$180MM (-68%) in 2014, \$165MM in 2015, \$175MM in 2016, \$210MM in 2018, and \$250MM in 2020.

GEP - Women's Health

Conbriza Approved In Europe; Viviant U.S. Status Uncertain

Viviant (bazedoxifene) is a selective estrogen receptor modulator (SERM) for both the treatment and prevention of osteoporosis, but it appears to offer little differentiation over Lilly's Evista. In April 2009, the EMEA approved Conbriza (E.U. trade name) for the treatment of postmenopausal osteoporosis in women at increased risk of fracture. Bazedoxifene launched in the E.U. and Japan in October 2010. Viviant was filed in June 2006 in the U.S. for osteoporosis prevention based on a 1,700 patient trial and radiologic endpoints. Data from a three-year fracture study in osteoporosis prevention were filed mid-2007, as part of Wyeth's response to the April 2007 approvable letter. In addition, a 7,600 patient osteoporosis treatment trial was part of an NDA filed in July 2007 for osteoporosis treatment. In November and December 2007, Wyeth submitted data from two Asian studies with more than 1,000 women. In December 2007, Wyeth received a second "approvable letter" with FDA requiring further analyses of the incidence of stroke and thromboembolic disease and citing concerns with data collection. No additional studies were requested in the second "approvable letter." In February 2008, at Wyeth's end-of-review conference with the FDA for the prevention indication, it agreed to conduct and submit further analyses of data from its clinical trials. However, given the recent approval of Duavee, Pfizer is reassessing next steps for Conbriza. We forecast Conbriza sales of \$100MM (+12%) in 2014, \$110MM in 2015, \$120MM in 2016, \$140MM in 2018, and \$160MM in 2020.

Premarin Franchise Poised For Modest Growth

We forecast that Premarin franchise sales will grow at a compound rate of 2% during 2013-20, despite the unfavorable results of the WHI (Women's Health Initiative) Prempro arm in 2002. Data from the WHI study published in JAMA demonstrated a higher neoplasm rate in patients on HRT despite discontinuation of the HRT. It is unclear whether there is a causal relationship. Our Premarin franchise sales forecasts are \$1,115MM (+2%) in 2014, \$1,130MM in 2015, \$1,150MM in 2016, \$1,190MM in 2018, and \$1,230MM in 2020.

The medical community generally concludes that HRT is appropriate for short-term symptom relief, and the FDA approved labeling along these lines in January 2003. However, usage in other settings, such as osteoporosis, likely is minimal. Premarin has been supported by the low-dose version. This lower strength has 40% less progestin and 30% less estrogen, with better tolerability and similar efficacy. In November 2008, FDA approved a low-dose regimen of Premarin vaginal cream to treat moderate to severe postmenopausal dyspareunia.

After Dip, Alliance Revenue Poised For Rebound

We forecast Alliance revenue, generated by co-promotion efforts for Eliquis (Bristol-Myers Squibb), Spiriva (Boehringer-Ingelheim), Rebif (Serono), and Enbrel (Amgen) to decline to \$1.145B (-14%) in 2014 as Spiriva co-promotion agreements wind down, grow modestly in 2015 to \$1.225B, then drop to \$895MM in 2016 as the Rebif agreement terminates and \$830MM in 2017 as Enbrel royalty ends. Thereafter, we expect an increase to \$950MM in 2018 and \$1.2B in 2020, supported solely by Eliquis (Bristol-Myers Squibb).

Pfizer 2013-20 Annual Alliance Revenue Buildup (\$MM)

Co-marketed Products	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR		2013-20 CGR		Portion Pfizer Books
									2014-20 CGR	2013-20 CGR	2014-20 CGR	2013-20 CGR	
Eliquis	\$146	\$680	\$1,080	\$1,400	\$1,650	\$1,900	\$2,150	\$2,400	+23%	NM	- JV sales; apixaban; filed for venous thromboembolism treatment and	-	
Spiriva	1,225	650	500	250	0	0	0	0	NM	NM	- JV sales; worldwide copromotion with BI; patent expires 3/14; agreement ends 2012-13 (EU), 2014 (US/Japan)	-	
Aricept	150	100	50	25	5	0	0	0	NM	NM	- JV profits; JV covers U.S., Japan, U.K., France, Germany; U.S. patent expired 11/10 but 23mg tablet has exclusivity to 7/13	- Assume JV sales; agreement duration subject of dispute - PFE claims end of 2015, Serono claims end of 2013	
Rebif	1,100	1,150	1,200	0	0	0	0	0	NM	NM	-	-	
Total	\$2,621	\$2,580	\$2,830	\$1,675	\$1,655	\$1,900	\$2,150	\$2,400	-1%	-1%	-	-	
Share of Eliquis sales	73	340	540	700	825	950	1075	1200	+23%	NM	-	-	
Share of Spiriva sales	900	468	360	180	0	0	0	0	NM	NM	-	-	
Share of Aricept JV profits	75	50	25	13	3	0	0	0	NM	NM	-	-	
Share of Rebif sales	275	288	300	0	0	0	0	0	NM	NM	-	-	
Alliance Revenue	\$1,325	\$1,145	\$1,225	\$895	\$830	\$950	\$1,075	\$1,200	+1%	-1%	-	-	
Alliance Rev. % of Sales	50.6%	44.4%	43.3%	53.4%	50.2%	50.0%	50.0%	50.0%	-	-	-	-	

Source: Cowen and Company

Wyeth Annual Product Co-Promotion Buildup (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR		2013-20 CGR		Comments
									2014-20 CGR	2013-20 CGR	2014-20 CGR	2013-20 CGR	
Enbrel	\$4,551	\$4,631	\$4,800	\$4,900	\$0	\$0	\$0	\$0	NM	NM	- Rheumatoid arthritis; North American rights reverted to AMGN on 10/31/13	-	
Assumed % share to WYE on Enbrel		33%	11%	10%	0%	0%	0%	0%			- WYE shares gross profit	-	
Share to PFE on Enbrel	1,305	545	535	\$490	\$0	\$0	\$0	\$0			- Starting 11/1/13, royalty goes to "other income" rather than sales	-	

Source: Cowen and Company

Patent/Exclusivity Expirations Below Industry Average

We estimate that 23% of Pfizer's EPS through 2020 are at risk from drugs going off patent.

Pfizer Patent Vulnerability

Company	Drug	Territory	Patent Exp. Date	U.S. Sales		Estimated U.S. Sales (\$MM)*	Non-U.S. Sales As % Of Total Sales	Estimated Non-U.S. Sales (\$MM)*	% Total Sales	% Total EPS (#)	
				Estimated WW Sales (\$MM)	As % Of Total Sales					EPS (#)	EPS
PFE	Viracept	U.S.	Apr-14	\$20	100%	\$20			0%	\$0.00	0%
	Celebrex	U.S.	May-14	2,918	64%	1,880			4%	0.07	3%
	Celebrex	E.U.	Nov-14	2,918			36%	1,038	2%	0.04	2%
	Lyrica	E.U.	2014	4,595			55%	2,541	5%	0.10	5%
	Enbrel	E.U.	Feb-15	3,940			100%	3,940	8%	0.16	7%
	Zyvox	U.S.	May-15	1,345	51%	691			1%	0.03	1%
	Rapamune	E.U.	Jun-15	320			61%	196	0%	0.01	0%
	Relpax	E.U.	Dec-15	345			39%	135	0%	0.01	0%
	Vfend	E.U.	Jan-16	810			93%	755	2%	0.03	1%
	Zyvox	E.U.	Jan-16	1,010			49%	491	1%	0.02	1%
	Lyrica	U.S.	Dec-18	4,415	45%	1,973			4%	0.09	3%
	Chantix	U.S.	2020	645	59%	377			1%	0.02	0%

*

Estimated sales in year prior to patent expiration

**Estimated sales in the year generic competition is expected

#Assumes 25% net margin

Source: Cowen and Company

Modest EPS Decline In 2014, Rebound Begins In 2015, Solid Growth Thereafter

1% EPS Decline Forecast In 2014

We forecast 2014 EPS of \$2.20 (-1%), on a 5% decline in revenue, to \$48.75B. The pressure on revenue stems from three factors: 1) continued loss of participation on Spiriva in markets globally; 2) receiving a royalty on Enbrel in North America, estimated at 12%, as opposed to 33% economics, and this royalty is reflected in "non-operating income"; 3) the Celebrex patent expiration in November 2014 in the E.U. and December 2015 in the U.S. Tempering top-line pressure is P&L management. Gross PM is estimated to be down 1pp to 81.0%; we show SG&A decline of 5% (to \$13.38B) and an R&D increase of 4% (to \$6.8B). We estimate a 0.5pp drop in the tax rate to 27.0%, and a 7% decline in the share count, to 6.416B.

Pfizer 2014 Guidance Versus Our Estimates

	Pfizer Guidance	Our Estimates
Reported Revenues	\$48.7 to \$50.7	\$48.75B
COGS	19-20%	19.0%
R&D Expenses	\$6.7 to \$7.2B	\$6.8B
SI&A Expenses	\$13.3 to \$14.3B	\$13.38B
Other (Income)/Deductions	(~\$200MM)	(\$200MM)
Tax Rate	~27.0%	27.0%
Operating Cash Flow	~\$18.5B	18.415B
Adjusted Diluted EPS	\$2.20 to \$2.30	\$2.20

Source: Cowen and Company, Company data

EPS Recovery Begins In 2015, With Solid Growth Thereafter

Pfizer's 2014-20 EPS growth could compound at 8%, a bit above the industry average, on 2% top-line growth, assuming: (1) one in four pipeline products contributes \$400MM in 2020, (2) operating expenses decline 1% per annum, (3) tax rate of 27%, and (4) decline in the share count. We forecast EPS of \$2.30 in 2015, \$2.45 in 2016, \$2.90 in 2018, and \$3.50 in 2020.

Pfizer 2013-15 Divisional P&L Buildup (\$MM) – Pro Forma*

	2013			2014E			2015E		
	Sales	Op. Inc.	P.M.	Sales	Op. Inc.	P.M.	Sales	Op. Inc.	P.M.
Global Innovative Products (GIP)	\$14,175	\$7,699	54.3%	\$13,735	\$6,686	48.7%	\$14,525	\$7,484	51.5%
Vaccines, Oncology, Consumer (VOC)	9,284	4,153	44.7%	10,023	4,576	45.7%	11,505	5,877	51.1%
Global Established Products (GEP)	27,761	17,437	62.8%	24,775	15,217	61.5%	21,325	12,613	59.1%
Other	232	-7,875	NM	215	-7,336	NM	200	-6,430	NM
Total Pfizer	\$51,453	21,414	41.6%	\$48,750	\$19,144	39.3%	\$47,555	\$19,543	41.1%
Interest Income		\$403			\$395			\$430	
Interest Expense		1,434			(1,355)			(1,330)	
Other Deductions		706			1,160			1,005	
Total Non-Op Income		(\$325)			\$200			\$105	
Pretax Income		\$21,128	41.1%		\$19,339	39.7%		\$19,648	41.3%
Tax Rate		27.5%			27.0%			27.0%	
Net Income before M.I.		\$15,318			\$14,123			\$14,343	
Minority Interests		30			30			40	
Net Income		\$15,288	29.7%		\$14,093	28.9%		\$14,303	30.1%
EPS - Diluted		\$2.22			\$2.20			\$2.30	
Shares (MM) - Diluted		6,894			6,416			6,225	
EPS - Basic		\$2.24			\$2.22			\$2.33	
Shares (MM) - Basic		6,813			6,337			6,145	

Source: Cowen and Company

Speculation On 2013-20 EPS Outcomes*

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	'13-'16 CGR	'13-'20 CGR	'14-'20 CGR Comments
Global Innovative Products (GIP)	\$0.31	\$0.28	\$0.32	\$0.37	\$0.42	\$0.45	\$0.41	\$0.46	6%	6%	9% - Enbrel fgn, Lyrica US/ROW, Chantix, Eliquis Alliance Revenue
Vaccines, Oncology, Consumer (VOC)	0.17	0.19	0.25	0.31	0.36	0.43	0.52	0.62	23%	21%	22% - Sutent, Palbociclib, Prevnar 13, Advil
Global Established Products (GEP)	0.70	0.64	0.55	0.50	0.48	0.47	0.48	0.49	-11%	-5%	-4% - Lipitor, Lyrica EU, Celebrex, Premarin, Viagra, Other AR
Other	1.05	1.08	1.17	1.27	1.40	1.55	1.65	1.93	7%	9%	10% - Corporate
PFE EPS - Diluted	\$2.22	\$2.20	\$2.30	\$2.45	\$2.65	\$2.90	\$3.05	\$3.50	3%	7%	8% - Versus +4%, +6% and +8% industry averages
% Change	1%	-1%	5%	7%	8%	9%	5%	15%			
PFE EPS - Basic	\$2.24	\$2.22	\$2.33	\$2.48	\$2.69	\$2.95	\$3.11	\$3.57	3%	7%	8%
% Change	1%	-1%	5%	7%	9%	10%	5%	15%			

Source: Cowen and Company

Pfizer 2013-20 Key Quarterly P&L Buildup (\$MM) – Pro Forma*

	Sales															
	Total \$MM	% Chg.	Gross P.M.	SG&A \$MM	% SIs	R&D \$MM	% SIs	Oper. P.M.	Non- Op	Tax Rate	Min. Int.	Net Inc.	Cash EPS	% Chg	Shares (MM)	
Q1	\$12,411	NM	82.0%	\$3,178	25.6%	\$1,618	13.0%	43.4%	(\$263)	26.8%	\$9	\$3,740	\$0.51	-11%	7269	
Q2	12,973	NM	83.1%	3,550	27.4%	1,521	11.7%	44.0%	(142)	27.9%	10	4,003	0.56	-9%	7117	
Q3	12,576	NM	82.7%	3,351	26.6%	1,625	12.9%	43.1%	(84)	27.6%	6	3,859	0.58	10%	6656	
Q4	13,493	NM	80.2%	4,093	30.3%	1,790	13.3%	36.6%	164	27.7%	5	3,685	0.56	19%	6533	
2013	\$51,453	NM	82.0%	\$14,100	27.4%	\$6,519	12.7%	41.6%	(\$325)	27.5%	\$30	\$15,288	\$2.22	1%	6894	
Q1	\$11,296	-9%	82.4%	\$3,018	26.7%	\$1,612	14.3%	41.1%	\$264	25.0%	\$9	\$3,666	\$0.57	10%	6476	
Q2	12,702	-2%	81.7%	3,486	27.4%	1,714	13.5%	40.5%	95	27.9%	9	3,769	0.58	4%	6444	
Q3E	12,015	-4%	81.0%	3,215	26.8%	1,680	14.0%	40.0%	(70)	27.5%	6	3,424	0.54	-8%	6396	
Q4E	12,730	-6%	79.0%	3,661	28.8%	1,794	14.1%	35.8%	(89)	27.5%	6	3,234	0.51	-10%	6346	
2014E	\$48,750	-5%	81.0%	\$13,380	27.4%	\$6,800	13.9%	39.3%	\$200	27.0%	\$30	\$14,093	\$2.20	-1%	6416	
Q1E	\$11,250	0%	81.7%	\$2,625	23.3%	\$1,545	13.7%	44.3%	\$15	27.0%	\$10	\$3,639	\$0.58	2%	6300	
Q2E	12,040	-5%	81.0%	3,100	25.7%	1,640	13.6%	41.3%	20	27.0%	10	3,635	0.58	-1%	6250	
Q3E	11,755	-2%	80.6%	2,855	24.3%	1,610	13.7%	42.1%	30	27.0%	10	3,628	0.59	9%	6200	
Q4E	12,510	-2%	78.5%	3,405	27.2%	1,725	13.8%	37.0%	40	27.0%	10	3,401	0.55	9%	6150	
2015E	\$47,555	-2%	80.4%	\$11,985	25.2%	\$6,520	13.7%	41.1%	\$105	27.0%	\$40	\$14,303	\$2.30	5%	6225	
2016P	\$47,695	0%	80.6%	\$11,700	24.5%	\$6,430	13.5%	42.1%	\$215	27.0%	\$50	\$14,767	\$2.45	7%	6035	
2017P	\$49,635	4%	80.8%	\$12,275	24.7%	\$6,650	13.4%	42.2%	\$350	27.0%	\$60	\$15,490	\$2.65	8%	5840	
2018P	\$51,315	3%	81.0%	\$12,575	24.5%	\$6,675	13.0%	43.0%	\$475	27.0%	\$70	\$16,373	\$2.90	9%	5645	
2019P	\$51,065	0%	80.8%	\$12,100	23.7%	\$6,615	13.0%	43.7%	\$600	27.0%	\$80	\$16,630	\$3.05	5%	5450	
2020P	\$54,460	7%	81.0%	\$12,550	23.0%	\$6,685	12.3%	45.2%	\$725	27.0%	\$90	\$18,402	\$3.50	15%	5255	

Source: Company data, Cowen and Company

Pfizer Quarterly Sales Dynamics (\$MM)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
CARDIOVASCULAR															
Champix/Chantix - U.S.	87	84	82	90	343	86	99	90	90	365	90	90	90	90	360
Champix/Chantix - EU (lc, ex fx).								20	10		20	20	20	20	10
Champix/Chantix - EU	32	30	26	28	116	24	23	20	10	75	20	20	15	10	65
Champix/Chantix - Estab. ROW	35	39	35	34	143	28	37	35	35	135	35	35	35	35	140
Champix/Chantix - Emerging ROW	12	13	11	10	46	9	11	10	10	40	10	10	10	15	45
Champix/Chantix - Worldwide	166	166	154	162	648	147	170	155	145	615	155	155	150	150	610
Bococizumab															
TOTAL CARDIOVASCULAR	\$168	\$168	\$164	\$162	\$848	\$147	\$170	\$155	\$145	\$815	\$155	\$155	\$150	\$150	\$610
% Chg	-7%	-3%	5%	-7%	-3%	-11%	2%	1%	-11%	-5%	5%	-9%	-3%	3%	-1%
CNS															
Lyrica - U.S.	\$438	\$491	\$509	\$525	\$1,963	\$514	\$601	\$600	\$610	\$2,325	\$565	\$650	\$650	\$660	\$2,525
Lyrica - Estab. ROW	171	174	152	183	680	156	185	150	170	660	155	185	150	170	660
Lyrica - Emerging ROW	112	125	113	139	494	110	114	120	150	495	115	120	125	155	515
Lyrica - Worldwide	726	790	774	847	3137	780	900	870	930	3480	835	955	925	985	3700
Tanezumab															
PF-5212377 (SAM-760)															
Ponezumab															
PF-2545920															
TOTAL CNS	\$726	\$790	\$774	\$847	\$3,137	\$780	\$900	\$870	\$930	\$3,480	\$835	\$955	\$925	\$985	\$3,700
% Chg	11%	12%	9%	10%	11%	7%	14%	12%	10%	11%	7%	6%	6%	6%	6%
ANTI-INFLAMMATORY															
Enbrel - EU (lc, ex fx).															
Enbrel - EU	556	598	600	659	2413	609	632	635	665	2540	615	635	660	700	2610
Enbrel - Estab. ROW	124	128	127	137	516	118	117	120	130	485	125	125	125	135	510
Enbrel - Emerging ROW	192	234	205	209	845	187	228	200	200	815	190	235	205	205	835
Enbrel - Total Ex US and Canada	877	960	932	1,005	3774	914	977	955	995	3840	930	995	990	1,040	3955
Xeljanz	11	22	35	46	114	52	68	80	90	290	100	110	120	130	460
ALO-02 Oxycodone-Naltrexone															
PF-4171327															
PF-5285401															
PF-547659															
PF-4236921															
TOTAL ANTI-INFLAMMATORY	\$888	\$982	\$967	\$1,051	\$3,888	\$966	\$1,045	\$1,035	\$1,085	\$4,130	\$1,030	\$1,105	\$1,110	\$1,170	\$4,415
% Chg	-1%	-1%	8%	10%	4%	9%	6%	7%	3%	6%	7%	6%	7%	8%	7%
PAIN FRANCHISE															
Remoxy															
Embeda															
Oxycondone NT															
Acurox/Other Acura Products															
TOTAL PAIN FRANCHISE															
% Chg															
METABOLIC															
Genotropin - U.S.	47	53	45	54	199	37	56	45	50	190	35	55	40	45	175
Genotropin - EU (lc, ex fx).															
Genotropin - EU	65	67	65	71	268	62	64	60	60	245	50	50	55	55	210
Genotropin - Estab. ROW	50	50	47	50	197	43	46	45	50	185	50	50	50	50	200
Genotropin - Emerging ROW	27	28	26	27	108	24	28	25	25	100	25	25	25	25	100
Genotropin - Worldwide	189	198	183	202	772	166	194	175	185	720	160	180	170	175	685

Source: Company data , Cowen and Company

Pfizer Quarterly Sales Dynamics (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Ertugliflozin						1	1	5	10	15	15	20	25	30	90
Duavree						45	66	48	51	210	40	51	45	45	45
BMP-2						48	55	56	58	217	50	59	60	65	70
Somavert															255
TOTAL METABOLIC	\$282	\$319	\$287	\$311	\$1,199	\$257	\$305	\$285	\$305	\$1,150	\$270	\$310	\$305	\$320	\$1,205
% Chg	-8%	-3%	-10%	-8%	-7%	-9%	-4%	-1%	-2%	-4%	5%	2%	7%	5%	5%
OTHER DRUGS															
Benefix - U.S.	\$88	\$109	\$101	\$97	\$395	\$92	\$115	\$105	\$100	\$410	\$85	\$100	\$95	\$90	\$370
Benefix - EU (lc, ex fx)															
Benefix - EU	57	62	67	71	257	66	69	65	65	265	55	50	50	45	200
Benefix - Estab. ROW	34	34	33	38	139	33	38	35	45	150	35	35	35	35	140
Benefix - Emerging ROW	10	12	12	7	41	10	5	10	10	35	10	10	5	5	30
Benefix - Worldwide	189	217	213	213	832	201	227	215	220	865	185	195	185	175	740
Refacto/Xyntha - U.S.	29	31	29	34	123	30	37	35	35	135	35	35	30	30	130
Refacto/Xyntha - EU (lc, ex fx)															
Refacto/Xyntha - EU	89	93	96	108	386	92	99	100	100	390	85	90	100	100	375
Refacto/Xyntha - Estab. ROW	18	18	16	18	70	14	17	25	25	80	20	20	20	15	75
Refacto/Xyntha - Emerging ROW	3	4	2	9	23	9	18	0	5	30	5	10	5	5	25
Refacto/Xyntha - Worldwide	139	146	148	169	602	145	171	160	165	640	145	155	155	150	605
Viagra - U.S.	245	280	294	313	1,132	241	287	285	310	1,125	275	275	275	275	1,100
Rapamune - U.S.	49	48	55	49	201	54	56	50	40	200	40	40	40	40	160
Rapamune - EU (lc, ex fx)															
Rapamune - EU	12	13	13	14	52	13	12	10	10	45	10	10	10	10	40
Rapamune - Estab. ROW	4	5	4	4	17	4	4	5	5	20	5	5	5	5	20
Rapamune - Emerging ROW	19	20	19	22	80	17	15	15	20	65	15	15	15	10	55
Rapamune - Worldwide	84	86	91	89	350	88	87	80	75	330	70	70	70	65	275
Toviaz	52	65	57	62	236	63	79	70	75	285	70	85	75	80	310
Taliglucerase alfa	5	5	10	10	30	10	10	15	15	50	20	20	25	25	90
Vyndael gel (tafamidis meglumine)															
PF-489791															
PF-5175157															
PF-4634817															
PD-360324															
PF-6473871 (EXC001)															
Rivipansel (GMI-1070)															
PF-4937319															
Xiaflex	4	4			8										600
Other GIP Products	166	198	189	182	735	132	180	175	175	660	150	150	150	150	600
TOTAL OTHER DRUGS	\$884	\$1,001	\$1,002	\$1,039	\$3,925	\$880	\$1,041	\$1,000	\$1,045	\$3,965	\$920	\$955	\$940	\$930	\$3,745
% Chg	24%	35%	27%	25%	28%	0%	4%	0%	1%	1%	5%	-8%	-6%	-11%	-6%
TOTAL GIP PHARMACEUTICALS	\$2,945	\$3,258	\$3,184	\$3,410	\$12,797	\$3,030	\$3,461	\$3,370	\$3,540	\$13,395	\$3,270	\$3,550	\$3,515	\$3,650	\$13,985
ALLIANCE REVENUE															
PFE Alliance Revenue	\$11	\$6	\$21	\$36	\$73	\$46	\$86	\$100	\$109	\$340	\$120	\$130	\$140	\$150	\$540
WYE Alliance Revenue	350	390	389	176	1,305										
ALLIANCE REVENUE	\$361	\$396	\$409	\$212	\$1,378	\$46	\$88	\$100	\$109	\$340	\$120	\$130	\$140	\$150	\$540
% Chg						NM	NM	NM	NM	NM	164%	52%	40%	38%	59%
TOTAL GIP	\$3,306	\$3,654	\$3,593	\$3,622	\$14,175	\$3,076	\$3,547	\$3,470	\$3,849	\$13,735	\$3,390	\$3,680	\$3,655	\$3,800	\$14,525
% Chg						-7%	-3%	-3%	1%	-3%	10%	4%	5%	4%	6%

Source: Company data , Cowen and Company

Pfizer Quarterly Sales Dynamics (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
ONCOLOGY															
Sutent - U.S.	\$84	\$92	\$85	\$90	\$351	\$78	\$93	\$90	\$95	\$355	\$85	\$100	\$95	\$100	\$380
Sutent - EU (lc, ex fx)								100	115		115	110	105	120	
Sutent - EU	101	96	96	109	402	105	105	100	110	420	110	105	105	120	440
Sutent - Etab. ROW	33	35	35	37	140	31	34	40	40	145	35	40	45	45	165
Sutent - Emerging ROW	84	89	62	76	311	54	78	60	70	260	60	80	65	75	280
Sutent - Worldwide	302	312	278	312	1204	268	310	290	315	1185	290	325	310	340	1265
Palbociclib (PD-332991)															
Xalkori (crizotinib)	53	67	73	89	282	88	108	120	130	445	140	150	160	170	620
Inlyta (axitinib)	63	71	83	102	319	88	101	110	120	420	125	130	135	140	530
Inotuzumab (PF-5208773)											5	10	15	20	50
Torisel	32	35	30	36	132	29	33	35	40	135	30	35	40	45	150
Bosulif	4	6	8	14	31	14	18	20	25	75	25	25	30	30	110
Dacomitinib (PF-299804)															
PF-5212384															
PF-3446962															
TOTAL ONCOLOGY	\$453	\$480	\$472	\$563	\$1,968	\$487	\$570	\$575	\$830	\$2,280	\$815	\$675	\$690	\$745	\$2,725
% Chg	26%	23%	18%	24%	23%	8%	16%	22%	14%	15%	26%	18%	20%	18%	21%
VACCINES															
Prevnar 13 - U.S.	\$449	\$417	\$469	\$468	\$1,804	\$471	\$469	\$500	\$500	\$1,940	\$525	\$525	\$550	\$550	\$2,150
Prevnar 13 - EU (lc, ex fx)								170	260		155	200	180	265	
Prevnar 13 - EU	167	176	164	251	758	148	189	170	250	755	150	190	175	265	780
Prevnar 13 - Etab. ROW	63	125	116	151	455	124	120	125	135	505	145	155	165	175	640
Prevnar 13 - Emerging ROW	166	251	210	249	876	184	319	250	300	1055	225	300	300	350	1175
Prevnar 13 - Worldwide	845	969	959	1,119	3893	927	1,097	1,045	1,185	4255	1,045	1,170	1,190	1,340	4745
Prevnar 7 - U.S.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Prevnar 7 - EU (lc, ex fx)								0	0		0	0	0	0	
Prevnar 7 - EU	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Prevnar 7 - Etab. ROW	81	0	0	0	81	0	0	0	0	0	0	0	0	0	0
Prevnar 7 - Emerging ROW	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Prevnar 7 - Worldwide	81	0	0	0	81	0	0	0	0	0	0	0	0	0	0
MnB (PF-5212366) (rLP2086)											50	100	150		
NeisVac-C											30	30	30	35	125
FSME-IMMUN/TicoVac											30	30	30	35	125
PF-6290510															
PF-6425090															
Meningitec	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
HibTITER								0	5		0	0	0	5	5
Vaccine, Other	3	5	6	5	19	0	0	5	5	10	5	5	5	20	
TOTAL VACCINES	\$926	\$969	\$959	\$1,119	\$3,874	\$927	\$1,097	\$1,050	\$1,195	\$4,270	\$1,110	\$1,235	\$1,305	\$1,520	\$5,170
% Chg	-15%	-5%	0%	0%	-5%	0%	13%	9%	7%	7%	20%	13%	24%	27%	21%
TOTAL VOC PHARMACEUTICALS	\$1,379	\$1,460	\$1,431	\$1,672	\$5,942	\$1,414	\$1,867	\$1,825	\$1,825	\$6,530	\$1,725	\$1,910	\$1,995	\$2,285	\$7,895
CONSUMER CARE PRODUCTS															
Advil franchise	\$240	\$205	\$258	\$250	\$953	\$209	\$219	\$270	\$260	\$960	\$215	\$225	\$280	\$270	\$990
Centrum	173	198	170	223	764	170	196	175	230	770	175	200	180	235	790
Caltrate	86	95	87	92	360	86	96	90	95	365	90	100	95	100	385
Robitussin	51	27	38	60	176	40	26	40	65	170	45	30	45	70	190
Chapstick	28	22	33	52	135	29	23	35	55	140	30	25	40	60	155
Other	233	253	202	266	954	226	352	220	285	1,085	235	340	230	295	1,100
TOTAL CONSUMER CARE	\$811	\$800	\$788	\$943	\$3,342	\$780	\$912	\$890	\$980	\$3,492	\$790	\$920	\$870	\$1,030	\$3,610
% Change	11%	4%	1%	1%	4%	-6%	14%	5%	5%	8%	4%	1%	5%	4%	3%
TOTAL VOC	\$2,190	\$2,260	\$2,219	\$2,615	\$9,284	\$2,174	\$2,579	\$2,455	\$2,815	\$10,023	\$2,515	\$2,830	\$2,865	\$3,295	\$11,505
% Chg						-1%	14%	11%	8%	8%	16%	10%	17%	17%	15%

Source: Company data , Cowen and Company

Pfizer Quarterly Sales Dynamics (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
CARDIOVASCULAR															
Lipitor - U.S.	\$171	\$86	\$78	\$97	\$432	\$50	\$96	\$50	\$50	\$245	\$40	\$40	\$35	\$35	\$150
Lipitor - EU (lc, ex fx)								50	50		50	50	25	25	
Lipitor - EU	73	83	71	92	319	73	79	50	50	250	50	50	25	25	150
Lipitor - Estab. ROW	129	130	122	129	510	89	90	80	80	340	75	75	70	70	290
Lipitor - Emerging ROW	<u>253</u>	<u>246</u>	<u>262</u>	<u>293</u>	<u>1054</u>	<u>245</u>	<u>278</u>	<u>265</u>	<u>300</u>	<u>1090</u>	<u>255</u>	<u>285</u>	<u>275</u>	<u>310</u>	<u>1125</u>
Lipitor - Worldwide	626	545	533	611	2315	457	543	445	480	1925	420	450	405	440	1715
Norvasc - U.S.	10	10	11	8	39	11	10	5	5	30	5	5	5	5	20
Norvasc - EU (lc, ex fx).								20	20		20	20	15	15	
Norvasc - EU	27	28	25	28	108	26	23	20	20	90	20	20	15	15	70
Norvasc - Estab. ROW	124	125	115	121	485	96	96	90	90	370	85	85	80	80	330
Norvasc - Emerging ROW	<u>140</u>	<u>150</u>	<u>152</u>	<u>155</u>	<u>597</u>	<u>145</u>	<u>153</u>	<u>155</u>	<u>155</u>	<u>610</u>	<u>155</u>	<u>155</u>	<u>160</u>	<u>160</u>	<u>630</u>
Norvasc - Worldwide	301	313	303	312	1229	278	282	270	270	1100	265	265	260	260	1050
Cardura - U.S.	1	1	1	1	4	1	1	0	0	0	0	0	0	0	0
Cardura - EU (lc, ex fx).								15	15		15	15	10	10	
Cardura - EU	22	22	20	22	86	21	20	15	15	70	15	15	10	10	50
Cardura - Estab. ROW	27	26	23	24	100	20	21	20	20	80	15	15	15	15	60
Cardura - Emerging ROW	<u>26</u>	<u>26</u>	<u>26</u>	<u>28</u>	<u>106</u>	<u>24</u>	<u>26</u>	<u>30</u>	<u>30</u>	<u>110</u>	<u>25</u>	<u>30</u>	<u>35</u>	<u>35</u>	<u>125</u>
Cardura - Worldwide	76	75	70	75	296	66	68	65	65	265	55	60	60	60	235
Caduet - U.S.	5	6	5	7	23	5	5	5	0	15	5	5	0	0	10
Caduet - EU (lc, ex fx).								0	0		5	0	0	0	
Caduet - EU	4	3	2	5	14	3	0	0	0	5	5	0	0	0	5
Caduet - Estab. ROW	35	36	35	36	142	30	17	30	30	105	30	30	25	25	110
Caduet - Emerging ROW	<u>12</u>	<u>11</u>	<u>10</u>	<u>11</u>	<u>44</u>	<u>12</u>	<u>10</u>	<u>10</u>	<u>10</u>	<u>40</u>	<u>10</u>	<u>10</u>	<u>5</u>	<u>5</u>	<u>30</u>
Caduet - Worldwide	56	56	52	59	223	50	32	45	40	165	50	45	30	30	155
Fragmin - U.S.	10	9	2	2	23	0	3	5	5	15	0	0	5	5	10
Fragmin - EU (lc, ex fx).								50	60		50	55	55	65	
Fragmin - EU	42	43	45	53	183	48	53	50	60	210	50	50	55	65	220
Fragmin- Estab. ROW	18	25	22	24	89	18	23	25	25	90	20	25	25	30	100
Fragmin - Emerging ROW	<u>16</u>	<u>17</u>	<u>14</u>	<u>17</u>	<u>64</u>	<u>15</u>	<u>16</u>	<u>10</u>	<u>10</u>	<u>50</u>	<u>10</u>	<u>10</u>	<u>10</u>	<u>10</u>	<u>40</u>
Fragmin - Worldwide	86	94	83	96	359	81	95	90	100	365	80	85	95	110	370
Inspra	52	59	53	69	233	61	62	65	70	260	65	65	65	75	270
Tikosyn	26	30	34	29	119	30	34	35	35	135	35	35	40	40	150
Accupril	26	27	23	27	103	10	11	10	10	40	10	10	5	5	30
Other	<u>100</u>	<u>100</u>	<u>100</u>	<u>100</u>	<u>400</u>	<u>100</u>	<u>103</u>	<u>100</u>	<u>100</u>	<u>405</u>	<u>100</u>	<u>100</u>	<u>100</u>	<u>100</u>	<u>400</u>
TOTAL CARDIOVASCULAR	\$1,349	\$1,299	\$1,251	\$1,378	\$5,278	\$1,133	\$1,230	\$1,125	\$1,170	\$4,660	\$1,080	\$1,115	\$1,060	\$1,120	\$4,375
% Chg	-38%	-36%	-17%	-2%	-26%	-16%	-5%	-10%	-15%	-12%	-5%	-9%	-6%	-4%	-6%

Source: Company data , Cowen and Company

Pfizer Quarterly Sales Dynamics (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
ANTI-INFECTIVES															
Zyvox - U.S.	\$176	\$170	\$165	\$177	\$688	\$165	\$172	\$170	\$185	\$690	\$170	\$100	\$50	\$50	\$370
Zyvox - EU (lc, ex fx).								85	90		85	95	90	90	95
Zyvox - EU	75	82	81	87	325	81	89	85	85	340	80	90	90	95	355
Zyvox - Estab. ROW	33	33	35	35	136	29	31	30	30	120	25	25	25	25	100
Zyvox - Emerging ROW	58	61	38	47	204	46	56	40	45	185	45	50	40	40	175
Zyvox - Worldwide	342	346	319	346	1353	321	348	325	345	1340	320	265	205	210	1000
Vfend - U.S.	17	14	18	12	61	12	11	10	10	45	10	10	5	5	30
Vfend - EU (lc, ex fx).								80	85		75	85	85	85	
Vfend - EU	71	77	74	83	305	74	77	80	80	310	70	80	85	85	320
Vfend - Estab. ROW	37	35	38	44	154	35	36	40	45	155	35	35	40	50	160
Vfend - Emerging ROW	62	51	63	79	255	56	97	65	85	305	60	100	65	90	315
Vfend - Worldwide	187	177	193	218	775	177	221	195	220	815	175	225	195	230	825
Zosyn - U.S.	36	44	47	45	172	36	37	35	35	145	25	25	25	25	100
Zosyn - EU (lc, ex fx).								5	5		5	5	5	5	0
Zosyn - EU	11	11	8	10	40	8	5	5	5	25	5	5	5	0	15
Zosyn - Estab. ROW	3	3	4	2	12	3	3	5	5	15	10	5	5	5	25
Zosyn - Emerging ROW	37	44	45	45	171	27	30	40	40	135	25	30	35	35	125
Zosyn - Worldwide	87	102	104	102	395	74	75	85	85	320	65	65	70	65	265
Zithromax - U.S.	4	2	3	2	7	2	4	0	0	5	5	0	0	0	5
Zithromax - EU (lc, ex fx).								10	10		10	10	10	10	
Zithromax - EU	18	14	12	15	59	16	15	10	10	50	10	10	10	10	40
Zithromax - Estab. ROW	40	30	25	35	130	24	18	15	15	70	15	15	15	15	60
Zithromax - Emerging ROW	54	41	44	52	191	50	39	45	55	190	50	45	50	55	200
Zithromax - Worldwide	116	83	84	104	387	92	76	70	80	320	80	70	75	80	305
Tygacil - U.S.	43	41	38	28	150	30	28	40	30	130	30	30	45	35	140
Tygacil - EU (lc, ex fx).								20	20		20	20	20	20	
Tygacil - EU	16	18	19	19	72	17	19	20	20	75	20	20	20	20	80
Tygacil - Estab. ROW	2	2	1	2	7	1	2	5	5	15	5	5	5	5	20
Tygacil - Emerging ROW	26	31	34	38	129	26	33	35	40	135	30	35	35	40	140
Tygacil - Worldwide	87	92	92	87	358	74	82	100	95	350	85	90	105	100	380
Eraxis	29	35	35	39	138	33	38	35	40	145	35	40	40	45	160
Diflucan	45	60	59	78	242	52	46	55	70	225	45	50	50	65	210
Cleocin	50	50	50	50	200	48	46	45	45	185	40	40	40	40	160
Minocin	5	5	5	5	20	4	5	0	0	10	5	0	0	0	5
Other	182	180	184	186	732	185	183	190	190	750	190	190	190	200	770
TOTAL ANTI-INFECTIVES	\$1,130	\$1,130	\$1,125	\$1,215	\$4,600	\$1,060	\$1,120	\$1,100	\$1,170	\$4,460	\$1,040	\$1,035	\$970	\$1,035	\$4,080
% Chg	-2%	-5%	-2%	0%	-3%	-6%	-1%	-2%	-4%	-3%	-2%	-8%	-12%	-12%	-9%

Source: Company data, Cowen and Company

Pfizer Quarterly Sales Dynamics (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
CNS															
Lyrica - EU (lc, ex fx)								200	175		175	150	100	75	
Lyrica - EU	340	344	361	413	1458	370	415	200	170	1155	165	145	100	75	485
Neurontin	52	56	50	58	216	45	58	45	50	200	40	45	45	45	175
Total Gabapentinoids	392	400	411	471	1,674	415	473	245	220	1,355	205	190	145	120	660
Pristiq - U.S.	131	137	134	138	540	134	149	145	145	575	145	155	155	155	610
Pristiq - EU (lc, ex fx)	0	0	0	1	1	2	3	0	0	0	0	0	0	0	0
Pristiq - EU	23	26	25	31	105	23	28	30	35	115	30	35	35	40	140
Pristiq - Estab. ROW	12	14	14	12	52	13	18	15	15	60	15	15	20	20	70
Pristiq - Worldwide	166	177	173	182	698	172	198	190	195	755	190	205	210	215	820
Zoloft - U.S.	14	2	14	14	44	13	13	5	5	35	0	5	5	5	15
Zoloft - EU (lc, ex fx)	15	17	15	16	63	14	14	15	15	10	10	10	10	10	40
Zoloft - EU	55	55	53	58	221	43	48	45	45	180	40	40	40	40	160
Zoloft - Estab. ROW	32	35	34	40	141	31	29	35	45	140	35	40	40	40	155
Zoloft - Worldwide	116	109	116	128	469	101	104	100	110	415	85	95	95	95	370
Geodon - U.S.	5	5	5	50	65	5	5	5	5	20	0	0	5	5	10
Geodon - EU (lc, ex fx)	8	10	10	8	36	8	5	5	5	5	5	5	5	5	20
Geodon - EU	5	5	5	5	20	5	5	10	10	30	5	10	10	10	35
Geodon - Estab. ROW	20	19	19	14	72	20	15	20	20	75	25	25	20	20	90
Geodon - Emerging ROW	38	39	39	77	194	38	30	40	40	150	35	40	40	40	155
Effexor - U.S.	36	56	36	45	173	26	36	30	40	130	25	25	25	25	100
Effexor - EU (lc, ex fx)	24	24	22	26	96	23	24	15	20	15	15	15	15	15	60
Effexor - EU	18	17	16	17	68	11	12	10	10	45	5	5	10	10	30
Effexor - Estab. ROW	27	28	22	26	103	22	24	25	30	100	25	30	30	30	115
Effexor - Worldwide	105	125	96	114	440	82	96	80	100	360	70	75	80	80	305
Aricept - U.S.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Aricept - EU (lc, ex fx)	14	11	9	9	43	0	0	5	10	10	5	5	5	5	25
Aricept - EU	40	40	36	44	160	37	16	30	30	115	25	25	20	20	90
Aricept - Estab. ROW	8	8	7	9	32	5	5	5	5	20	0	5	5	5	15
Aricept - Worldwide	62	59	52	62	235	42	21	40	45	150	35	35	30	30	130
Xanax/Xanax XR	70	65	69	72	276	59	68	65	65	255	55	65	55	60	235
Ativan	34	33	30	36	133	33	32	25	25	115	30	25	25	25	105
Dilantin	43	39	35	40	157	28	38	30	35	130	25	35	30	30	120
Relpax	86	94	83	96	359	87	98	80	90	355	80	90	75	80	325
Halcion	19	18	18	19	74	20	17	15	15	65	15	15	10	10	50
Other	13	12	14	11	50	15	15	15	15	60	15	15	15	15	60
TOTAL CNS	\$1,144	\$1,171	\$1,186	\$1,308	\$4,759	\$1,082	\$1,190	\$925	\$955	\$4,185	\$840	\$885	\$810	\$800	\$3,335
% Chg	-12%	-4%	-2%	7%	-3%	-5%	2%	-19%	-27%	-12%	-23%	-26%	-12%	-16%	-20%

Source: Cowen and Company

Pfizer Quarterly Sales Dynamics (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
ANTI-INFLAMMATORY															
Celebrex - U.S.	424	477	508	524	1933	402	520	500	450	1,870	150	150	50	40	390
Celebrex - EU (Ic, ex fx).								35	25		20	20	15	15	15
Celebrex - EU	38	36	36	41	151	34	37	35	25	130	20	20	15	15	70
Celebrex - Estab. ROW	107	112	115	130	464	105	110	110	125	450	110	110	110	110	440
Celebrex - Emerging ROW	84	90	93	103	370	83	95	100	105	385	85	100	105	110	400
Celebrex - Worldwide	653	715	752	798	2918	624	762	745	705	2835	365	380	280	275	1300
Dynastat	29	30	33	38	130	30	38	35	40	145	35	35	40	40	150
Coxib Franchise	682	745	785	836	3,049	654	800	780	745	2,980	400	415	320	315	1,450
Arthrotec	23	26	21	22	92	17	16	15	15	65	15	15	15	15	60
Other	27	22	22	26	97	25	24	25	25	99	25	25	25	25	100
TOTAL ANTI-INFLAMMATORY	\$732	\$793	\$828	\$884	\$3,237	\$696	\$840	\$820	\$785	\$3,144	\$440	\$455	\$360	\$355	\$1,610
% Chg	-1%	3%	6%	3%	3%	-5%	6%	-1%	-11%	-3%	-37%	-46%	-56%	-55%	-49%
PAIN FRANCHISE															
Flecto Patch	31	37	28	34	130	27	32	35	40	135	30	35	40	40	145
Thrombin-JMI	23	27	23	25	98	23	25	20	20	90	20	20	20	20	80
Levoxyd	10	1	0	9	2	2	2	0	0	5	5	0	0	0	5
Other															
TOTAL PAIN FRANCHISE	\$64	\$65	\$51	\$50	\$230	\$52	\$59	\$55	\$60	\$230	\$55	\$55	\$60	\$60	\$230
% Chg	-29%	-20%	-38%	-46%	-33%	-19%	-9%	8%	20%	0%	6%	-7%	9%	0%	0%
ONCOLOGY															
Aromasin - U.S.	3	5	5	3	16	5	5	5	5	20	5	5	0	0	10
Aromasin - EU (Ic, ex fx).								0	0		0	0	0	0	0
Aromasin - EU	14	0	0	15	29	0	0	0	0	0	0	0	0	0	0
Aromasin - Estab. ROW	9	10	10	8	37	10	10	5	5	30	5	5	5	5	20
Aromasin - Emerging ROW	25	20	20	24	89	25	19	25	25	95	25	25	25	30	105
Aromasin - Worldwide	51	35	35	50	172	40	34	35	35	145	35	35	30	35	135
Ellence/Pharmorubicin	27	24	26	29	106	21	22	20	25	90	20	15	20	20	75
Camptosar	35	15	15	16	81	12	17	10	10	50	10	10	5	5	30
Other	88	85	87	87	347	75	77	75	75	300	65	65	60	60	250
TOTAL ONCOLOGY	\$201	\$160	\$163	\$182	\$706	\$148	\$150	\$140	\$145	\$583	\$130	\$125	\$115	\$120	\$490
% Chg	-5%	-23%	-17%	2%	-11%	-27%	-6%	-14%	-20%	-17%	-12%	-17%	-18%	-17%	-16%

Source: Company data , Cowen and Company

Pfizer Quarterly Sales Dynamics (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
OPHTHALMOLOGY															
Xalatan - U.S.	\$8	\$7	\$8	\$7	\$30	\$6	\$5	\$5	\$0	\$15	\$0	\$0	\$5	\$5	\$10
Xalatan - EU (lc, ex fx).								25	25		20	20	20	20	20
Xalatan - EU	39	38	40	44	162	33	32	25	25	115	20	20	20	20	80
Xalatan - Estab. ROW	58	58	56	60	232	48	50	50	50	200	40	45	45	45	175
Xalatan - Emerging ROW	42	44	36	44	166	32	41	40	40	155	35	35	35	35	140
Xalatan - Worldwide	147	147	140	155	590	119	128	120	115	480	95	100	105	105	405
Moxidectin						5	6	5	5	20	5	5	10	10	30
Macugen	2	2	5	1	8	0	1	5	5	10	0	5	5	5	15
TOTAL OPHTHALMOLOGY	\$149	\$149	\$145	\$154	\$598	\$124	\$135	\$130	\$125	\$510	\$100	\$110	\$120	\$120	\$450
% Chg	-35%	-30%	-24%	-19%	-27%	-17%	-10%	-10%	-19%	-15%	-19%	-19%	-8%	-4%	-12%
METABOLIC															
Premarin - U.S.	220	252	254	275	\$1,001	228	252	260	285	1,025	230	255	265	290	1,040
Premarin - EU (lc, ex fx).								5	5		0	0	5	5	5
Premarin - EU	2	2	3	2	9	2	2	5	5	15	0	0	5	5	10
Premarin - Estab. ROW	9	9	8	11	37	7	9	10	10	35	10	10	10	10	45
Premarin - Emerging ROW	13	10	11	11	45	11	11	10	10	40	10	10	10	10	35
Premarin - Worldwide Franchise	244	273	276	299	1092	248	274	285	310	1115	250	275	290	315	1130
Medrol - U.S.	40	39	31	38	148	43	43	35	40	160	50	50	40	45	185
Medrol - EU (lc, ex fx).								25	25		25	25	30	30	30
Medrol - EU	22	23	22	23	91	23	25	25	25	100	25	25	30	30	110
Medrol - Estab. ROW	10	10	9	10	39	8	9	10	15	40	10	10	15	15	50
Medrol - Emerging ROW	41	51	45	50	187	32	38	40	45	155	30	35	40	40	145
Medrol - Worldwide	113	123	107	121	465	106	115	110	125	455	115	120	125	130	490
Depo Provera	37	54	52	55	198	53	40	50	55	200	55	45	50	60	210
Conbriza/Viviant	20	22	22	25	89	20	23	25	30	100	25	25	30	30	110
Estring U.S.	17	19	18	20	74	17	19	20	20	75	20	20	20	25	85
Salazopyrin	26	26	24	30	106	24	23	25	25	95	25	25	20	20	90
Glyset	5	5	0	0	10	5	5	0	0	10	5	5	0	0	10
Glucotrol Line	5	5	5	12	28	3	5	5	5	20	5	5	5	0	15
Provera	5	5	5	10	25	5	5	5	5	20	5	5	5	0	15
Other	156	159	159	157	631	155	156	165	160	635	155	155	165	165	640
TOTAL METABOLIC	\$629	\$692	\$668	\$730	\$2,719	\$636	\$665	\$690	\$735	\$2,725	\$660	\$680	\$710	\$745	\$2,795
% Chg	-4%	-1%	-1%	5%	0%	1%	-4%	3%	1%	0%	4%	2%	3%	1%	3%

Source: Company data , Cowen and Company

Pfizer Quarterly Sales Dynamics (\$MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
OTHER DRUGS															
Viagra - EU (lc, ex fx)								20	20				15	15	
Viagra - EU	93	81	54	37	265	26	20	20	85	20	20	15	15	70	
Viagra - Estab. ROW	40	37	36	39	152	32	34	30	30	125	25	25	25	100	
Viagra - Emerging ROW	83	86	76	87	332	75	86	70	80	310	70	80	65	75	290
Viagra - Worldwide	216	204	166	163	750	133	140	120	130	520	115	125	105	115	460
Detrol LA/Detrol - U.S.	103	105	89	78	375	7	5	5	5	20	5	5	0	0	10
Detrol LA/Detrol - EU (lc, ex fx)								5	5		5	5	5	0	
Detrol LA/Detrol - EU	15	15	11	12	53	5	15	5	5	30	5	5	5	0	15
Detrol LA/Detrol - Estab. ROW	22	22	19	23	87	20	25	20	25	90	25	25	25	25	100
Detrol LA/Detrol - Emerging ROW	11	13	12	12	48	5	13	10	10	40	10	10	10	10	40
Detrol LA/Detrol - Worldwide	151	155	131	125	562	37	58	40	45	180	45	45	40	35	165
Revatio - U.S.	14	20	18	15	67	15	13	10	5	45	10	10	5	5	30
Revatio - EU (lc, ex fx)								35	45		40	35	35	40	
Revatio - EU	37	38	37	45	158	42	37	35	45	160	40	35	35	40	150
Revatio - Estab. ROW	13	12	12	15	52	12	12	15	15	55	15	15	15	20	65
Revatio - Emerging ROW	8	8	8	7	31	7	6	10	5	30	5	5	10	5	25
Revatio - Worldwide	72	78	75	82	308	76	68	70	70	285	70	65	65	70	270
Lybrel	5	5	5	10	26	5	5	10	10	30	5	10	10	10	35
Protonix	43	45	38	38	165	45	49	35	35	165	40	45	35	35	155
Ansaid	5	0	0	0	5	5	0	0	0	5	0	0	0	5	5
Zoton	5	5	5	5	20	5	5	0	0	10	0	0	0	5	5
Lodine, Lodine XL	5	0	0	0	5	5	0	0	0	5	0	0	0	5	5
Other	570	685	656	633	2,544	528	589	600	575	2,290	500	550	575	550	2,175
TOTAL OTHER DRUGS	\$1,073	\$1,178	\$1,076	\$1,057	\$4,385	\$839	\$914	\$875	\$865	\$3,490	\$775	\$840	\$830	\$830	\$3,275
% Chg	-27%	-22%	-15%	-29%	-23%	-22%	-22%	-19%	-18%	-20%	-8%	-8%	-5%	-4%	-6%
TOTAL PHARMACEUTICALS	\$6,473	\$6,637	\$6,442	\$6,958	\$26,511	\$5,780	\$6,303	\$5,860	\$6,010	\$23,965	\$5,120	\$5,300	\$5,035	\$5,185	\$20,640
ALLIANCE REVENUE															
PFE Alliance Revenue	\$388	\$358	\$276	\$228	\$1,250	\$210	\$210	\$195	\$196	\$810	\$170	\$170	\$170	\$175	\$685
ALLIANCE REVENUE	\$388	\$358	\$276	\$228	\$1,250	\$210	\$210	\$195	\$196	\$810	\$170	\$170	\$170	\$175	\$685
% Chg	-34%	-37%	-52%	-62%	-46%	NM	NM	NM	NM	NM	-19%	-19%	-13%	-11%	-15%
TOTAL GEP	\$6,861	\$6,995	\$6,718	\$7,186	\$27,761	\$5,990	\$6,513	\$6,055	\$6,206	\$24,775	\$5,290	\$5,470	\$5,205	\$5,360	\$21,325
% Chg						-13%	-7%	-10%	-14%	-11%	-12%	-16%	-14%	-14%	-14%
MISCELLANEOUS															
Other	\$53	\$63	\$46	\$70	\$232	\$57	\$64	\$35	\$60	\$215	\$55	\$60	\$30	\$55	\$200
MISCELLANEOUS	\$53	\$63	\$46	\$70	\$232	\$57	\$64	\$35	\$60	\$215	\$55	\$60	\$30	\$55	\$200
% Chg.	-20%	-3%	-26%	3%	-11%	8%	1%	-24%	-14%	-7%	-4%	-6%	-14%	-8%	-7%
PFIZER TOTAL SALES	\$12,410	\$12,973	\$12,576	\$13,493	\$51,453	\$11,296	\$12,702	\$12,015	\$12,730	\$48,750	\$11,250	\$12,040	\$11,755	\$12,510	\$47,555
% Chg	NM	NM	NM	NM	NM	-9%	-2%	-4%	-6%	-5%	0%	-5%	-2%	-2%	-2%

Source: Cowen and Company

Pfizer Annual Sales Dynamics (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
CARDIOVASCULAR											
Champix/Chantix - U.S.	343	365	360	370	380	390	400	410	+2%	+3%	
Champix/Chantix - EU (lc, ex fx)											
Champix/Chantix - EU	116	75	65	50	30	20	10	5	-36%	-36%	
Champix/Chantix - Etab. ROW	143	135	140	145	150	155	160	165			
Champix/Chantix - Emerging ROW	46	40	45	50	55	60	65	70			
Champix/Chantix - Worldwide	648	615	610	615	615	625	635	650	+1%	+0%	Varenicline; smoking cessation; pressured by suicide concerns/label
Bococizumab											
TOTAL CARDIOVASCULAR	\$648	\$815	\$810	\$815	\$715	\$825	\$935	\$1,050	\$0	+7%	5% of GIP in 2013; 4% in 2014; 6% in 2020
% Chg	-3%	-5%	-1%	1%	16%	15%	13%	12%			
CNS											
Lyrica - U.S.	\$1,963	\$2,325	\$2,525	\$2,800	\$3,100	\$3,400	\$200	\$100	-41%	-35%	Patent expiration December 2018
Lyrica - Etab. ROW	680	660	660	680	700	720	740	760			
Lyrica - Emerging ROW	494	495	515	535	555	575	595	615			
Lyrica - Worldwide	3137	3480	3700	4015	4355	4695	1535	1475	-13%	-10%	Epilepsy monoxit, central neuropathic pain due to spinal injury, peripheral neuropathic pain (US), post op pain, CR (qd dosing)
Tanezumab											
PF-5212377 (SAM-760)											
Ponezumab											
PF-2545920											
TOTAL CNS	\$3,137	\$3,480	\$3,700	\$4,015	\$4,455	\$4,885	\$1,885	\$1,875	-10%	-7%	22% of GIP in 2013; 25% in 2014; 11% in 2020
% Chg	11%	11%	6%	9%	11%	10%	-63%	2%			
ANTI-INFLAMMATORY											
Enbrel - EU (lc, ex fx).											
Enbrel - EU	2413	2540	2610	2700	2775	2850	2925	3000	+3%	+3%	
Enbrel - Etab. ROW	516	485	510	535	560	585	610	635			
Enbrel - Emerging ROW	845	815	835	855	875	895	915	935			
Enbrel - Total Ex US and Canada	3774	3840	3955	4090	4210	4330	4450	4570	+3%	+3%	Rheumatoid/psoriatic arthritis; rights in foreign mkt ex U.S./Canada; patent expires 2/15 (EU)
Xeljanz	114	290	460	700	900	1100	1300	1500	+32%	NM	Tofacitinib; oral JAK3 inhibitor; RA approved in U.S.; Phase III psoriasis, UC, PA; Phase II AS, Crohn's, atopic dermatitis; several year delay in EU as new data needed
ALO-02 Oxycodone-Naltrexone											
PF-4171327											
PF-5285401											
PF-547659											
PF-4236921											
TOTAL ANTI-INFLAMMATORY	\$3,888	\$4,130	\$4,415	\$4,815	\$5,280	\$5,705	\$6,150	\$6,595	+8%	+8%	27% of GIP in 2013; 30% in 2014; 39% in 2020
% Chg	4%	6%	7%	9%	9%	8%	8%	7%			
PAIN FRANCHISE											
Remoxy											
Oxycondone NT											
Acuerox/Other Acura Products											
TOTAL PAIN FRANCHISE	\$55	\$310	\$525	\$700	\$925	\$1,150	\$1,375	+71%	NM	0% of GIP in 2013; 1% in 2014; 8% in 2020	
% Chg	464%	69%	33%	32%	24%	20%					
METABOLIC											
Genotropin - U.S.	199	190	175	160	145	130	115	100	-10%	-9%	
Genotropin - EU (lc, ex fx.)											
Genotropin - EU	268	245	210	200	175	150	125	100	-14%	-13%	
Genotropin - Etab. ROW	197	185	200	210	220	230	240	250			
Genotropin - Emerging ROW	108	100	100	100	100	100	100	100			
Genotropin - Worldwide	772	720	685	670	640	610	580	550	-4%	-5%	Growth hormone (children, adults)

Source: Company data , Cowen and Company

Pfizer Annual Sales Dynamics (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
Ertugliflozin				100	200	300	400	500	NM	NM	Diabetes; SGLT2 inhibitor; Phase III; MRK/PFE 60/40 split
Duavée	15	90	150	200	250	300	350	+69%	NM	Bazedoxifene + Premarin; osteoporosis/menopausal symptoms; U.S. rollout underway, \$3.71/tablet; EU decision H2:14	
BMP-2	210	180	175	170	165	160	155	150	-3%	-5%	rhBMP-2/ACs; indicated for long bone fractures and spinal fusion
Somavert	217	235	255	275	295	315	335	355	+7%	+7%	Pegvisomant; growth hormone antagonist for acromegaly; via Sensus
TOTAL METABOLIC	\$1,199	\$1,150	\$1,205	\$1,385	\$1,500	\$1,635	\$1,770	\$1,905	+9%	+7%	8% of GIP in 2013; 8% in 2014; 11% in 2020
% Chg	-7%	-4%	5%	13%	10%	9%	8%	8%			
OTHER DRUGS											
Benefix - U.S.	\$395	\$410	\$370	\$325	\$275	\$225	\$175	\$125	-18%	-15%	
Benefix - EU (lc, ex fx)											
Benefix - EU	257	265	200	175	150	125	100	145	-10%	-8%	
Benefix - Etab. ROW	139	150	140	130	120	110	100	90			
Benefix - Emerging ROW	41	35	30	25	20	15	10	5			
Benefix - Worldwide	832	865	740	655	565	475	385	365	-13%	-11%	Hemophilia B; foreign rights reverted to WYE on 7/1/07; competition pressures
Refacto/Xyntha - U.S.	123	135	130	120	110	100	90	80	-8%	-6%	
Refacto/Xyntha - EU (lc, ex fx)											
Refacto/Xyntha - EU	386	390	375	370	355	340	325	310	-4%	-3%	
Refacto/Xyntha - Etab. ROW	70	80	75	70	65	60	55	50			
Refacto/Xyntha - Emerging ROW	23	30	25	25	25	25	25	25			
Refacto/Xyntha - Worldwide	602	640	605	585	555	525	495	465	-5%	-4%	Hemophilia A; Xyntha (albumin free) supports franchise; competitive
Viagra - U.S.	1,132	1,125	1,100	1,100	1,100	250	150	50	-40%	-36%	Substance patent expired 3/12 but U.S. use patent upheld; Teva can launch 12/17; Cialis generics 11/17
Rapamune - U.S.	201	200	160	120	80	50	25	10	-39%	-35%	Immunosuppressant; kidney transplant rejection; oral tab boosts; patent exp 1/14 U.S., generics launched
Rapamune - EU (lc, ex fx)											
Rapamune - EU	52	45	40	20	10	5	5	5	-31%	-28%	Patent exp 6/15 EU
Rapamune - Etab. ROW	17	20	20	20	20	20	20	20			
Rapamune - Emerging ROW	80	65	55	45	35	25	15	5			
Rapamune - Worldwide	350	330	275	205	145	100	65	40	-30%	-27%	
Toviaz	236	285	310	330	350	370	390	410	NM	NM	Fesoterodine; overactive bladder; EU and U.S.
Taliglucerase alfa	30	50	90	125	175	225	275	325	NM	NM	Gaucher's disease; approved; with Protalix
Vyndaqel (tafamidis meglumine)		10	25	50	100	150	200	250	NM	NM	TTR dissociation inhib; transthyretin familial amyloid polyneuropathy (U.S.); PDE5; diabetic nephropathy; Phase II
PF-489791					25	50	75	100	NM	NM	Acetyl-CoA carboxylase inhibitor; diabetic mellitus; Phase II
PF-5175157					25	50	75	100	NM	NM	CCR2/5 antagonist; diabetic nephropathy, diabetic macular edema; Phase II
PF-4634817					25	50	75	100	NM	NM	M-CSF inhibitor; sarcoidosis, lupus (biologic); Phase II
PD-360324					25	50	75	100	NM	NM	CTGF; dermal scarring; Phase II
PF-6473871 (EXC001)					25	50	75	100	NM	NM	Pan-selectin antagonist; vaso-occlusive crisis associated with Sickle Cell Disease; Phase II
Rivipansel (GMI-1070)					25	50	75	100	NM	NM	
PF-4937319					10	20	30	40	NM	NM	Partial glucokinase activator; diabetes; Phase II
Xiaflex	8								NM	NM	PFE had ex-U.S. rights but agreement ended 4/24/13
Other GIP Products	735	660	600	550	500	450	400	350			
TOTAL OTHER DRUGS	\$3,925	\$3,985	\$3,745	\$3,800	\$3,850	\$2,885	\$2,840	\$2,895	-5%	-4%	28% of GIP In 2013; 29% in 2014; 17% in 2020
% Chg	28%	1%	-6%	-4%	1%	-22%	-1%	2%			
TOTAL GIP PHARMACEUTICALS	\$12,797	\$13,395	\$13,985	\$14,935	\$16,280	\$16,850	\$14,680	\$15,695	+3%	+3%	
ALLIANCE REVENUE											
PFE Alliance Revenue	\$73	\$340	\$540	\$700	\$825	\$950	\$1,075	\$1,200	+23%	+49%	Eliquis (with BMY)
WYE Alliance Revenue	<u>1,305</u>										North American rights to Enbrel reverted to AMGN in 11/1/13; royalties to "other income"
ALLIANCE REVENUE	\$1,378	\$340	\$540	\$700	\$825	\$950	\$1,075	\$1,200	+23%	-2%	10% of GIP In 2013; 2% in 2014; 7% in 2020
% Chg		NM	59%	30%	18%	15%	13%	12%			
TOTAL GIP	\$14,175	\$13,735	\$14,525	\$15,635	\$17,105	\$17,800	\$15,755	\$16,895	+4%	+3%	28% of Pfizer total In 2013; 28% in 2014; 31% in 2020
% Chg	-3%	6%	8%	9%	4%	-11%	7%				

Source: Company data , Cowen and Company

Pfizer Annual Sales Dynamics (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
ONCOLOGY											
Sutent - U.S.	\$351	\$355	\$380	\$400	\$420	\$440	\$460	\$480	+5%	+5%	Multiple tyrosine kinase inhibitors; patent challenged under paragraph IV; patent expires 2021
Sutent - EU (lc, ex fx)											
Sutent - EU	402	420	440	475	500	525	550	575	+5%	+5%	
Sutent - Etab. ROW	140	145	165	185	205	225	245	265			
Sutent - Emerging ROW	311	260	280	300	320	340	360	380			
Sutent - Worldwide	1204	1185	1265	1360	1445	1530	1615	1700	+6%	+5%	Approved for Gleevec-resistant GIST and RCC; CRC PIII; GU and GI PII
Palbociclib (PD-332991)					250	500	1,000	2,000	3,000	NM	CDK4/6 inhibitor; 1st line advanced breast cancer approval unlikely on Phase II data; many other tumors in trials
Xalkori (crizotinib)	282	445	620	700	800	900	1,000	1,100	+16%	+21%	Oral c-Met and ALK inhibitor; marketed in U.S. for tx of advanced NSCLC in small percent of patients (3-4% of lung CA pts); filed Japan H1:11
Inlyta (axitinib)	319	420	530	625	700	775	850	925	+14%	NM	Anti-angiogenesis inhib; 2nd line renal; Phase II for lung, thyroid, hepatic, melanoma, glioblastoma, liver
Inotuzumab (PF-5208773)				50	100	150	200	250	NM	NM	CD-22 calcineurin conjugate; ALL Phase II; NHL trials stopped
Torisel	132	135	150	165	175	185	195	205	+7%	+6%	Temsirolimus; mkt for renal cell cancer; mantle cell in fgn mks; not pursuing in U.S.; pat exp 4/14 U.S., 4/20 ex U.S.
Bosulif	31	75	110	130	150	170	190	210	NM	NM	Bosutinib; abl/src kinase inhibitor; previously tx CML (US), CML (EU); Phase III data mixed; approved U.S.; Phase II polycystic kidney disease
Dacomitinib (PF-299804)					25	50	75	100	NM	NM	pan-HER inhibitor; NSCLC; previously tx and advanced studies failed; tx naïve trial continues in Phase III
PF-5212384					25	50	75	100	NM	NM	PI3K-mTOR inhibitor; 3rd line colorectal cancer; Phase II
PF-3446962					25	50	75	100	NM	NM	ALK1 inhibitor; 2nd line hepatocellular carcinoma (biologic); Phase II
TOTAL ONCOLOGY	\$1,908	\$2,260	\$2,725	\$3,380	\$3,995	\$4,810	\$6,825	\$7,740	+23%	+22%	21% of VOC In 2013; 29% in 2014; 39% in 2020
% Chg	23%	15%	21%	22%	20%	23%	29%	22%			
VACCINES											
Prevnar 13 - U.S.	\$1,804	\$1,940	\$2,150	\$2,350	\$2,550	\$2,750	\$2,950	\$3,150	+8%	+8%	ACIP recommended in immunocompromised adults >65y/o post CAPITA data
Prevnar 13 - EU (lc, ex fx)											
Prevnar 13 - EU	758	755	780	820	840	860	880	1085	+6%	+5%	
Prevnar 13 - Etab. ROW	455	505	640	750	850	950	1050	1150			
Prevnar 13 - Emerging ROW	876	1055	1175	1275	1375	1475	1575	1675			
Prevnar 13 - Worldwide	3893	4255	4745	5,195	5,615	6,035	6,455	7,060	+9%	+9%	13 valent pneumococcal conjugate vaccine
Prevnar 7 - U.S.	0	0	0	0	0	0	0	0	NM	NM	
Prevnar 7 - EU (lc, ex fx)											
Prevnar 7 - EU	0	0	0	0	0	0	0	0			
Prevnar 7 - Etab. ROW	81	0	0	0	0	0	0	0			
Prevnar 7 - Emerging ROW	0	0	0	0	0	0	0	0			
Prevnar 7 - Worldwide	81	0	0	0	0	0	0	0	NM	NM	
MnB (PF-5212366) (rLP2086)			150	250	350	450	550	650	NM	NM	Menengococcal B disease; filed June 2014 for adolescence and young adults, Phase I (infants)
NeisVac-C			125	130	135	145	150	155	NM	NM	Menigitis C; marketed; from BAX; acquired for \$635MM
FSME-IMMUN/TicoVac			125	130	135	145	150	155	NM	NM	Tick-borne encephalitis; marketed in 30 countries; from BAX; acquired for \$635MM
PF-6290510					25	50	75	100	NM	NM	4-antigen staphylococcus aureus vaccine; Phase II
PF-6425090					25	50	75	100	NM	NM	Clostridium difficile vaccine; Phase II
Meningitec	0	0	0	0	0	0	0	0	NM	NM	Menengococcal group C vaccine; U.K., Spain, Italy
HibTITER	5	5	5	5	5	5	5	5	+0%	+0%	Haemophilus influenzae; pediatric vaccine
Vaccine, Other	19	10	20	20	20	20	20	20	+12%	+1%	
TOTAL VACCINES	\$3,974	\$4,270	\$5,170	\$5,790	\$6,310	\$6,800	\$7,480	\$8,245	+12%	+11%	49% of VOC In 2013; 49% in 2014; 41% in 2020
% Chg	-5%	7%	21%	11%	10%	9%	8%	10%			
TOTAL VOC PHARMACEUTICALS	\$5,942	\$6,850	\$7,885	\$9,080	\$10,305	\$11,810	\$13,805	\$15,985	+16%	+15%	84% of VOC In 2013; 65% in 2014; 79% in 2020
CONSUMER CARE PRODUCTS											
Advil franchise	\$953	\$960	\$990	\$1,025	\$1,075	\$1,125	\$1,175	\$1,225	+4%	+4%	Ibuprofen; NSAID
Centrum	764	770	790	810	830	850	870	890	+2%	+2%	Vitamins
Caltrate	360	365	385	405	425	445	465	485	+5%	+4%	
Robutussin	176	170	190	210	230	250	270	290	+9%	+7%	Cough suppressant
Chapstick	135	140	155	165	175	185	195	205	+7%	+6%	Lip balm
Other	954	1,085	1,100	1,125	1,150	1,175	1,200	1,225	+2%	+4%	
TOTAL CONSUMER CARE	\$3,342	\$3,492	\$3,810	\$3,740	\$3,885	\$4,030	\$4,175	\$4,320	+4%	+4%	36% of VOC In 2013; 35% in 2014; 21% in 2020
% Change	4%	5%	3%	4%	4%	4%	4%	3%			
TOTAL VOC	\$9,284	\$10,023	\$11,505	\$12,800	\$14,190	\$15,840	\$17,980	\$20,305	+12%	+12%	18% of Pfizer total In 2013; 21% in 2014; 37% in 2020
% Chg		8%	15%	11%	11%	12%	14%	13%			

Source: Company data , Cowen and Company

Pfizer Annual Sales Dynamics (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
CARDIOVASCULAR											
Lipitor - U.S.	\$432	\$245	\$150	\$100	\$50	\$25	\$10	\$5	-48%	-47%	Multisource generics launched 5/31/12
Lipitor - EU (lc, ex fx)											
Lipitor - EU	319	250	150	125	100	75	50	25	-32%	-30%	E.U. basic patents expired in H1:12 with pedi extension
Lipitor - Estab. ROW	510	340	290	250	200	100	75	50			Japanese basic patents expired in 6/11
Lipitor - Emerging ROW	1054	1090	1125	1225	1325	1425	1525	1625			
Lipitor - Worldwide	2315	1925	1715	1,700	1,675	1,625	1,660	1,705	-2%	-4%	Modest cholesterol reduction market growth anticipated
Norvasc - U.S.	39	30	20	10	5	5	5	5	-26%	-25%	
Norvasc - EU (lc, ex fx)											
Norvasc - EU	108	90	70	50	40	30	20	10	-31%	-29%	
Norvasc - Estab. ROW	485	370	330	300	250	200	150	100			
Norvasc - Emerging ROW	597	610	630	650	670	690	710	730			
Norvasc - Worldwide	1229	1100	1050	1,010	965	925	885	845	-4%	-5%	Generic competition eroding franchise, tempered by emerging ROW
Cardura - U.S.	4	0	0	0	0	0	0	0	NM	NM	
Cardura - EU (lc, ex fx)											
Cardura - EU	86	70	50	20	10	5	5	5	-36%	-33%	
Cardura - Estab. ROW	100	80	60	50	40	30	20	10			
Cardura - Emerging ROW	106	110	125	135	145	155	165	175			
Cardura - Worldwide	296	265	235	205	195	190	190	190	-5%	-6%	Generic competition eroding franchise, tempered by emerging ROW
Caduet - U.S.	23	15	10	5	5	5	5	5	-17%	-20%	
Caduet - EU (lc, ex fx)											
Caduet - EU	14	5	5	5	5	5	5	5	+0%	-14%	
Caduet - Estab. ROW	142	105	110	100	90	80	70	60			
Caduet - Emerging ROW	44	40	30	20	10	5	5	5			
Caduet - Worldwide	223	165	155	130	110	95	85	75	-12%	-14%	Lipitor/Norvasc combination; generics launched
Fragmin - U.S.	23	15	10	5	5	5	5	5	-17%	-20%	Dalteparin; LMW heparin; UCAD, hip, abdom. surg.; pat. exp. 12/04
Fragmin - EU (lc, ex fx)											
Fragmin - EU	183	210	220	230	240	250	260	270	+4%	+6%	
Fragmin - Estab. ROW	89	90	100	105	110	115	120	125			
Fragmin - Emerging ROW	64	50	40	30	20	10	5	5			
Fragmin - Worldwide	359	365	370	370	375	380	390	405	+2%	+2%	
Inspira	233	260	270	285	300	315	330	345	+5%	+6%	SAB; hypertension and post MI
Tikosyn	119	135	150	160	170	180	190	200	+7%	+8%	Dofetilide; atrial arrhythmia; very limited potential
Accupril	103	40	30	20	10	5	5	5	-29%	-35%	Generic competition pressures; litigation continues
Other	400	405	400	400	400	400	400	400	-0%	+0%	
TOTAL CARDIOVASCULAR	\$5,278	\$4,660	\$4,375	\$4,280	\$4,200	\$4,115	\$4,135	\$4,170	-2%	-3%	19% of GEP in 2013; 19% in 2014; 24% in 2020
% Chg	-26%	-12%	-6%	-2%	-2%	-2%	0%	1%			

Source: Company data , Cowen and Company

Pfizer Annual Sales Dynamics (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
ANTI-INFECTIVES											
Zyvox - U.S.	\$688	\$695	\$370	\$100	\$75	\$50	\$25	\$10	-51%	-45%	Patent expires 5/15
Zyvox - EU (lc, ex fx).											
Zyvox - EU	325	345	365	150	100	50	25	10	-45%	-39%	Patent expires 1/16
Zyvox - Estab. ROW	136	120	100	90	80	70	60	50			
Zyvox - Emerging ROW	204	185	175	165	155	145	135	125			
Zyvox - Worldwide	1353	1345	1010	505	410	315	245	195	-28%	-24%	Gram + infections; launched in 27 countries
Vfend - U.S.	61	50	40	20	10	5	5	5	-32%	-30%	Via settlement, generics entered U.S. market in Q1:11
Vfend - EU (lc, ex fx).											
Vfend - EU	305	325	335	100	75	50	25	10	-44%	-39%	Patent expires 1/16
Vfend - Estab. ROW	154	155	160	165	170	175	180	185			
Vfend - Emerging ROW	255	260	275	290	300	310	320	330			
Vfend - Worldwide	775	790	810	575	555	540	530	530	-6%	-5%	Voriconazole
Zosyn - U.S.	172	145	100	80	60	40	20	10	-36%	-33%	Generics marketed; new form patent exp 2023
Zosyn - EU (lc, ex fx).											
Zosyn - EU	40	25	15	10	5	5	5	5	-24%	-26%	Patent exp mid-'07; new form rolling out but ability to protect limited; generics
Zosyn - Estab. ROW	12	20	25	30	35	40	45	50			
Zosyn - Emerging ROW	171	145	130	120	110	100	90	80			
Zosyn - Worldwide	395	335	270	240	210	185	160	145	-13%	-13%	IV antibiotic
Zithromax - U.S.	7	0	5	5	5	5	5	5	#NUM!	-5%	U.S. patent expired 11/05; generics pressuring
Zithromax - EU (lc, ex fx).											
Zithromax - EU	59	50	40	30	20	10	5	5	-32%	-30%	
Zithromax - Estab. ROW	130	100	80	60	40	20	10	5			Japan patent expiration 2013
Zithromax - Emerging ROW	191	195	205	215	225	235	245	255			
Zithromax - Worldwide	387	345	330	310	290	270	265	270	-4%	-5%	Broad spectrum antibiotic but in decline
Tygacil - U.S.	150	145	150	155	160	165	170	175	+3%	+2%	
Tygacil - EU (lc, ex fx).											
Tygacil - EU	72	75	80	85	90	95	100	105	+6%	+6%	
Tygacil - Estab. ROW	7	15	20	25	30	35	40	45			
Tygacil - Emerging ROW	129	130	135	140	145	150	155	160			
Tygacil - Worldwide	358	370	385	405	425	445	465	485	+5%	+4%	Tigecycline; serious gram +, -, anaerobic, atypical, resistant infections
Eraxis	138	150	160	170	180	190	200	210	+6%	+6%	Echinocandin antifungal; esophageal candidiasis
Diflucan	242	230	210	190	170	150	130	110	-12%	-11%	U.S. and foreign patents expired
Cleocin	200	185	160	140	120	100	80	60	-17%	-16%	Older macrolide antibiotic; declining sales due to generics
Minocin	20	10	5	5	5	5	5	5	-11%	-18%	Minocycline; moderate/severe acne
Other	732	750	770	790	810	830	850	870	+3%	+2%	
TOTAL ANTI-INFECTIVES	\$4,800	\$4,510	\$4,110	\$3,330	\$3,175	\$3,030	\$2,930	\$2,880	-7%	-6%	17% of GEP in 2013; 18% in 2014; 16% in 2020
% Chg	-3%	-2%	-9%	-19%	-5%	-5%	-3%	-2%			

Source: Cowen and Company

Pfizer Annual Sales Dynamics (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
ANTI-INFECTIVES											
Zyvox - U.S.	\$688	\$690	\$370	\$100	\$75	\$50	\$25	\$10	-51%	-45%	Patent expires 5/15
Zyvox - EU (lc, ex fx).											
Zyvox - EU	325	340	355	150	100	50	25	10	-44%	-39%	Patent expires 1/16
Zyvox - Estab. ROW	136	120	100	90	80	70	60	50			
Zyvox - Emerging ROW	204	185	175	165	155	145	135	125			
Zyvox - Worldwide	1353	1340	1000	505	410	315	245	195	-27%	-24%	Gram + infections; launched in 27 countries
Vfend - U.S.	61	45	30	20	10	5	5	5	-31%	-30%	Via settlement, generics entered U.S. market in Q1:11
Vfend - EU (lc, ex fx).											
Vfend - EU	305	310	320	100	75	50	25	10	-44%	-39%	Patent expires 1/16
Vfend - Estab. ROW	154	155	160	165	170	175	180	185			
Vfend - Emerging ROW	255	305	315	325	335	345	355	365			
Vfend - Worldwide	775	815	825	610	590	575	565	565	-6%	-4%	Voriconazole
Zosyn - U.S.	172	145	100	80	60	40	20	10	-36%	-33%	Generics marketed; new form patent exp 2023
Zosyn - EU (lc, ex fx).											
Zosyn - EU	40	25	15	10	5	5	5	5	-24%	-26%	Patent exp mid-'07; new form rolling out but ability to protect limited; generics
Zosyn - Estab. ROW	12	15	25	30	35	40	45	50			
Zosyn - Emerging ROW	171	135	125	115	105	95	85	75			
Zosyn - Worldwide	395	320	265	235	205	180	155	140	-13%	-14%	IV antibiotic
Zithromax - U.S.	7	5	5	5	5	5	5	5	+0%	-5%	U.S. patent expired 11/05; generics pressuring
Zithromax - EU (lc, ex fx).											
Zithromax - EU	59	50	40	30	20	10	5	5	-32%	-30%	
Zithromax - Estab. ROW	130	70	60	50	40	20	10	5			Japan patent expiration 2013
Zithromax - Emerging ROW	191	190	200	210	220	230	240	250			
Zithromax - Worldwide	387	320	305	295	285	265	260	265	-3%	-5%	Broad spectrum antibiotic but in decline
Tygacil - U.S.	150	130	140	150	160	170	180	190	+7%	+3%	
Tygacil - EU (lc, ex fx).											
Tygacil - EU	72	75	80	85	90	95	100	105	+6%	+6%	
Tygacil - Estab. ROW	7	15	20	25	30	35	40	45			
Tygacil - Emerging ROW	129	135	140	145	150	155	160	165			
Tygacil - Worldwide	358	350	380	405	430	455	480	505	+6%	+5%	Tigecycline; serious gram +, -, anaerobic, atypical, resistant infections
Eraxis	138	145	160	170	180	190	200	210	+6%	+6%	Echinocandin antifungal; esophageal candidiasis
Diflucan	242	225	210	190	170	150	130	110	-11%	-11%	U.S. and foreign patents expired
Cleocin	200	185	160	140	120	100	80	60	-17%	-16%	Older macrolide antibiotic; declining sales due to generics
Minocin	20	10	5	5	5	5	5	5	-11%	-18%	Minocycline; moderate/severe acne
Other	732	750	770	790	810	830	850	870	+3%	+2%	
TOTAL ANTI-INFECTIVES	\$4,600	\$4,460	\$4,080	\$3,345	\$3,205	\$3,065	\$2,970	\$2,925	-7%	-6%	17% of GEP in 2013; 18% in 2014; 17% in 2020
% Chg	-3%	-3%	-9%	-18%	-4%	-4%	-3%	-2%			

Source: Company data , Cowen and Company

Pfizer Annual Sales Dynamics (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
CNS											
Lyrica - EU (lc, ex fx)											
Lyrica - EU	1458	1155	485	250	150	50	25	10	-55%	-51%	Patent expiration July 2014
Neurontin	216	200	175	155	135	115	95	75	-15%	-14%	Generic competition pressures
Total Gabapentinoids	1,674	1,355	660	405	285	165	120	85	-37%	-35%	
Pristiq - U.S.	540	575	610	650	690	730	770	815	+6%	+6%	Depression; 0.9% share 7/14
Pristiq - EU (lc, ex fx)											
Pristiq - EU	1	5	0	0	0	0	0	0			
Pristiq - Estab. ROW	105	115	140	160	180	200	220	240			
Pristiq - Emerging ROW	52	60	70	80	90	100	110	120			
Pristiq - Worldwide	698	755	820	890	960	1,030	1,100	1,175	+8%	+8%	WW depression market growing modestly; vasomotor symptom
Zoloft - U.S.	44	35	15	10	5	5	5	5	-28%	-27%	Generic competition pressures
Zoloft - EU (lc, ex fx)											
Zoloft - EU	63	60	40	30	20	10	5	5	-34%	-30%	Patent expiration February 2013
Zoloft - Estab. ROW	221	180	160	140	120	100	80	60			Launch in Japan possible but not near term
Zoloft - Emerging ROW	141	140	155	165	175	185	195	205			
Zoloft - Worldwide	469	415	370	345	320	300	285	275	-7%	-7%	
Geodon - U.S.	65	20	10	5	5	5	5	5	-21%	-31%	Patent expiration 3/12
Geodon - EU (lc, ex fx)											
Geodon - EU	36	25	20	10	5	5	5	5	-24%	-25%	
Geodon - Estab. ROW	20	30	35	40	45	50	55	60			
Geodon - Emerging ROW	72	75	90	100	110	120	130	140			
Geodon - Worldwide	194	150	155	155	165	180	195	210	+6%	+1%	Schizophrenia; adjunct bipolar depression
Effexor - U.S.	173	130	100	75	50	25	10	5	-42%	-40%	XR generic competition post 6/10
Effexor - EU (lc, ex fx)											
Effexor - EU	96	80	60	40	20	10	5	5	-37%	-34%	Patent expired 12/08 in most major markets
Effexor - Estab. ROW	68	45	30	20	10	5	5	5			Japanese filing withdrawn
Effexor - Emerging ROW	103	100	115	125	135	145	155	165			
Effexor - Worldwide	440	360	305	260	215	185	175	180	-11%	-12%	WW depression market growing modestly
Aricept - U.S.	0	0	0	0	0	0	0	0	NM	NM	
Aricept - EU (lc, ex fx)											
Aricept - EU	43	15	25	15	10	5	5	5	-17%	-27%	Direct sales under license agreement
Aricept - Estab. ROW	160	115	90	80	70	60	50	40			
Aricept - Emerging ROW	32	20	15	10	5	5	5	5			
Aricept - Worldwide	235	150	130	105	85	70	60	50	-17%	-20%	
Xanax/Xanax XR	276	255	235	215	195	175	155	135	-10%	-10%	Anxiety; generic competition to XR form; XR patent pending
Ativan	133	115	105	95	85	75	65	55	-12%	-12%	Old anxiety drug; off-patent; sold U.S. rights to Biovail
Dilantin	157	130	120	110	100	90	80	70	-10%	-11%	Pressure from newer anti-epilepsy drugs
Relpax	359	355	325	275	225	175	125	75	-23%	-20%	Migraine; eletriptan; patent expiration 8/13
Halcion	74	65	50	35	20	5	5	5	-35%	-32%	Insomnia; international growth helping to offset U.S. generics
Other	50	60	60	60	60	60	60	60	+0%	+3%	
TOTAL CNS	\$4,759	\$4,185	\$3,335	\$2,950	\$2,715	\$2,510	\$2,425	\$2,375	-9%	-9%	17% of GEP in 2013; 17% in 2014; 14% in 2020
% Chg	-3%	-12%	-20%	-12%	-8%	-8%	-3%	-2%			

Source: Company data , Cowen and Company

Pfizer Annual Sales Dynamics (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
ANTI-INFLAMMATORY											
Celebrex - U.S.	1933	1,870	390	100	75	50	25	10	-58%	-53%	Subst pat. exp. 5/14, court rejected RE methods of tx OA pat. exp. 12/2/15 (incl pedi); settled, one generic to enter 12/14
Celebrex - EU (lc, ex fx).											
Celebrex - EU	151	130	70	60	50	40	30	20	-27%	-25%	Patent expires 11/14
Celebrex - Estab. ROW	464	450	440	430	420	410	400	390			
Celebrex - Emerging ROW	370	385	400	415	430	445	460	475			
Celebrex - Worldwide	2918	2835	1300	1,005	975	945	915	895	-17%	-16%	
Dynastat	130	145	150	160	170	180	190	200	+6%	+6%	Injectable Coxib
Coxib Franchise	3,049	2,980	1,450	1,165	1,145	1,125	1,105	1,095	-15%	-14%	Coxib for osteoarthritis
Arthrotec	92	65	60	40	20	10	5	5	-35%	-34%	Diclofenac + misoprostol
Other	97	99	100	100	100	100	100	100	+0%	+0%	
TOTAL ANTI-INFLAMMATORY	\$3,237	\$3,144	\$1,610	\$1,305	\$1,285	\$1,235	\$1,210	\$1,200	-15%	-13%	12% of GEP in 2013; 13% in 2014; 7% in 2020
% Chg	3%	-3%	-49%	-19%	-3%	-2%	-2%	-1%			
PAIN FRANCHISE											
Flector Patch	130	135	145	155	165	175	185	195	+6%	+6%	Diclofenac (NSAID) topical patch for acute inflammatory pain
Thrombin-JMI	98	90	80	70	60	50	40	30	-17%	-16%	Bovine-derived hemostat for post-surgical wound healing
Levoxyl	2	5	5	5	5	5	5	5	NM	+14%	Hypothyroidism; generic competition in 7/04
Other											
TOTAL PAIN FRANCHISE	\$230	+0%	+0%	1% of GEP in 2013; 1% in 2014; 1% in 2020							
% Chg	-33%	0%	0%	0%	0%	0%	0%	0%			
ONCOLOGY											
Aromasin - U.S.	16	20	10	5	5	5	5	5	-21%	-15%	Competitor generics launched June 2011
Aromasin - EU (lc, ex fx).											
Aromasin - EU	29	0	0	0	0	0	0	0	NM	NM	
Aromasin - Estab. ROW	37	30	20	15	10	5	5	5			
Aromasin - Emerging ROW	89	95	105	115	125	135	145	155			
Aromasin - Worldwide	172	145	135	135	140	145	155	165	+2%	-1%	Exemestane; breast cancer, 2nd and 3rd-line
Ellence/Pharmorubicin	106	90	75	65	55	45	35	25	-19%	-19%	Epirubicin; breast cancer; adjuvant therapy; U.S.
Camptosar	81	50	30	20	10	5	5	5	-32%	-33%	Irinotecan; colorectal, other tumors in devel; U.S. pat. exp.: 2/08; Europe 2009
Other	347	300	250	200	150	100	50	25	-34%	-31%	Breast cancer, other solid tumors; generic competition; foreign
TOTAL ONCOLOGY	\$706	\$583	\$490	\$420	\$355	\$295	\$245	\$220	-15%	-15%	3% of GEP in 2013; 2% in 2014; 1% in 2020
% Chg	-11%	-17%	-16%	-14%	-15%	-17%	-17%	-10%			

Source: Company data , Cowen and Company

Pfizer Annual Sales Dynamics (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
OPHTHALMOLOGY											
Xalatan - U.S.	\$30	\$15	\$10	5	5	5	5	5	-17%	-23%	Patent expired 3/11
Xalatan - EU (lc, ex fx).											
Xalatan - EU	162	115	80	50	25	10	5	5	-41%	-39%	
Xalatan - Estab. ROW	232	200	175	150	125	100	75	50			
Xalatan - Emerging ROW	166	155	140	130	120	110	100	90			
Xalatan - Worldwide	590	480	405	335	275	225	185	150	-18%	-18%	Latanaprost; glaucoma; growing despite competition; Xalcom in Europe
Moxidectin		20	30	40	50	60	70	200	NM	NM	Glutamate-gated chloride channel binding; onchocerciasis (river blindness); Phase III
Macugen	8	10	15	15	15	15	15	15	+7%	+9%	Macular edema degeneration; Lucentis drives decline; ex U.S. rights from OSI
TOTAL OPHTHALMOLOGY	\$598	\$510	\$450	\$390	\$340	\$300	\$270	\$365	-5%	-7%	2% of GEP in 2013; 2% in 2014; 2% in 2020
% Chg	-27%	-15%	-12%	-13%	-13%	-12%	-10%	35%			
		\$0									
METABOLIC											
Premarin - U.S.	\$1,001	1,025	1,040	1,060	1,080	1,100	1,120	1,140	+2%	+2%	
Premarin - EU (lc, ex fx).											
Premarin - EU	9	15	10	10	10	10	10	10	-7%	+1%	
Premarin - Estab. ROW	37	35	45	50	55	60	65	70			
Premarin - Emerging ROW	45	40	35	30	25	20	15	10			
Premarin - Worldwide Franchise	1092	1115	1130	1,150	1,170	1,190	1,210	1,230	+2%	+2%	Low dose supports
Medrol - U.S.	148	160	185	205	225	245	265	285	+10%	+10%	
Medrol - EU (lc, ex fx).											
Medrol - EU	91	100	110	120	130	140	150	160	+8%	+8%	
Medrol - Estab. ROW	39	40	50	55	60	65	70	75			
Medrol - Emerging ROW	187	155	145	135	125	115	105	95			
Medrol - Worldwide	465	455	490	515	540	565	590	615	+5%	+4%	
Depo Provera	198	200	210	220	230	240	250	260	+4%	+4%	Exclusivity expired 10/95, but tough formulation
Conbrizva/Viviant	89	100	110	120	130	140	150	160	+8%	+9%	Osteoporosis; NDA filing for tx and prevention H2:09; VTE/stroke analysis required; launched in EU and Japan
Estring U.S.	74	75	85	90	95	100	105	110	+7%	+6%	Urogenital estrogen deficiency
Salazopyrin	106	95	90	80	70	60	50	40	-13%	-13%	50% of IBD market; rheumatoid arthritis; En Tabs support
Glyset	10	10	10	10	10	10	10	10	+0%	+0%	Oral agent for Type II diabetes; combo-therapy
Glucotrol Line	28	20	15	10	5	5	5	5	-21%	-22%	XL formulation offsets generic erosion; XL patent exp. 2009
Provera	25	20	15	10	5	5	5	5	-21%	-21%	U.S. franchise decline partly offset by international growth
Other	631	635	640	645	650	655	660	665	+1%	+1%	
TOTAL METABOLIC	\$2,719	\$2,725	\$2,795	\$2,850	\$2,905	\$2,970	\$3,035	\$3,100	+2%	+2%	10% of GEP in 2013; 11% in 2014; 18% in 2020
% Chg	0%	0%	3%	2%	2%	2%	2%	2%			

Source: Company data , Cowen and Company

Pfizer Annual Sales Dynamics (\$MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
OTHER DRUGS											
Viagra - EU (lc, ex fx)											
Viagra - EU	265	85	70	50	30	10	5	5	-38%	-43%	Patent expired 6/13
Viagra - Estab. ROW	152	125	100	90	80	70	60	50			
Viagra - Emerging ROW	332	310	290	270	250	230	210	190			
Viagra - Worldwide	750	520	460	410	360	310	275	245	-12%	-15%	Oral treatment for MED
Detrol LA/Detrol - U.S.	375	20	10	5	5	5	5	5	-21%	-46%	Generics launched 1/14
Detrol LA/Detrol - EU (lc, ex fx)											
Detrol LA/Detrol - EU	53	30	15	10	5	5	5	5	-26%	-29%	
Detrol LA/Detrol - Estab. ROW	87	90	100	110	120	130	140	150			
Detrol LA/Detrol - Emerging ROW	48	40	40	50	60	70	80	90			
Detrol LA/Detrol - Worldwide	562	180	165	175	190	210	230	250	+6%	-11%	Overactive bladder
Revatio - U.S.	67	45	30	20	10	5	5	5	-31%	-31%	Patent expired 3/12 + 6 months pedi exclusivity
Revatio - EU (lc, ex fx)											
Revatio - EU	158	160	150	140	130	120	110	100	-8%	-6%	
Revatio - Estab. ROW	52	55	65	75	85	95	105	115			
Revatio - Emerging ROW	31	30	25	20	15	10	5	5			
Revatio - Worldwide	308	285	270	255	240	230	225	225	-4%	-4%	
Lybrel	26	30	35	40	45	50	55	60	+12%	+13%	Low dose, continuous contraceptive; U.S. rollout underway but sampling heavy; EU filing withdrawn
Protonix	165	165	155	145	135	125	115	105	-7%	-6%	Generic competition
Ansaid	5	5	5	5	5	5	5	5	+0%	+0%	
Zoton	20	10	5	5	5	5	5	5	-11%	-18%	Lansoprazole; from Takeda; ex U.S. only; patent expired in U.K. 12/05
Lodine, Lodine XL	5	5	5	5	5	5	5	5	+0%	+0%	NSAID; patent expired
Other	2,544	2,290	2,175	2,075	1,975	1,875	1,775	1,675	-5%	-6%	
TOTAL OTHER DRUGS	\$4,385	\$3,490	\$3,275	\$3,115	\$2,960	\$2,815	\$2,690	\$2,575	-5%	-7%	18% of GEP in 2013; 14% in 2014; 15% in 2020
% Chg	-23%	-20%	-6%	-5%	-5%	-5%	-4%	-4%			
TOTAL PHARMACEUTICALS	\$26,511	\$23,965	\$20,640	\$18,885	\$18,175	\$17,535	\$17,210	\$17,160	-5%	-6%	
ALLIANCE REVENUE											
PFE Alliance Revenue	\$1,250	\$810	\$685	\$195	\$5				NM	NM	Spiriva (BI), Rebif (Serono), Aricept (Eisai)
ALLIANCE REVENUE	\$1,250	\$810	\$685	\$195	\$5				NM	NM	5% of GEP in 2013; 3% in 2014; 0% in 2020
% Chg	-46%	NM	-15%	-72%							
TOTAL GEP	\$27,761	\$24,775	\$21,325	\$19,080	\$18,180	\$17,535	\$17,210	\$17,160	-6%	-7%	54% of Pfizer total in 2013; 51% in 2014; 32% in 2020
% Chg	-11%	-14%	-11%	-5%	-4%	-2%	0%				
MISCELLANEOUS											
Other	\$232	\$215	\$200	\$180	\$160	\$140	\$120	\$100	-12%	-11%	Bulk steroids, specialty intermediates; good profitability
MISCELLANEOUS	\$232	\$215	\$200	\$180	\$160	\$140	\$120	\$100	-12%	-11%	0% of Pfizer total in 2013; 0% in 2014; 0% in 2020
% Chg.	-11%	-7%	-7%	-10%	-11%	-13%	-14%	-17%			
PFIZER TOTAL SALES	\$51,453	\$48,750	\$47,555	\$47,695	\$49,635	\$51,315	\$51,065	\$54,460	+2%	+1%	
% Chg	NM	-5%	-2%	0%	4%	3%	0%	7%			

Source: Company data , Cowen and Company

Pfizer 2013-20 Alliance Revenue Buildup (\$MM)

Co-marketed Products	2013	2014-20 CGR								2013-20 CGR	Portion Pfizer Books
		2014E	2015E	2016P	2017P	2018P	2019P	2020P			
Eliquis	\$146	\$680	\$1,080	\$1,400	\$1,650	\$1,900	\$2,150	\$2,400	+23%	NM	- JV sales; apixaban; filed for venous thromboembolism treatment and prevention
Spiriva	1,225	650	500	250	0	0	0	0	NM	NM	- JV sales; worldwide copromotion with BI; patent expires 3/14; agreement ends 2012-13 (EU), 2014 (US/Japan)
Aricept	150	100	50	25	5	0	0	0	NM	NM	- JV profits; JV covers U.S., Japan, U.K., France, Germany; U.S. patent expired 11/10 but 23mg tablet has exclusivity to 7/13
Rebif	1,100	1,150	1,200	0	0	0	0	0	NM	NM	- Assume JV sales; agreement duration subject of dispute - PFE claims end of 2015, Serono claims end of 2013
Total	\$2,621	\$2,580	\$2,830	\$1,675	\$1,655	\$1,900	\$2,150	\$2,400	-1%	-1%	
Share of Eliquis sales	73	340	540	700	825	950	1075	1200	+23%	NM	
Share of Spiriva sales	900	468	360	180	0	0	0	0	NM	NM	
Share of Aricept JV profits	75	50	25	13	3	0	0	0	NM	NM	
Share of Rebif sales	275	288	300	0	0	0	0	0	NM	NM	
Alliance Revenue	\$1,325	\$1,145	\$1,225	\$895	\$830	\$950	\$1,075	\$1,200	+1%	-1%	
Alliance Rev. % of Sales	50.6%	44.4%	43.3%	53.4%	50.2%	50.0%	50.0%	50.0%			

Source: Cowen and Company

Wyeth Product Co-Promotion Buildup (\$MM)

	2013	2014-20 CGR								2013-20 CGR	Comments
		2014E	2015E	2016P	2017P	2018P	2019P	2020P			
Enbrel	\$4,551	\$4,631	\$4,800	\$4,900	\$0	\$0	\$0	\$0	NM	NM	- Rheumatoid arthritis; North American rights reverted to AMGN on 10/31/13
Assumed % share to WYE on Enbrel		33%	11%	10%	0%	0%	0%	0%			- WYE shares gross profit
Share to PFE on Enbrel	1,305	545	535	\$490	\$0	\$0	\$0	\$0			- Starting 11/1/13, royalty goes to "other income" rather than sales

Source: Cowen and Company

Pfizer 2013-20 Summary Balance Sheet (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Assets:								
Cash & Equivalents	\$2,183	\$5,106	\$7,167	\$8,496	\$10,279	\$12,486	\$14,607	\$17,820
Short-Term Investments	30,225	30,200	30,200	30,200	30,200	30,200	30,200	30,200
Receivables	9,357	10,015	9,770	9,800	10,200	10,405	10,495	11,040
Inventories	6,166	6,050	6,090	6,060	6,230	6,385	6,400	6,750
Other Current Assets	<u>8,313</u>	<u>7,555</u>	<u>7,135</u>	<u>7,155</u>	<u>7,445</u>	<u>7,695</u>	<u>7,660</u>	<u>7,895</u>
Total Current Assets	\$56,244	\$58,926	\$60,362	\$61,711	\$64,354	\$67,171	\$69,362	\$73,705
Property, Plant & Equipment	\$12,397	\$12,200	\$11,900	\$11,900	\$12,400	\$12,850	\$12,750	\$13,600
Intangibles	81,904	80,000	78,000	76,000	75,000	75,000	75,000	75,000
Other Long-Term Assets	<u>21,556</u>	<u>21,000</u>						
Total Long-Term Assets	<u>\$115,857</u>	<u>\$113,200</u>	<u>\$110,900</u>	<u>\$108,900</u>	<u>\$108,400</u>	<u>\$108,850</u>	<u>\$108,750</u>	<u>\$109,600</u>
Total Assets	\$172,101	\$172,126	\$171,262	\$170,611	\$172,754	\$176,021	\$178,112	\$183,305
Liabilities:								
Short-Term Debt	\$6,027	\$6,000	\$6,000	\$6,000	\$6,000	\$6,000	\$6,000	\$6,000
Accounts Payable	3,234	3,045	3,065	3,050	3,135	3,210	3,220	3,395
Other Current Liabilities	<u>14,105</u>	<u>13,900</u>	<u>13,950</u>	<u>14,000</u>	<u>14,500</u>	<u>14,850</u>	<u>14,900</u>	<u>15,700</u>
Total Current Liabilities	\$23,366	\$22,945	\$23,015	\$23,050	\$23,635	\$24,060	\$24,120	\$25,095
Long-Term Debt	\$30,462	\$30,500	\$30,000	\$29,500	\$29,000	\$28,500	\$28,000	\$27,500
Other Long-Term Liabilities	<u>41,653</u>	<u>40,000</u>						
Total Liabilities	\$95,481	\$93,445	\$93,015	\$92,550	\$92,635	\$92,560	\$92,120	\$92,595
Net Equity	\$76,620	\$78,681	\$78,247	\$78,061	\$80,119	\$83,461	\$85,992	\$90,710

Source: Company data, Cowen and Company

Pfizer 2013-20 Working Capital Analysis (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Inventories	\$6,166	\$6,050	\$6,090	\$6,060	\$6,230	\$6,385	\$6,400	\$6,750
COGS	\$9,272	\$9,259	\$9,317	\$9,273	\$9,528	\$9,766	\$9,790	\$10,328
Inventory Turns	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Months	8.0	7.8	7.8	7.8	7.8	7.8	7.8	7.8
Accounts Receivable	\$9,357	\$10,015	\$9,770	\$9,800	\$10,200	\$10,405	\$10,495	\$11,040
Sales	\$51,453	\$48,750	\$47,555	\$47,695	\$49,635	\$51,315	\$51,065	\$54,460
Receivables Days	66.4	75.0	75.0	75.0	75.0	74.0	75.0	74.0
Other Current Assets	\$8,313	\$7,555	\$7,135	\$7,155	\$7,445	\$7,695	\$7,660	\$7,895
% of Sales	16.2%	15.5%	15.0%	15.0%	15.0%	15.0%	15.0%	14.5%
Accounts Payable	\$3,234	\$3,045	\$3,065	\$3,050	\$3,135	\$3,210	\$3,220	\$3,395
COGS	\$9,272	\$9,259	\$9,317	\$9,273	\$9,528	\$9,766	\$9,790	\$10,328
Payables Days	127.3	120.0	120.0	120.0	120.0	120.0	120.0	120.0
Other Current Liabilities	\$14,105	\$13,900	\$13,950	\$14,000	\$14,500	\$14,850	\$14,900	\$15,700
% of COGS	152.1%	150.0%	150.0%	151.0%	152.0%	152.0%	152.0%	152.0%
Net Working Capital (Ex. Cash, Debt)	\$6,497	\$6,675	\$5,980	\$5,965	\$6,240	\$6,425	\$6,435	\$6,590

Source: Company data, Cowen and Company

Pfizer 2013-20 Cash Flow Analysis (\$MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P
Operating Activities								
Adjusted net Income	\$15,288	\$14,093	\$14,303	\$14,767	\$15,490	\$16,373	\$16,630	\$18,402
Depreciation/amortization	6,410	6,000	6,000	6,000	6,500	6,500	6,500	6,500
Change in Working Capital	15	(178)	695	15	(275)	(185)	(10)	(155)
Other, net	(3,948)	(1,500)	(1,500)	(1,500)	(1,500)	(1,500)	(1,500)	(1,500)
Net Cash Provided By Operations	\$17,765	\$18,415	\$19,498	\$19,282	\$20,215	\$21,188	\$21,620	\$23,247
Investing Activities								
Capital Expenditures	(\$1,206)	(\$1,300)	(\$1,300)	(\$1,350)	(\$1,350)	(\$1,400)	(\$1,400)	(\$1,400)
Asset Sales (net)	0	0	0	0	0	0	0	0
Acquisitions	(15)	0	0	0	0	0	0	0
Other, net	(9,404)	(2,500)	(2,500)	(2,500)	(2,500)	(2,500)	(2,500)	(2,500)
Net Cash Provided By Investing	(\$10,625)	(\$3,800)	(\$3,800)	(\$3,850)	(\$3,850)	(\$3,900)	(\$3,900)	(\$3,900)
Financing Activities								
Long-Term & ST Debt Financings	\$10,941	\$4,500	\$0	\$0	\$0	\$0	\$0	\$0
Equity Financings	0	0	0	0	0	0	0	0
Net Debt Payments	(\$4,905)	(\$3,500)	(\$500)	(\$500)	(\$500)	(\$500)	(\$500)	(\$500)
Dividend Payments	(6,580)	(6,692)	(7,138)	(7,603)	(8,082)	(8,581)	(9,099)	(9,634)
Share Repurchase	(16,290)	(6,000)	(6,000)	(6,000)	(6,000)	(6,000)	(6,000)	(6,000)
Other, net	1,859	0	0	0	0	0	0	0
Net Cash Provided By Financing	(\$14,975)	(\$11,692)	(\$13,638)	(\$14,103)	(\$14,582)	(\$15,081)	(\$15,599)	(\$16,134)
Net Change in Cash & Equivalents	(\$7,898)	\$2,923	\$2,060	\$1,329	\$1,784	\$2,207	\$2,121	\$3,213
Ending Cash & Equivalents	\$2,183	\$5,106	\$7,167	\$8,496	\$10,279	\$12,486	\$14,607	\$17,820

Source: Company data, Cowen and Company

PFE DCF Analysis

9/26/14											
Assumptions											
Share Price	\$30		<i>Output</i>								
			Equity Value		\$226,332						
			Estimated Share Price		\$35						
Discount Rate	10.0%		Net Cash		(\$4,081)						
Shares Outstanding	6,396		Enterprise Value		\$230,413						

PFE DCF ANALYSIS

	2013A	2014E	2015P	2016P	2017P	2018P	2019P	2020P	2021P	2022P	2023P	2024P	2025P	Terminal
Total Revenues	\$51,453	\$48,750	\$47,555	\$47,695	\$49,635	\$51,315	\$51,065	\$54,460	\$57,200	\$59,500	\$61,900	\$63,450	\$65,050	
% Change	-13%	-5%	-2%	+0%	+4%	+3%	-0%	+7%	+5%	+4%	+4%	+3%	+3%	
Cost of Goods	\$9,272	\$9,259	\$9,317	\$9,273	\$9,528	\$9,766	\$9,790	\$10,328	\$10,982	\$11,424	\$11,947	\$12,309	\$12,685	
Gross Profit	\$42,179	\$39,491	\$38,238	\$38,422	\$40,107	\$41,549	\$41,275	\$44,132	\$46,218	\$48,076	\$49,953	\$51,141	\$52,365	
Gross Margin - Total	82.0%	81.0%	80.4%	80.6%	80.8%	81.0%	80.8%	81.0%	80.8%	80.8%	80.7%	80.6%	80.5%	
SG&A	\$14,100	\$13,380	\$11,985	\$11,700	\$12,275	\$12,575	\$12,100	\$12,550	\$13,442	\$13,983	\$14,732	\$15,228	\$15,937	
% of Revs	27.4%	27.4%	25.2%	24.5%	24.7%	24.5%	23.7%	23.0%	23.5%	23.5%	23.8%	24.0%	24.5%	
R&D	\$6,519	\$6,800	\$6,520	\$6,430	\$6,650	\$6,675	\$6,615	\$6,685	\$7,036	\$7,438	\$7,738	\$8,058	\$8,457	
% of Revs	12.7%	13.9%	13.7%	13.5%	13.4%	13.0%	13.0%	12.3%	12.3%	12.5%	12.5%	12.7%	13.0%	
Operating Expenses	\$20,619	\$20,180	\$18,505	\$18,130	\$18,925	\$19,250	\$18,715	\$19,235	\$20,478	\$21,420	\$22,470	\$23,286	\$24,394	
% of Revenues	40.1%	41.4%	38.9%	38.0%	38.1%	37.5%	36.6%	35.3%	35.8%	36.0%	36.3%	36.7%	37.5%	
Operating Income	\$21,560	\$19,311	\$19,733	\$20,292	\$21,182	\$22,299	\$22,560	\$24,897	\$25,740	\$26,656	\$27,484	\$27,855	\$27,972	
% Operating Margin	41.9%	39.6%	41.5%	42.5%	42.7%	43.5%	44.2%	45.7%	45.0%	44.8%	44.4%	43.9%	43.0%	
Non-operating income	\$706	\$1,160	\$1,005	\$1,050	\$1,100	\$1,150	\$1,200	\$1,250	\$1,275	\$1,300	\$1,325	\$1,350	\$1,375	
EBIT	\$22,266	\$20,471	\$20,738	\$21,342	\$22,282	\$23,449	\$23,760	\$26,147	\$27,015	\$27,956	\$28,809	\$29,205	\$29,347	
% of Revs	43.3%	42.0%	43.6%	44.7%	44.9%	45.7%	46.5%	48.0%	47.2%	47.0%	46.5%	46.0%	45.1%	
D&A	6,410	6,000	6,000	6,000	6,500	6,500	6,500	6,500	6,500	6,550	6,600	6,650	6,650	
EBITDA	28,676	26,471	26,738	27,342	28,782	29,949	30,260	32,647	33,515	34,506	35,409	35,855	35,997	
% of Revs	55.7%	54.3%	56.2%	57.3%	58.0%	58.4%	59.3%	59.9%	58.6%	58.0%	57.2%	56.5%	55.3%	
Net Interest Income (Expense)	(\$1,031)	(\$960)	(\$900)	(\$835)	(\$750)	(\$675)	(\$600)	(\$525)	(\$500)	(\$475)	(\$450)	(\$425)	(\$400)	
Pre-Tax Income	\$21,235	\$19,511	\$19,838	\$20,507	\$21,532	\$22,774	\$23,160	\$25,622	\$26,515	\$27,481	\$28,359	\$28,780	\$28,947	
Taxes	\$5,811	\$5,217	\$5,305	\$5,480	\$5,751	\$6,082	\$6,180	\$6,840	\$7,080	\$7,337	\$7,572	\$7,684	\$7,729	
Income Tax Rate	27.5%	26.7%	26.7%	26.7%	26.7%	26.7%	26.7%	26.7%	26.7%	26.7%	26.7%	26.7%	26.7%	
Net Income	\$16,456	\$15,255	\$15,433	\$15,862	\$16,530	\$17,368	\$17,580	\$19,307	\$19,935	\$20,619	\$21,237	\$21,520	\$21,618	
% of Revs	32.0%	31.3%	32.5%	33.3%	33.3%	33.8%	34.4%	35.5%	34.9%	34.7%	34.3%	33.9%	33.2%	
NOPAT	\$16,456	\$15,255	\$15,433	\$15,862	\$16,530	\$17,368	\$17,580	\$19,307	\$19,935	\$20,619	\$21,237	\$21,520	\$21,618	
Adjustments:														
Capex	(\$1,206)	(\$1,300)	(\$1,300)	(\$1,350)	(\$1,350)	(\$1,400)	(\$1,400)	(\$1,500)	(\$1,500)	(\$1,550)	(\$1,550)	(\$1,600)		
Depreciation & Amortization	\$6,410	\$6,000	\$6,000	\$6,000	\$6,500	\$6,500	\$6,500	\$6,500	\$6,500	\$6,600	\$6,650	\$6,650		
Change In Working Capital	\$15	(\$178)	\$695	\$15	(\$275)	(\$185)	(\$10)	(\$155)	(\$250)	(\$300)	(\$350)	(\$350)		
Free Cash Flow	\$21,675	\$19,777	\$20,828	\$20,527	\$21,405	\$22,283	\$22,670	\$24,252	\$24,685	\$25,369	\$25,937	\$26,270	\$26,318	\$263,178

Source: Company data, Cowen and Company.

Pfizer Key Upcoming Events

Time Frame	Event Type	Product	Event
2014	Clinical	Bococizumab Ertugliflozin Xeljanz PF-00489791 (PDE5i)	Phase III LDL-lowering and CV Outcomes trials ongoing Multiple Phase III studies underway with sitagliptin Full data for Pivotal 1 and 2 Phase III psoriasis Phase II data at American Society of Nephrology, Nov. 2014
	Regulatory	ALO-02 Palbociclib Xeljanz	Filing by year end (chronic low back pain) NDA acceptance on or before 10/18/14 for ER+ breast cancer Filing for plaque psoriasis in late 2014/early 2015
	Corporate	AstraZeneca Baxter vaccines acquisition	Six-month waiting period ends late November, allowing Pfizer to bid again on AZN Closing by year end

Source: Company data

PFIZER R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Analgesia/Anesthesia							
Remoxy					Jun-08		Tamper-resistant formulation of oxycodone ER; via King acquisition
Oxycodone NT			.	.			ALO-02; oxycodone ER plus low dose naltrexone; via King acquisition
Tanezumab		.	.	.			PF-4383119; pain; mAb blocks nerve growth factor; PIII for OA signs and symptoms PII for cancer pain; biologic; clinical hold lifted
PF-05089771		.	.	.			Chronic pain
PF-06372865		.	.	.			Chronic pain
Arthritis/Inflammation							
Celebrex					Aug-09		Chronic pain
Xeljanz (tofacitinib)		.	.	.			JAK 3 inhibitor; filed in EU for rheumatoid arthritis, PIII psoriasis, ulcerative colitis, psoriatic arthritis; PII for ankylosing spondylitis; Crohn's disease, topical psoriasis, atopic dermatitis
PF-4171327		.	.	.			Selective glucocorticoid receptor modulator; rheumatoid arthritis; inflammation
Dekavil		.					Rheumatoid arthritis; biologic
PF-05280586		.					Rheumatoid arthritis (potential rituximab biosimilar)
PF-06410293		.					Rheumatoid arthritis (potential adalimumab biosimilar)
PF-06438179		.					Rheumatoid arthritis (potential infliximab biosimilar)
Blood And Clotting Products							
PF-05230907		.					Intracerebral hemorrhage (biologic)
PF-05280602		.					Hemophilia (biologic)
Cancer/Oncology/Hematology							
Palbociclib			.		Aug-14		PF-0332991; filed for HER2- advanced breast cancer ; PIII for 1st line advanced breast cancer; recurrent advanced breast cancer; high-risk early breast cancer
Dacomitinib			.				PF-00299804; pan-HER inhibitor; 1st line EGFR Mutant NSCLC
Inotuzumab ozogamicin			.				Calicheamycin (toxin that binds to cancer cells) conjugate for acute lymphoblastic leukemia
Sutent			.				VEGFR angiogenesis inhibitor; pan kinase inhibitor; adjuvant renal cell carcinoma
Inlyta (axitinib)		.	.				VEGFR tyrosine kinase inhibitor; PIII for renal cell carcinoma adjuvant (Asia); PII for liver cancer
Xalkori (crizotinib)		.	.				PF-2341066; oral c-Met and ALK inhibitor; ALK-positive 1st line NSCLC; PI for combo with pembrolizumab
Bosutinib		.					Bcr-Abl inhibitor; polycystic kidney disease
PF-03446962		.					ALK1 inhibitor; 2nd-line hepatocellular carcinoma (biologic)
PF-05212384		.					P13K-mTOR inhibitor; 3rd line colorectal cancer
Rivipansel		.					GMI-1070; pan-selectin antagonist; vaso-occlusive crisis associated with Sickle Cell Disease
PD-0325901		.					Cancer (in combination with PF-04691502)
PF-03084014		.					Cancer
PF-04449913		.					SMO antagonist; acute myelocytic leukemia
PF-05082566		.					Cancer (biologic)
PF-05280014		.					erbB2 TK inhibitor; metastatic breast cancer (potential trastuzumab biosimilar)
PF-0620414		.					Cachexia
PF-06263507		.					Cancer (biologic)
PF-06439535		.					Cancer (potential bevacizumab biosimilar)

PFIZER R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
PF-06463922		.					Cancer
PF-06647263		.					Cancer (biologic)
PF-06650808		.					Cancer (biologic)
Cardiovascular							
Vyndaqel (Tafamidis meglumine)			.		Dec-11		Transthyretin dissociation inhibitor; transthyretin amyloid polyneuropathy; filed in U.S.; PIII for adult symptomatic transthyretin cardiomyopathy
RN316 (PF-04950615)			.				Bococizumab; PCSK9 inhibitor; hypercholesterolemia and dyslipidemia; biologic
PF-06282999		.					Acute coronary syndrome
Central Nervous System							
Lyrica			.				Pregabalin; PIII for peripheral neuropathic pain; CR, once-daily dosing
PF-04360365			.				Ponezumab; beta amyloid inhibitor; cerebral amyloid angiopathy (biologic)
PF-05212377			.				SAM-760; 5HT6 antagonist; Alzheimer's disease
PF-04958242		.					Schizophrenia
PF-05236812 (AAB-003)		.					Alzheimer's disease (biologic)
PF-06412562		.					Cognitive disorder
PF-06649751		.					Parkinson's disease
PF-06669571		.					Cognitive disorder
Dermatologic							
PF-06473871		.					EXC 001; CTGF inhibitor; dermal scarring
PF-06263276		.					Psoriasis (topical)
Diabetes							
Ertugliflozin			.				PF-04971729; SGLT-2 inhibitor; Type 2 diabetes
PF-00489791			.				PDE5 inhibitor; diabetic nephropathy
PF-04634817		.					CCR2/5 antagonist; diabetic nephropathy; diabetic macular edema
PF-04937319		.					Partial glucokinase activator; Type 2 diabetes
PF-05175157	⇒	.					Acetyl-CoA carboxylase inhibitor; Type 2 diabetes
PF-06291874		.					Type 2 diabetes (biologic)
PF-06342674		.					Type 1 diabetes mellitus (biologic)
Endocrine/Metabolic/Hormones							
Aprela			.				Bazedoxifene plus conjugated estrogen; filed in EU and U.S. for menopausal vasomotor symptoms
Viviant					Jun-06		Prevention and treatment of postmenopausal osteoporosis
Gene Therapy							
PF-02545920			.				PDE10 inhibitor; Huntington's Disease; adjunctive treatment for schizophrenia
Immunological							
PD-0360324		.					M-CSF inhibitor; sarcoidosis; lupus (biologic)
PF-00547659		.					MAdCAM inhibitor; Crohn's disease, ulcerative colitis (biologic)
PF-04236921		.					IL-6 inhibitor; Crohn's disease; lupus; biologic
PF-05285401		.					Multipotent adult progenitor cell; ulcerative colitis (biologic)
PF-04965842		.					Lupus
PF-06252616		.					Duchenne muscular dystrophy (biologic)
PF-06480605		.					Crohn's disease (biologic)
PF-06687859		.					Spinal muscular atrophy
PF-06743649		.					Gout
Respiratory							
PF-03715455		.					COPD

PFIZER R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
PF-06444752		.					Asthma
Vaccines							
MnB rLP2086 (PF-05212366)				⇒	Aug-14		Meningococcal B disease; adolescent and young adults; received FDA Breakthrough Therapy designation 3/2014
PF-06290510			.				4-antigen staphylococcus aureus vaccine (SA4Ag)
PF-05402536		.					Smoking cessation
PF-06425090		⇒	.				Clostridium difficile; received FDA Fast-Track designation in August 2014
Total Drugs In Development	0	36	19	11	7		73

Progress since last update in bold; movement marked by arrow

Investor Relations Contacts: Chuck Triano 212-733-3901
Ryan Crowe 212-733-8160

Roche Holding Ltd (ADR)

Visible Growth, Solid News Flow

Price: \$36.99 (09/30/2014)
Price Target: \$42.00

OUTPERFORM (1)

Steve Scala, R.Ph., CFA
617.946.3923
steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA
617.946.3857
kathy.miner@cowen.com

Jean Perreault
617.946.3967
jean.perreault@cowen.com

Key Data	
Symbol	OTC PK: RHHBY
52-Week Range:	\$38.71 - 31.75
Market Cap (MM):	\$254,328.2
Net Debt (MM):	\$6,708.0
Cash/Share:	NA
Dil. Shares Out (MM):	5,620.5
Enterprise Value (MM):	NA
ROIC:	NA
ROE (LTM):	NA
BV/Share:	NA
Dividend:	\$1.11
Yield:	3.00%

FY (Dec)	2013A	2014E	2015E
Earnings Per Share			
Q1	-	-	-
Q2	CHF7.58	CHF7.57A	CHF7.88
Q3	-	-	-
Q4	CHF6.69	CHF7.13	CHF7.42
Year	CHF14.26	CHF14.70	CHF15.30
Core EPS			

Revenue (MM)			
Year	CHF46,780.0	CHF46,175.0	CHF46,865.0

The Cowen Insight

Strong core franchises with high earnings visibility, a pipeline that is delivering, and a reasonable valuation support our positive stance.

Roche offers at least average, but highly visible, EPS growth potential through 2020, supported by a handful of still robust franchises, including Avastin, Rituxan, and Herceptin. While these products are unlikely to deliver upside to expectations, we believe they are equally unlikely to disappoint. The pipeline has a few high-potential products, and recent approvals have had strong launches. Biogenetics are a manageable risk, given Roche's efforts to advance the standard of care. A powerful Diagnostics Division is well positioned for the emergence of personalized medicine. Despite these strengths, Roche's P/E multiple is just above the group average.

3% EPS Growth In 2014; Highly Visible Growth Through 2020

EPS are expected to grow 3% to CHF14.70 in 2014, on a 1% decline in revenues. Growth accelerates to the mid- to high-single digits for 2015-2020. Core EPS are pegged at CHF21.55 in 2020, implying 2014-20 compound EPS growth of 7%, which is about in line with the group average. However, we believe there is greater than average possibility of upside to these forecasts. The pending InterMune acquisition helps offset the impact of patent expirations during 2018-20.

Promising Recently Launched And Pipeline Agents Have High Potential

Kadcyla and Perjeta (breast cancer) have enjoyed good rollouts and fortify the HER-2 franchise. Gazyva similarly could advance the standard of care in CLL/NHL, and protect the Rituxan franchise. Lampalizumab looks like a breakthrough in dry AMD, and etrolizumab holds promise in both Crohn's and UC. While still early, Roche has a unique strategy in immune oncology with its PD-L1 approach and extensive use of biomarkers, and 25 different ADCs (antibody drug conjugates) in development that promise improved profiles, particularly less toxicity.

Many Pipeline-Related News Events Upcoming

Key data in H2:2014 include results of MARIANNE (Kadcyla/Perjeta in 1st line metastatic breast cancer), Phase II data for alectinib in NSCLC, Gazyva GREEN study at ASH, potential Avastin approval in ovarian (U.S.) and cervical (E.U.) cancer, pirfenidone PDUFA 11/23/14 in IPF, and updates on anti-PD-L1 in solid tumors.

Visible Growth Through 2020

Modest EPS Growth Expected In 2014

We look for 3% EPS growth, to CHF14.70, on a 1% decline in revenues, to CHF46.175B in 2014. Patent expirations on Cellcept and Xeloda and possible Rituxan biosimilar in the E.U. temper the outlook. Gross profit margin is forecast to expand 1.3pp to 79.8%, SG&A is expected to decline 3% to CHF9.852B, R&D is expected to increase 1% to CHF8.815B and net financial income should improve by CHF406MM. The tax rate is expected to be up 0.9pp at 23.6%. All told, it looks like a year of margin improvement, despite the patent expirations.

Roche 2014 Guidance Versus Our Estimates

	Guidance*	Our Estimates**
Group Sales	Grow low- to mid-single digit	-1%
Core EPS	To grow ahead of sales	3%

*CER

**Reflects impact of exchange at current rates

Source: Cowen and Company

Roche Pipeline Sales Estimates (CHF MM)

	2012	2013	2014-20							2013-20		
			2014E	2015E	2016P	2017P	2018P	2019P	2020P	CGR	CGR	Comments
Perjeta - WW	56	326	885	1,390	1,850	2,500	3,100	3,700	4,300	30%	NM	HER2-positive metastatic breast cancer
Kadcyla - WW		234	560	1,020	1,500	1,950	2,400	2,850	3,300	34%	NM	HER2-positive metastatic BC; 2nd line
Actemra - WW	842	1,037	1,195	1,435	1,685	1,935	2,185	2,360	2,535	13%	14%	SQ approved in U.S., CHMP positive opinion; Patent expires 2018
Esbriet			280	550	1,100	1,375	1,650	1,825	NM	NM	NM	Pirfenidone; IPF; PDUFA 11/23/14; via InterMune acquisition for \$8.3B; assumed to close 1/1/15
RG7446					250	500	1,000	NM	NM	NM	NM	PD-L1 Mab; mNSCLC (2016, 2nd/3rd line); bladder cancer (2016); Phase II; +Avastin in RCC; NDA 2017+
RG7601					100	200	400	800	NM	NM	NM	Bcl-2 inhibitor; CLL rel/refract 17pdL NDA 2016, DLBL Phase II NDA 2017+
Zelboraf - WW	234	354	295	360	420	480	540	600	660	14%	9%	BRAF inhibitor; malignant melanoma; adjuvant in Phase III
Gazyva		3	55	130	200	300	400	500	600	49%	NM	Obinutuzumab; approved for CLL: Non-Hodgkin's lymphoma (data 2015/17); anti-CD20 Mab
Ocrelizumab				200	300	400	500	600	NM	NM	NM	Multiple sclerosis: RMS, PPMS; Phase III solid; NDA 2015
Erivedge - WW	29	75	140	210	270	330	390	450	520	24%	NM	Hedgehog inhib.; FDA approval for advanced BCC, advanced BC, AML Phase II; \$75,000/course
Lampalizumab						200	400	NM	NM	NM	NM	Anti-factor D Fab antibody to prevent AMD associated geographic atrophy; NDA 2017+
Cobimetinib			100	200	300	400	NM	NM	NM	NM	NM	RG7421; MEK inhibitor; malignant melanoma; combo with Zelboraf filing in 2014
Suvenyl			25	50	75	100	NM	NM	NM	NM	NM	CHU; topoisomerase I inhibitor; enthesopathy; Phase III
Lebrikizumab			25	50	100	NM	NM	NM	NM	NM	NM	Anti-L1L3mAB; asthma Phase III NDA 2016; IPF NDA 2017+
CSF-1R Mab			25	50	75	NM	NM	NM	NM	NM	NM	RG7155; solid tumors and PVNs; NDA 2017+
Quilizumab			25	50	75	NM	NM	NM	NM	NM	NM	RG7449; anti-M1 prime Mab; asthma Phase II; NDA 2017+
Inclacumab			25	50	75	NM	NM	NM	NM	NM	NM	RG1512; p-selectin Mab; ACS/CVD; Phase II
Decoglurant/basimiglurant			25	50	75	NM	NM	NM	NM	NM	NM	RG1576; mGluR5 antagonist and mGluR2 antagonist; treatment resistant depression; Phase II; NDA 2017+
Pictilisib			25	50	75	NM	NM	NM	NM	NM	NM	RG7604; PI3K inhibitor b-spanning; solid tumors, NHL, lymphoma; Phase II; Phase III decision pending; NDA 2017+
Taselisib			25	50	75	NM	NM	NM	NM	NM	NM	RG7593; CD22 ADC; hemi tumors; Phase II; NDA 2017+
Pinatuzumab vedotin			25	50	75	NM	NM	NM	NM	NM	NM	RG7596; CD70 ADC; hemi tumors; Phase II; NDA 2017+
Polatuzumab vedotin			25	50	75	NM	NM	NM	NM	NM	NM	RG7653; ALK inhibitor; NSCLC; Phase II; Phase III decision pending; NDA 2017+
RG7597			25	50	75	NM	NM	NM	NM	NM	NM	RG7653; ALK inhibitor; NSCLC; Phase II; Phase III decision pending; NDA 2017+
Alectinib			25	50	75	NM	NM	NM	NM	NM	NM	RG7653; ALK inhibitor; NSCLC; Phase II; Phase III decision pending; NDA 2017+
RG7686			25	50	75	NM	NM	NM	NM	NM	NM	RG7653; ALK inhibitor; NSCLC; Phase II; Phase III decision pending; NDA 2017+
Ang2-VEGF Mab			25	50	75	NM	NM	NM	NM	NM	NM	RG7221; colorectal cancer; NDA 2017+
RG7667			25	50	75	NM	NM	NM	NM	NM	NM	CMV; Phase II; NDA 2017+
Setrobruvir			25	50	75	NM	NM	NM	NM	NM	NM	RG7790; HCV; Phase II
Etralizumab			25	50	75	NM	NM	NM	NM	NM	NM	RG7413; IgG1 antibody targeting beta 7 integrin subunit; ulcerative colitis/Crohn's disease; Phase II; NDA 2017+
R1577			25	50	75	NM	NM	NM	NM	NM	NM	MAO-B inhibitor; Alzheimer's; Phase II; NDA 2017+
Crenezumab (A-beta)			25	50	75	NM	NM	NM	NM	NM	NM	RG1412; Alzheimer's; Phase II; Phase III likely to target mild/moderate patients; NDA 2017+
Gantenerumab (A-beta)			25	50	75	NM	NM	NM	NM	NM	NM	RG1460; Alzheimer's; Phase II; target mild/prodromal patients; NDA 2017+
Danoprevir			25	50	75	NM	NM	NM	NM	NM	NM	RG7227; Protease inhibitor; hepatitis C; Phase II; NDA 2017+
Mercitanibine			25	50	75	NM	NM	NM	NM	NM	NM	RG7128; nucleoside analog HCV polymerase inhibitor; Phase II; NDA 2017+
Bioperatin			10	20	30	40	NM	NM	NM	NM	NM	Glycine transporter 1 inhib; schizophrenia neg symptoms trials failed/suboptimal control trials ongoing; OCD Phase II
Total Pipeline	1,161	2,028	3,130	4,825	6,675	9,130	12,035	15,165	18,880	35%	42%	
Total Pharma Sales	35,232	36,304	35,650	35,910	36,990	38,085	38,590	41,000	42,320	3%	2%	
Pipeline as % of Pharma	3%	6%	9%	13%	18%	24%	30%	37%	44%			

Source: Cowen and Company

4-8% EPS Growth Forecast In 2015-20

Due to moderating growth of top franchises and patent expirations on several others, we expect 4-8% EPS growth during 2015-20, supported by recent launches, the InterMune acquisition, and the pipeline. Franchises subject to generic competition during this time include Xeloda, Mabthera/Rituxan and Herceptin (in the E.U.), Boniva, Cellcept, Xolair, Pulmozyme, Pegasys, Actemra, and Activase. Gross profit margin is expected to increase by 0.5-0.7pp in each year through 2020. SG&A is expected to

expand approximately 2-4% each year through 2020, while R&D is projected to grow a more modest 1-2% each year through 2020. Steady improvement is forecast for net financial expense after the step-up in 2015 due to the InterMune acquisition; CHF930MM in financial expense is forecast in 2020. The tax rate is forecast to remain steady at 23% in each year through 2020. Core EPS is pegged at CHF15.30 in 2015 and CHF21.55 in 2020, implying a 2013-20 compound EPS growth rate of 6%, which is consistent with the group average.

Roche EPS Buildup 2013-20 (CHF MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	CGR '13-'16	CGR '13-'20	CGR '14-'20	
Avastin	2.17	2.34	2.57	2.83	3.07	3.16	3.25	3.11	9%	5%	5%	Bevacizumab; advanced CRC, NSCLC, ovarian, relapsed glioblastoma, breast (EU only), ovarian, cervical
Mabthera/Rituxan	2.41	2.57	2.70	2.69	2.62	2.54	2.51	2.41	4%	0%	-1%	Rituximab; non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis
Perjeta	0.11	0.33	0.55	0.77	1.10	1.44	1.80	2.19	90%	53%	37%	HER2-positive metastatic breast cancer
Kadcyla	0.08	0.21	0.40	0.63	0.86	1.11	1.39	1.68	98%	54%	42%	HER2-positive metastatic BC, 2nd line
Herceptin	2.11	2.25	2.31	2.26	2.14	1.99	1.81	1.60	2%	-4%	-5%	Trastuzumab; HER2-positive breast cancer; Gastric; SQ
Actemra	0.36	0.44	0.57	0.70	0.85	1.01	1.15	1.29	25%	20%	20%	Rheumatoid arthritis; approved in first line 10/12; Patent expires 2020
Lucentis	0.59	0.63	0.69	0.74	0.79	0.85	0.73	0.64	8%	1%	0%	Ranibizumab; wet age-related macular degeneration; Eylea a competitive challenge
Tarceva	0.46	0.47	0.50	0.52	0.55	0.57	0.51	0.41	4%	-2%	-2%	Erlotinib; non-small cell lung cancer; pancreatic cancer
Zelboraf	0.12	0.11	0.14	0.18	0.21	0.25	0.29	0.34	13%	15%	21%	BRAF inhibitor; malignant melanoma; adjuvant in Phase III
Cellcept	0.30	0.29	0.26	0.23	0.20	0.17	0.14	0.11	-9%	-14%	-15%	Mycophenolate mofetil; transplantation
Erivedge	0.03	0.05	0.08	0.11	0.15	0.18	0.22	0.27	63%	39%	31%	BRAF inhibitor; malignant melanoma; adjuvant in Phase III
Pegasys	0.46	0.39	0.28	0.25	0.23	0.20	0.17	0.14	-18%	-15%	-16%	Peginterferon alfa-2a; hepatitis B and C; interferon-free regimens and shorter duration may clip use
Tamiflu	0.22	0.20	0.16	0.17	0.18	0.19	0.19	0.20	-9%	-1%	0%	Oseltamivir; treatment and prevention of influenza A and B
Pipeline products	0.00	0.02	0.05	0.19	0.32	0.72	1.25	1.85	NM	NM	112%	Gazyva, Lampalizumab, Ocrelizumab, PD1, Alzheimer's assets, many others
Other products	3.75	3.26	2.85	2.66	2.89	3.16	3.12	3.18	-11%	-2%	0%	Epogin, Xeloda, Mircera most significant; patent expirations clip in 2014-15
Diagnostics	1.09	1.12	1.19	1.27	1.35	1.42	1.77	2.13	5%	10%	11%	Tissue diagnostics and Applied Science growing most rapidly; Diabetes Care lags
Core EPS (Diluted)	14.26	14.70	15.80	16.20	17.80	18.95	20.30	21.55	4%	6%	7%	Versus industry averages of +4%, +6% and +8%
% change	6%	3%	4%	6%	8%	8%	7%	6%				

Source: Cowen and Company

Patent Exposure Above Industry Average

Roche is well positioned from the patent perspective, with many key franchises protected until 2020. Near-term patent exposure in Xeloda (12/13), Cellcept (IV and suspension patents in 2013-14), and Boniva (3/12) are reflected in our models. All told, 49% of Roche EPS is at risk through 2020 from worldwide patent expirations. This is above the industry average exposure of 41%.

U.S. Patent Exposure 2013-20

Company	Drug	Territory	Patent Exp. Date	U.S. Sales		Estimated U.S. Sales (\$MM)*	Non-U.S. Sales As % Of Total Sales	Estimated Non-U.S. Sales (\$MM)*	% Total Sales	% Total EPS	
				Estimated WW Sales (\$MM)	As % Of Total Sales					EPS (#)	EPS
ROCHE	Rituxan	E.U.	2014	CHF 6,951			52%	CHF 3,591	8%	CHF 0.93	6%
	Herceptin	E.U.	Jul-14	6,079			70%	4,231	9%	1.10	7%
	Rituxan	U.S.	2015	6,940	48%	3,354			7%	0.87	6%
	Xolair	U.S.	2015	877	100%	877			2%	0.23	1%
	Valcyte	U.S.	Sep-15	705	53%	375			1%	0.10	1%
	Valcyte	E.U.	Sep-16	630			47%	294	1%	0.08	6%
	Tamiflu	E.U.	Feb-16	400			49%	198	0%	0.05	7%
	Tamiflu	U.S.	Dec-16	400	51%	202			0%	0.05	5%
	Pegasys	E.U.	2017	595			76%	455	1%	0.12	1%
	Avastin	U.S.	2018	6,975	42%	2,928			6%	0.76	1%
	Actemra	E.U.	2018	1,935			68%	1,322	3%	0.34	0%
	Actemra	U.S.	2018	1,935	32%	613			1%	0.16	0%
	Avastin	E.U.	Dec-19	6,825			58%	3,960	7%	1.03	0%
	Herceptin	U.S.	2019	4,285	30%	1,303			2%	0.34	1%
	Lucentis	U.S.	2019	1,830	100%	1,830			3%	0.48	4%
	Tarceva	E.U.	Mar-20	1,050			50%	526	1%	0.14	2%
	Mircera	E.U.	2020	645			100%	645	1%	0.17	1%

*Estimated sales in year prior to patent expiration

**Estimated sales in the year generic competition is expected

#Assumes 25% net margin

Source: Company data, Thomson Pharma, FDA Orange Book, Cowen and Company

Roche Estimated 2013-20 P&L Buildup (CHF MM)

	Total Sales		Gross Margin	SG&A		R&D		Op. Margin	Net Financial Income	Pretax Margin	Tax Rate	Net Inc.	Core EPS (Dilut)	Y/Y % Chg.	Shares (MM)
	CHF MM	% Chg.		CHF MM	%SIs	CHF MM	%SIs								
H1	23,295	4%	79.0%	4781	20.5%	4143	17.8%	40.7%	(838)	37.1%	23.1%	6542	7.58	10%	864
H2	23,485	2%	78.0%	5335	22.7%	4557	19.4%	35.8%	(861)	32.2%	22.2%	5774	6.69	1%	863
2013	46,780	3%	78.5%	10116	21.6%	8700	18.6%	38.3%	(1,699)	34.6%	22.7%	12,316	14.26	6%	865
H1	22,974	-1%	80.5%	4882	21.3%	4204	18.3%	41.0%	(658)	38.1%	24.1%	6641	7.57	0%	863
H2E	23,196	-1%	79.1%	4970	21.4%	4611	19.9%	37.8%	(635)	35.0%	23.0%	6260	7.13	7%	863
2014E	46,175	-1%	79.8%	9852	21.3%	8815	19.1%	39.4%	(1,293)	36.6%	23.6%	12,688	14.70	3%	863
H2E	23,205	1%	81.3%	4890	21.1%	4250	18.3%	41.9%	(755)	38.7%	23.0%	6798	7.88	4%	863
H2E	23,660	2%	80.2%	5090	21.5%	4675	19.8%	38.9%	(725)	35.8%	23.0%	6406	7.42	4%	863
2015E	46,865	1%	80.7%	9980	21.3%	8925	19.0%	40.4%	(1,480)	37.2%	23.0%	13,204	15.30	4%	863
2016P	48,430	3%	81.2%	10340	21.4%	9125	18.8%	41.0%	(1,370)	38.1%	23.0%	13,976	16.20	6%	863
2017P	49,950	3%	81.9%	10525	21.1%	9200	18.4%	42.4%	(1,260)	39.9%	23.0%	15,099	17.50	8%	863
2018P	51,880	4%	82.5%	10775	20.8%	9300	17.9%	43.8%	(1,150)	41.6%	23.0%	16,356	18.95	8%	863
2019P	53,715	4%	83.0%	11035	20.5%	9400	17.5%	45.0%	(1,040)	43.0%	23.0%	17,520	20.30	7%	863
2020P	55,460	3%	83.5%	11365	20.5%	9500	17.1%	45.9%	(930)	44.2%	23.0%	18,599	21.55	6%	863

*Reflects ADR stock split as of 2/27/14

Source: Company data, Cowen and Company estimates

Roche Quarterly Sales Dynamics (CHF MM)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
PHARMACEUTICALS															
Avastin - U.S. (lc, ex fx)								715	610		680	640	705	625	
- U.S.	661	629	694	591	2575	670	630	695	615	2610	690	655	710	625	2680
- Europe (lc, ex fx)								500	500		520	505	510	515	
- Europe	466	481	489	483	1919	499	484	490	495	1970	515	500	510	515	2040
- Japan (lc, ex fx)								185	210		185	170	180	210	
- Japan	159	183	177	198	717	175	157	175	205	710	190	170	180	210	750
- International	241	273	257	272	1043	221	261	260	275	1015	230	270	270	285	1055
Avastin - WW	1527	1566	1617	1544	6254	1565	1532	1620	1590	6305	1625	1595	1670	1635	6525
Mabthera/Rituxan - U.S (lc, ex fx)								935	775		820	790	905	775	
- U.S.	850	807	917	755	3329	799	825	910	780	3315	835	805	910	775	3325
- Europe (lc, ex fx)								505	490		480	495	475	465	
- Europe	477	482	487	472	1918	503	515	495	485	2000	475	490	475	465	1905
- Japan (lc, ex fx)								65	75		60	60	65	80	
- Japan	54	64	62	69	249	56	48	60	75	240	60	60	65	80	265
- International	315	352	339	449	1455	309	305	330	440	1385	300	300	325	435	1360
Mabthera/Rituxan - WW	1696	1705	1805	1745	6951	1667	1693	1795	1780	6940	1670	1655	1775	1755	6855
Herceptin - U.S. (lc, ex fx)								490	420		455	445	455	400	
- U.S.	476	420	479	412	1787	473	464	475	420	1830	465	455	455	400	1775
- Europe (lc, ex fx)								550	545		545	550	520	515	
- Europe	558	552	544	537	2191	568	570	540	535	2215	540	545	520	515	2120
- Japan (lc, ex fx)								65	75		65	55	55	65	
- Japan	66	75	71	82	294	70	60	60	75	265	65	55	55	65	240
- International	472	463	418	454	1807	415	462	420	460	1755	415	460	410	450	1735
Herceptin - WW	1572	1510	1512	1485	6079	1526	1556	1495	1490	6065	1485	1515	1440	1430	5870
Perjeta - U.S. (lc, ex fx)								140	150		160	170	180	190	
- U.S.	44	44	48	83	219	110	127	135	150	520	165	175	180	190	710
- Europe (lc, ex fx)								60	70		80	90	100	110	
- Europe	5	13	19	31	68	41	51	60	70	220	80	90	100	110	380
- Japan (lc, ex fx)								25	30		35	40	45	50	
- Japan			5	18	23	18	19	25	30	90	35	40	45	50	170
- International	1	1	6	8	16	9	13	15	20	55	25	30	35	40	130
Perjeta - WW	50	58	78	140	326	178	210	235	270	885	305	335	360	390	1390
Kadcyla - US (lc, ex fx)								80	90		100	110	120	130	
- U.S.	18	64	70	70	222	73	70	80	90	315	100	110	120	130	460
- Europe (lc, ex fx)								45	55		65	75	85	95	
- Europe		1	2	6	9	25	38	45	55	165	65	75	85	95	320
- Japan (lc, ex fx)								15	20		25	30	35	40	
- Japan								9	10	15	35	20	25	30	110
- International			1	2	3	4	8	15	20	45	25	30	35	40	130
Kadcyla - WW	18	65	73	78	234	102	125	150	180	560	210	240	270	300	1020

Source: Company data, Cowen and Company.

Roche Quarterly Sales Dynamics (CHF MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Zelboraf - U.S. (lc, ex fx)								15	15		20	20	25	25	
- U.S.	32	35	28	28	123	19	17	15	15	65	20	20	25	25	90
- Europe (lc, ex fx)								45	45		50	50	55	55	
- Europe	46	45	51	52	194	52	48	45	45	190	50	50	55	55	210
- Japan (lc, ex fx)															
- Japan															
- International	6	7	10	14	37	8	11	10	10	40	10	15	15	20	60
Zelboraf - WW	84	87	89	94	354	79	76	70	70	295	80	85	95	100	360
Eribedige - U.S. (lc, ex fx)								20	25		25	25	30	30	
- U.S.	13	15	18	20	66	14	21	20	25	80	25	25	30	30	110
- Europe (lc, ex fx)								10	15		15	15	20	20	
- Europe			2	6	8	9	10	10	15	45	15	15	20	20	70
- Japan (lc, ex fx)															
- Japan															
- International															
Eribedige - WW	13	15	20	27	75	24	33	35	45	140	45	45	60	60	210
Pegasys - U.S. (lc, ex fx)								50	40		30	25	20	15	
- U.S.	109	92	62	44	307	63	74	50	40	225	30	25	20	15	90
- Europe (lc, ex fx)								60	50		45	40	35	30	
- Europe	96	100	80	80	356	77	67	60	50	255	45	40	35	30	150
- Japan (lc, ex fx)								15	15		10	10	5	5	
- Japan	13	14	13	12	52	13	19	15	15	60	10	10	5	5	30
- International	157	143	148	149	597	134	135	130	125	525	120	115	110	105	450
Pegasys - WW	375	349	303	285	1312	287	295	255	230	1065	205	190	170	155	720
Tarceva - U.S. (lc, ex fx)								155	135		150	190	155	140	
- U.S.	156	169	148	131	604	141	184	150	135	610	155	195	155	140	645
- Europe (lc, ex fx)								80	80		75	75	75	75	
- Europe	87	88	84	84	343	76	78	80	80	315	75	75	75	75	300
- Japan (lc, ex fx)								20	25		25	20	20	20	
- Japan	21	24	25	29	99	25	24	20	25	95	25	20	20	20	85
- International	72	74	70	77	293	62	61	60	70	255	60	60	60	60	240
Tarceva - WW	336	355	327	321	1339	304	347	310	310	1275	315	350	310	295	1270
Actemra - U.S. (lc, ex fx)								95	100		105	110	115	120	
- U.S.	73	77	83	81	314	86	94	90	100	370	105	110	115	120	450
- Europe (lc, ex fx)								110	115		120	125	130	135	
- Europe	83	91	91	95	360	99	108	110	115	430	120	125	130	135	510
- Japan (lc, ex fx)								55	65		60	60	65	75	
- Japan	41	49	50	57	197	53	47	50	65	215	60	60	65	75	260
- International	41	41	43	41	166	35	46	50	50	180	50	55	55	55	215
Actemra - WW	238	258	267	274	1037	273	295	300	330	1195	335	350	365	385	1435
Cellcept - U.S. (lc, ex fx)								45	40		35	30	30	25	
- U.S.	54	53	51	46	204	48	47	45	40	180	35	30	30	25	120
- Europe (lc, ex fx)								55	55		50	50	50	50	
- Europe	61	58	60	59	238	55	55	55	55	220	50	50	50	50	200
- Japan (lc, ex fx)								15	15		15	15	15	10	
- Japan	15	18	17	18	68	14	14	15	15	60	15	15	15	10	55
- International	99	107	88	70	364	98	82	80	60	320	90	70	70	50	280
Cellcept - WW	229	236	216	193	874	215	198	195	170	780	190	165	165	135	655

Source: Company data, Cowen and Company.

Roche Quarterly Sales Dynamics (CHF MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Cymevene/Valcyte - U.S. (lc, ex fx)								95	100		90	85	85	90	
- U.S.	78	92	91	97	358	94	94	90	100	380	90	85	85	90	350
- Europe (lc, ex fx)								35	50		40	35	30	45	
- Europe	44	42	36	52	174	46	46	35	50	175	40	35	30	45	150
- Japan (lc, ex fx)															
- Japan															
- International	44	33	39	45	161	37	36	35	40	150	35	30	30	35	130
Cymevene/Valcyte - WW	166	167	166	194	693	177	176	160	190	705	165	150	145	170	630
Tamiflu - U.S. (lc, ex fx)								0	125		75	0	0	125	
- U.S.	203	10	26	189	428	178	10	0	125	315	75	0	0	125	200
- Europe (lc, ex fx)								0	0		50	0	0	0	
- Europe	8	1	0	9	18	71	1	0	0	70	50	0	0	0	50
- Japan (lc, ex fx)								0	15		75	0	0	0	
- Japan	84	4	(1)	18	105	60	2	0	15	75	75	0	0	0	75
- International	40	30	9	5	84	35	15	0	40	90	50	0	0	25	75
Tamiflu - WW	335	45	34	221	635	344	28	0	180	550	250	0	0	150	400
Xolair - U.S. (lc, ex fx)								225	220		225	250	240	240	
Xolair - U.S.	185	201	204	200	790	205	232	220	220	875	230	255	240	240	965
Xolair - WW	185	201	204	200	790	205	232	220	220	877	230	255	240	240	965
Lucentis - U.S. (lc, ex fx)								440	450		410	425	430	460	
Lucentis - U.S.	393	427	431	438	1689	407	421	425	455	1710	415	435	430	460	1740
Lucentis WW	393	427	431	438	1689	407	421	425	455	1710	415	435	430	460	1740
Mircera - U.S. (lc, ex fx)								30	30		30	30	30	30	
- U.S.								30	30		30	30	30	30	
- Europe (lc, ex fx)								60	65		55	50	60	70	
- Europe	24	26	26	28	104	26	26	30	30	110	30	30	30	30	120
- Japan (lc, ex fx)								55	55		55	50	60	70	
- Japan	44	53	55	62	214	51	43	55	65	215	55	50	60	70	235
- International	26	27	26	28	107	26	31	30	30	115	30	30	35	35	130
Mircera - WW	94	106	107	118	425	103	100	115	125	440	115	110	125	135	485
NeoRocormon/Epoprin - U.S. (lc, ex fx)								50	45		45	45	45	40	
- U.S.								15	15		15	10	10	15	
- Europe (lc, ex fx)								60	60		15	10	10	15	
- Europe	57	56	55	50	218	49	49	50	45	195	45	45	45	40	175
- Japan (lc, ex fx)								15	15		15	10	10	15	
- Japan	25	26	25	24	100	16	13	15	15	60	15	10	10	15	50
- International	49	56	51	46	202	47	57	50	45	200	45	55	45	45	190
NeoRocormon/Epoprin - WW	131	138	131	120	520	112	119	115	105	455	105	110	100	100	415

Source: Company data, Cowen and Company.

Roche Quarterly Sales Dynamics (CHF MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Pulmozyme - U.S. (lc, ex fx)								90	90		80	80	75	80	
- U.S.	93	86	85	91	355	91	90	85	90	355	80	80	75	80	315
- Europe (lc, ex fx)								25	25		25	25	20	20	
- Europe	31	31	31	31	124	31	31	25	25	110	25	25	20	20	90
- Japan (lc, ex fx)															
- Japan															
- International	16	21	18	38	93	16	19	15	35	85	15	20	15	30	80
Pulmozyme - WW	140	138	134	160	572	138	140	125	150	550	120	125	110	130	485
Activase - U.S. (lc, ex fx)								160	160		175	165	155	160	
- U.S.	178	137	162	158	635	170	165	155	160	650	180	170	155	160	665
- Europe (lc, ex fx)															
- Europe															
- Japan (lc, ex fx)															
- Japan															
- International	12	14	11	11	48	11	13	10	10	45	10	15	10	5	40
Activase - WW	190	151	173	169	683	181	178	165	170	695	190	185	165	165	705
Xeloda - U.S. (lc, ex fx)								20	15		10	5	5	5	
- U.S.	160	155	165	136	616	130	29	20	15	195	10	5	5	5	25
- Europe (lc, ex fx)															
- Europe	81	82	80	72	315	34	24	20	15	95	10	10	5	5	30
- Japan (lc, ex fx)															
- Japan	26	28	26	27	107	24	20	20	15	80	15	15	10	10	50
- International	116	123	122	110	471	105	108	110	110	435	110	110	115	115	450
Xeloda - WW	383	388	393	345	1509	293	181	170	155	805	145	140	135	135	555
Boniva - U.S. (lc, ex fx)								5	5		5	5	5	5	
- U.S.	11	9	7	8	35	9	5	5	5	25	5	5	5	5	20
- Fgn (lc, ex fx)															
- Fgn	48	44	44	38	174	40	39	35	35	150	30	30	20	20	100
Boniva - WW	59	53	51	46	209	49	44	40	40	173	35	35	25	25	120
Neutrogen - U.S. (lc, ex fx)											40	40	35	35	
- U.S.											40	40	35	35	
- Fgn (lc, ex fx)															
- Fgn	56	55	56	50	217	48	43	40	40	170	40	40	35	35	150
Neutrogen - WW	56	55	56	50	217	48	43	40	40	171	40	40	35	35	150
Xenical - U.S. (lc, ex fx)								5	5		5	5	5	5	
- U.S.	5	6	5	6	22	3	5	5	5	20	5	5	5	5	20
- Fgn (lc, ex fx)															
- Fgn	29	41	27	36	133	23	25	25	30	105	20	20	20	25	85
Xenical - WW	34	47	32	42	155	26	30	30	35	121	25	25	25	30	105
Rocephin - U.S. (lc, ex fx)								1							
- U.S.															
- Europe (lc, ex fx)															
- Europe	14	11	7	12	44	15	10	5	10	40	10	10	5	5	30
- Japan (lc, ex fx)															
- Japan	10	11	11	11	43	8	8	5	5	25	5	5	5	5	20
- International	44	49	46	44	183	45	46	45	40	175	45	40	40	40	165
Rocephin - WW	68	71	64	67	270	68	65	55	55	240	60	55	50	50	215

Source: Company data, Cowen and Company.

Roche Quarterly Sales Dynamics (CHF MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Nutropin - U.S. (lc, ex fx)								60	50		45	50	50	45	
- U.S.	72	69	67	60	268	52	57	60	50	220	45	50	50	45	190
- Europe (lc, ex fx)															
- Europe															
- Japan (lc, ex fx)															
- Japan															
- International	1	2	2	1	6	1	1	0	0	0	0	0	0	0	0
Nutropin - WW	73	71	69	61	274	53	58	60	50	220	45	50	50	45	190
Madopar - U.S. (lc, ex fx)								30	30		30	30	30	30	
- U.S.															
- Europe (lc, ex fx)															
- Europe	28	28	28	28	112	26	27	30	30	115	30	30	30	30	120
- Japan (lc, ex fx)															
- Japan	4	5	5	5	19	4	4	5	5	20	5	5	5	5	20
- International	48	45	44	45	182	30	45	45	45	165	35	45	45	45	170
Madopar - WW	80	78	77	78	313	60	76	80	80	300	70	80	80	80	310
Esbriet											55	65	75	85	280
RG7446															
RG7601															
Gazyva															
Ocrelizumab															
Lampalizumab															
Cobimetinib															
Suvenyl															
Lebrikutzumab															
CSF-1R Mab															
Ipatasertib															
Quilizumab															
Basimglurant															
Decoglurant/basimglurant															
Pictilisib															
Tasellisib															
Pinatuzumab vedotin															
Polatuzumab vedotin															
RG7597															
RG71662															
Alectinib															
RG7686															
Ang2-VEGF Mab															
RG7667															
Etrolizumab															
R1577															
Crenezumab (A-beta)															
Gantenerumab (A-beta)															
V1 receptor antagonist															
RG7745															
RG7929															
FIXa/FX biospecific Mab															
RG7599															
Mericitabine															
Danoprevir															
Inclacumab															
Setrobuvir															
IL-31R Mab															
Bitoperlin															
Other	645	652	599	616	2512	548	533	500	501	2080	500	500	500	500	2000
TOTAL PHARMACEUTICALS	9,170	8,892	9,028	9,114	38,304	9,040	8,794	8,775	9,036	38,660	9,000	8,860	8,830	9,130	35,910
% Change	6%	2%	3%	1%	3%	-1%	-2%	-3%	-1%	-2%	0%	1%	2%	1%	1%

Source: Company data, Cowen and Company.

Roche Quarterly Sales Dynamics (CHF MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
DIAGNOSTICS															
Professional Diagnostics - U.S. (lc, ex fx)								305	330		315	325	315	350	
Professional Diagnostics - U.S.	271	294	286	311	1162	294	306	295	330	1225	320	330	315	350	1315
Professional Diagnostics - Fgn (lc, ex fx)								1200	1250		1150	1265	1240	1300	
Professional Diagnostics - Fgn	1066	1178	1132	1202	4578	1098	1206	1180	1235	4720	1140	1260	1240	1300	4940
Professional Diagnostics - WW	1337	1472	1418	1513	5740	1392	1512	1475	1565	5945	1460	1590	1555	1650	6255
Diabetes Care - U.S. (lc, ex fx)								100	120		100	110	95	120	
Diabetes Care - U.S.	94	144	112	132	482	100	110	95	120	425	100	110	95	120	425
Diabetes Care - Fgn (lc, ex fx)								455	535		445	500	450	535	
Diabetes Care - Fgn	445	522	464	546	1977	438	492	445	530	1905	440	495	450	535	1920
Diabetes Care - WW	539	666	576	678	2459	538	602	540	650	2330	540	605	545	655	2345
Molecular Diagnostics - U.S. (lc, ex fx)								150	150		135	145	145	150	
Molecular Diagnostics - U.S.	132	145	144	146	567	129	139	145	150	565	135	150	145	150	580
Molecular Diagnostics - Fgn (lc, ex fx)								240	270		250	265	245	275	
Molecular Diagnostics - Fgn	254	266	247	278	1045	241	253	235	265	995	250	265	245	275	1035
Molecular Diagnostics - WW	386	411	391	424	1612	370	392	380	415	1555	385	415	390	425	1615
Tissue Diagnostics - U.S. (lc, ex fx)								100	115		95	110	100	120	
Tissue Diagnostics - U.S.	95	100	95	110	400	89	105	95	115	405	95	110	100	120	425
Tissue Diagnostics - Fgn (lc, ex fx)								70	80		75	80	75	85	
Tissue Diagnostics - Fgn	62	65	64	74	265	67	73	70	80	290	75	80	75	85	315
Tissue Diagnostics - WW	157	165	159	184	665	156	178	165	195	695	170	190	175	205	740
Total Diagnostics	2,419	2,714	2,544	2,799	10,476	2,456	2,684	2,560	2,825	10,525	2,555	2,800	2,665	2,935	10,955
% Change	1%	4%	2%	1%	2%	2%	-1%	1%	1%	0%	4%	4%	4%	4%	4%
TOTAL SALES	11,589	11,706	11,572	11,913	46,780	11,496	11,478	11,335	11,860	46,175	11,555	11,650	11,595	12,065	46,865
% Change	5%	3%	3%	1%	3%	-1%	-2%	-2%	0%	-1%	1%	1%	2%	2%	1%

Source: Company data, Cowen and Company.

Roche Annual Sales Dynamics (CHF MM)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
PHARMACEUTICALS											
Avastin - U.S. (lc, ex fx)											
- U.S.	2575	2610	2680	2750	2800	2500	2200	1900	-5%	-4%	Growth driven by CRC and ovarian; patents expire 2017-19
- Europe (lc, ex fx)											
- Europe	1919	1970	2040	2125	2200	2275	2350	2000	0%	1%	Patents expire 12/19
- Japan (lc, ex fx)											
- Japan	717	710	750	800	825	850	875	900	4%	3%	
- International	1043	1015	1055	1100	1150	1200	1250	1300	4%	3%	
Avastin - WW	6254	6305	6525	6775	6975	6825	6675	6100	-1%	0%	Bevacizumab; advanced CRC, NSCLC, ovarian, relapsed glioblastoma, breast (EU only), ovarian, cervical filing
Mabthera/Rituxan - U.S (lc, ex fx)											
- U.S.	3329	3315	3325	3100	2800	2500	2250	2000	-8%	-7%	Patents expire 2018; Gazyva might clip
- Europe (lc, ex fx)											
- Europe	1918	2000	1905	1700	1500	1300	1200	1000	-11%	-9%	Earlier use after anti-TNF failure driving growth; SQ CHMP positive opinion; patent expires 2014
- Japan (lc, ex fx)											
- Japan	249	240	265	290	310	330	350	370	7%	6%	
- International	1455	1385	1360	1350	1350	1350	1350	1350	0%	-1%	
Mabthera/Rituxan - WW	6951	6940	6855	6440	5960	5480	5150	4720	-6%	-5%	Rituximab; non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis
Herceptin - U.S. (lc, ex fx)											
- U.S.	1787	1830	1775	1500	1250	1000	750	500	-19%	-17%	Patents expire 2019; anticipate treatment moves to Perjeta/Kadcyla combination
- Europe (lc, ex fx)											
- Europe	2191	2215	2120	2000	1800	1600	1400	1200	-10%	-8%	Patent expires 7/14
- Japan (lc, ex fx)											
- Japan	294	265	240	225	205	185	165	145	-10%	-10%	
- International	1807	1755	1735	1700	1600	1500	1400	1300	-5%	-5%	
Herceptin - WW	6079	6065	5870	5425	4855	4285	3715	3145	-10%	-9%	Trastuzumab; HER2-positive breast cancer; gastric; SQ
Perjeta - U.S. (lc, ex fx)											
- U.S.	219	520	710	850	950	1050	1150	1250	16%	NM	Rollout underway
- Europe (lc, ex fx)											
- Europe	68	220	380	550	900	1200	1500	1800	42%	NM	Rollout underway
- Japan (lc, ex fx)											
- Japan	23	90	170	250	350	450	550	650	39%	NM	
- International	16	55	130	200	300	400	500	600	49%	NM	Approved in Mexico and Switzerland
Perjeta - WW	326	885	1390	1850	2500	3100	3700	4300	30%	NM	HER2-positive metastatic breast cancer
Kadcyla - U.S (lc, ex fx)											
- U.S.	222	315	460	600	750	900	1050	1200	25%	NM	Rollout underway
- Europe (lc, ex fx)											
- Europe	9	165	320	500	700	900	1100	1300	41%	NM	Rollout underway
- Japan (lc, ex fx)											
- Japan	3	35	110	200	250	300	350	400	50%	NM	Launched 4/14
- International	3	45	130	200	250	300	350	400	44%	NM	
Kadcyla - WW	234	560	1020	1500	1950	2400	2850	3300	34%	NM	HER2-positive metastatic BC; 2nd line

Source: Company data, Cowen and Company.

Roche Annual Sales Dynamics (CHF MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
Zelboraf - U.S. (lc, ex fx)											
- U.S.	123	65	90	110	130	150	170	190	20%	NM	BRAF positive melanoma patients
- Europe (lc, ex fx)											
- Europe	194	190	210	230	250	270	290	310	9%	NM	BRAF positive melanoma patients
- Japan (lc, ex fx)											
- Japan											Chugai has rights, pays Roche a royalty
- International	37	40	60	80	100	120	140	160	26%	NM	Approved in New Zealand, Australia, Brazil, India, Israel
Zelboraf - WW	354	295	360	420	480	540	600	660	14%	9%	BRAF inhibitor; malignant melanoma; adjuvant in Phase III
Erlivedge - U.S. (lc, ex fx)											
- U.S.	66	80	110	140	170	200	230	270	22%	NM	Rollout underway
- Europe (lc, ex fx)											
- Europe	8	45	70	90	110	130	150	170	25%	NM	
- Japan (lc, ex fx)											
- Japan											NM
- International	1	15	30	40	50	60	70	80	32%	NM	Approved in Mexico, Israel, South Korea; filed in Australia and Canada
Erlivedge - WW	75	140	210	270	330	390	450	520	24%	NM	Hedgehog inhib.; FDA apprvd for advanced BCC, advanced BC, AML Phase II; \$75,000/course
Pegasys - U.S. (lc, ex fx)											
- U.S.	307	225	90	50	50	50	50	50	-22%	-23%	
- Europe (lc, ex fx)											
- Europe	356	255	150	125	100	75	50	25	-32%	-32%	Patent expires 2017
- Japan (lc, ex fx)											
- Japan	52	60	30	20	15	10	5	5	-34%	-28%	
- International	597	525	450	400	350	300	250	200	-15%	-14%	
Pegasys - WW	1312	1065	720	595	515	435	355	280	-20%	-20%	Peginterferon alfa-2a; hepatitis B and C; interferon-free regimens and shorter duration may clip use
Tarceva - U.S. (lc, ex fx)											
- U.S.	604	610	645	675	700	725	600	400	-7%	-6%	Patent expires 11/18
- Europe (lc, ex fx)											
- Europe	343	315	300	285	270	250	230	210	-7%	-7%	Patent expires 3/20
- Japan (lc, ex fx)											
- Japan	99	95	85	70	60	50	40	30	-17%	-16%	
- International	293	255	240	225	210	195	180	165	-7%	-8%	
Tarceva - WW	1339	1275	1270	1255	1240	1220	1050	805	-7%	-7%	Erlotinib; non-small cell lung cancer, pancreatic cancer
Actemra - U.S. (lc, ex fx)											
- U.S.	314	370	450	550	650	750	850	950	17%	17%	Rheumatoid arthritis; approved in first line 10/12; Patent expires 2020
- Europe (lc, ex fx)											
- Europe	360	430	510	575	650	725	725	725	9%	11%	Patent expires 2018
- Japan (lc, ex fx)											
- Japan	197	215	260	310	360	410	460	510	15%	15%	
- International	166	180	215	250	275	300	325	350	12%	11%	
Actemra - WW	1037	1195	1435	1685	1935	2185	2360	2535	13%	14%	SQ approved in U.S., CHMP positive opinion; Patent expires 2018
Cellcept - U.S. (lc, ex fx)											
- U.S.	204	180	120	80	40	20	10	5	-45%	-41%	Patent expired on oral form, IV and suspension patents until 2013-14
- Europe (lc, ex fx)											
- Europe	238	220	200	180	160	140	120	100	-12%	-12%	Patent expired in 11/10
- Japan (lc, ex fx)											
- Japan	68	60	55	50	45	40	35	30	-11%	-11%	
- International	364	320	280	240	200	160	120	80	-21%	-19%	
Cellcept - WW	874	780	655	550	445	360	285	215	-19%	-18%	Mycophenolate mofetil; transplantation

Source: Company data, Cowen and Company.

Roche Annual Sales Dynamics (CHF MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
Cymevene/Valcyte - U.S. (lc, ex fx)											
- U.S.	358	380	350	300	250	200	150	100	-20%	-17%	Patent expires 9/15
- Europe (lc, ex fx)											
- Europe	174	175	150	130	110	90	70	50	-19%	-16%	Patent expires 9/16
- Japan (lc, ex fx)											
- Japan											
- International	161	150	130	120	110	100	90	80	-10%	-10%	
Cymevene/Valcyte - WW	693	705	630	550	470	390	310	230	-17%	-15%	
Tamiflu - U.S. (lc, ex fx)											
- U.S.	428	315	200	200	200	200	200	200	-7%	-10%	Patent expires 12/16
- Europe (lc, ex fx)											
- Europe	18	70	50	50	50	50	50	50	NM	NM	Patent expires 2/16
- Japan (lc, ex fx)											
- Japan	105	75	75	75	75	75	75	75	0%	-5%	
- International	84	90	75	75	75	75	75	75	-3%	-2%	
Tamiflu - WW	635	550	400	400	400	400	400	400	-5%	-6%	Oseltamivir; treatment and prevention of influenza A and B
Xolair - U.S. (lc, ex fx)											
Xolair - U.S.	790	875	965	1050	1125	1200	1275	1350			
Xolair - WW	790	877	965	1050	1125	1200	1275	1350	7%	8%	Approved in U.S. in chronic idiopathic urticaria
Lucentis - U.S. (lc, ex fx)											
Lucentis - U.S.	1689	1710	1740	1770	1800	1830	1500	1250			AMD, RVO, DME (approved 8/12); growth expected in DME and RVO
Lucentis WW	1689	1710	1740	1770	1800	1830	1500	1250	-5%	-4%	Patent expires 2019; CATT showed Lucentis and Avastin comparable, but Lucentis might be safer
Mircera - U.S. (lc, ex fx)											
- U.S.											Could launch in 2014-15 but outlook unclear
- Europe (lc, ex fx)											
- Europe	104	110	120	130	140	150	160	170	8%	7%	
- Japan (lc, ex fx)											
- Japan	214	215	235	255	275	295	315	335	8%	7%	
- International	107	115	130	140	150	160	170	180	8%	8%	
Mircera - WW	425	440	485	525	565	605	645	685	8%	7%	Patent expires 2020
NeoRocmormon/Epopigin - U.S. (lc, ex fx)											
- U.S.											
- Europe (lc, ex fx)											
- Europe	218	195	175	155	135	115	95	75	-15%	-14%	
- Japan (lc, ex fx)											
- Japan	100	60	50	40	30	20	10	5	-34%	-35%	
- International	202	200	190	180	170	160	150	140	-6%	-5%	
NeoRocmormon/Epopigin - WW	520	455	415	375	335	295	255	220	-11%	-12%	Epoetin beta; anemia

Source: Company data, Cowen and Company.

Roche Annual Sales Dynamics (CHF MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
Pulmozyme - U.S. (lc, ex fx)											
- U.S.	355	355	315	275	225	175	125	75	-23%	-20%	
- Europe (lc, ex fx)											
- Europe	124	110	90	70	50	30	10	5	-40%	-37%	
- Japan (lc, ex fx)											
- Japan											
- International	93	85	80	75	70	65	60	55	-7%	-7%	
Pulmozyme - WW	572	550	485	420	345	270	195	135	-21%	-19%	Patent expired 2012
Activase - U.S. (lc, ex fx)											
- U.S.	635	650	665	675	685	695	705	715	2%	2%	
- Europe (lc, ex fx)											
- Europe											
- Japan (lc, ex fx)											
- Japan											
- International	48	45	40	35	30	25	20	15	-17%	-15%	
Activase - WW	683	695	705	710	715	720	725	730	1%	1%	Patent expired 2/10
Xeloda - U.S. (lc, ex fx)											
- U.S.	616	195	25	15	5	5	5	5	-46%	-50%	Patent expires Q1:14
- Europe (lc, ex fx)											
- Europe	315	95	30	20	10	5	5	5	-39%	-45%	Patent expires 12/13
- Japan (lc, ex fx)											
- Japan	107	80	50	40	30	20	10	5	-37%	-35%	
- International	471	435	450	470	490	510	530	550	4%	2%	
Xeloda - WW	1509	805	555	545	535	540	550	565	-6%	-13%	Capecitabine; colorectal, breast, stomach cancer
Boniva - U.S. (lc, ex fx)											
- U.S.	35	25	20	10	5	5	5	5	NM	NM	Patent expired 3/12
- Fgn (lc, ex fx)											
- Fgn	174	150	100	75	50	25	10	5	-43%	-40%	
Boniva - WW	209	173	120	85	55	30	15	10	-38%	-35%	
Neutrogenin - U.S. (lc, ex fx)											
- U.S.											
- Fgn (lc, ex fx)											
- Fgn	217	170	150	130	110	90	70	50	-18%	-19%	
Neutrogenin - WW	217	171	150	130	110	90	70	50	-19%	-19%	
Xenical - U.S. (lc, ex fx)											
- U.S.	22	20	20	20	20	20	20	20	0%	-1%	
- Fgn (lc, ex fx)											
- Fgn	133	105	85	65	45	25	15	5	-40%	-37%	
Xenical - WW	155	121	105	85	65	45	35	25	-23%	-23%	
Rocephin - U.S. (lc, ex fx)											
- U.S.											
- Europe (lc, ex fx)											
- Europe	44	40	30	25	20	15	10	5	-29%	-27%	
- Japan (lc, ex fx)											
- Japan	43	25	20	15	10	5	5	5	-24%	-26%	
- International	183	175	165	155	145	135	125	115	-7%	-6%	
Rocephin - WW	270	240	215	195	175	155	140	125	-10%	-10%	

Source: Company data, Cowen and Company.

Roche Annual Sales Dynamics (CHF MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
Nutropin - U.S. (lc, ex fx)											
- U.S.	268	220	190	170	150	130	110	90	-14%	-14%	
- Europe (lc, ex fx)											
- Europe											
- Japan (lc, ex fx)											
- Japan											
- International	6	0	0	0	0	0	0	0	NM	NM	
Nutropin - WW	274	220	190	170	150	130	110	90	-14%	-15%	
Madopar - U.S. (lc, ex fx)											
- U.S.											
- Europe (lc, ex fx)											
- Europe											
- Japan (lc, ex fx)											
- Japan	112	115	120	120	120	120	120	120	1%	1%	
- International	19	20	20	20	20	20	20	20	0%	1%	
Madopar - WW	182	165	170	175	180	185	190	195	3%	1%	
Esbriet	313	300	310	315	320	325	330	335	2%	1%	Parkinson's disease; off patent
RG7446											
RG7601											
Gazyva	3	55	130	200	300	400	500	600	49%	NM	Obinutuzumab; approved for CLL; Non-Hodgkin's lymphoma (data 2015/17); anti-CD20 Mab
Ocrelizumab											
Lampalizumab											
Cobimetinib											
Suvenyl											
Lebrikituzumab											
CSF-1R Mab											
Ipatasertib											
Quilizumab											
Basmiglurant											
Decoglurant/basmiglurant											
Pictilisib											
Taselisib											
Pinatuzumab vedotin											
Polatuzumab vedotin											
RG7597											
RG7162											
Alectinib											
RG7668											
Ang2-VEGF Mab											
RG7667											
Etralizumab											
R1577											
Crenezumab (A-beta)											
Gantenerumab (A-beta)											
V1 receptor antagonist											
RG7745											
RG7929											
Fixa/FX biospecific Mab											
RG7599											
Mericitabine											
Danoprevir											
Inclacumab											
Setrobuvir											
IL-31R Mab											
Bitoperlin											
Other	10	20	30	40	NM	NM	Glycine transporter 1 inhib; schizophrenia neg symptoms trials failed/suboptimal control trials ongoing; OCD Phase II				
TOTAL PHARMACEUTICALS	36,304	35,650	35,910	36,990	38,085	39,590	41,000	42,320	3%	2%	
% Change	3%	-2%	1%	3%	3%	4%	4%	3%			

Source: Company data, Cowen and Company.

Roche Annual Sales Dynamics (CHF MM) (continued)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	2014-20 CGR	2013-20 CGR	Comments
DIAGNOSTICS											
Professional Diagnostics - U.S. (lc, ex fx)											
Professional Diagnostics - U.S.	1162	1225	1315	1400	1475	1550	1625	1700	6%	6%	
Professional Diagnostics - Fgn (lc, ex fx)											
Professional Diagnostics - Fgn	4578	4720	4940	5200	5400	5600	5800	6000	4%	4%	
Professional Diagnostics - WW	5740	5945	6255	6600	6875	7150	7425	7700	4%	4%	Immunoassays, clinical chemistry, coagulation monitoring. Custom biotech
Diabetes Care - U.S. (lc, ex fx)											
Diabetes Care - U.S.	482	425	425	450	475	500	525	550	4%	2%	
Diabetes Care - Fgn (lc, ex fx)											
Diabetes Care - Fgn	1977	1905	1920	1940	1960	1980	2000	2020	1%	0%	
Diabetes Care - WW	2459	2330	2345	2390	2435	2480	2525	2570	2%	1%	Blood glucose monitoring; Accu-Chek meters
Molecular Diagnostics - U.S. (lc, ex fx)											
Molecular Diagnostics - U.S.	567	565	580	590	610	630	650	670	3%	2%	
Molecular Diagnostics - Fgn (lc, ex fx)											
Molecular Diagnostics - Fgn	1045	995	1035	1075	1115	1155	1195	1235	4%	2%	
Molecular Diagnostics - WW	1612	1555	1615	1665	1725	1785	1845	1905	3%	2%	Virology, blood screening, Genome sequencing, PCR
Tissue Diagnostics - U.S. (lc, ex fx)											
Tissue Diagnostics - U.S.	400	405	425	445	465	485	505	525	4%	4%	
Tissue Diagnostics - Fgn (lc, ex fx)											
Tissue Diagnostics - Fgn	265	290	315	340	365	390	415	440	7%	8%	
Tissue Diagnostics - WW	665	695	740	785	830	875	920	965	6%	5%	Advanced tissue staining
Total Diagnostics	10,476	10,525	10,955	11,440	11,865	12,290	12,715	13,140	4%	3%	In Q2:13, Applied Science integrated into Molecular and Diagnostics Businesses
% Change	2%	0%	4%	4%	4%	4%	3%	3%			
TOTAL SALES	46,780	46,175	46,865	48,430	49,950	51,880	53,715	55,460	3%	2%	
% Change	3%	-1%	1%	3%	3%	4%	4%	3%			

Source: Company data, Cowen and Company.

Roche Annual P&L Buildup 2013-20 (CHF MM)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CGR '14-20	CGR 13-20
Total Sales	46,780	46,175	46,865	48,430	49,950	51,880	53,715	55,460	3%	2%
Y/Y Chg.	3%	-1%	1%	3%	3%	4%	4%	3%		
Royalty income	1606	1615	1715	1775	1825	1875	1925	1975	3%	3%
Income from out-licensing agreements	118	114	145	175	195	215	235	255	14%	12%
Income from disposal of products and other	108	574	150	170	190	210	230	250	-13%	13%
Royalties & other op. income	1832	2303	2010	2,120	2,210	2,300	2,390	2,480	1%	4%
Total revenues	48,612	48,473	48,875	50,550	52,160	54,180	56,105	57,940	3%	3%
Y/Y Chg.	2%	0%	1%	3%	3%	4%	4%	3%		
Manuf COGS and period costs	8,678	8,344	7,745	7,630	7,630	7,800	8,000	8,180	0%	-1%
Royalty expense	1,527	1,487	1,599	1,635	1,617	1,578	1,542	1,484	0%	0%
Collaboration and profit-sharing agreements	1,680	1,767	1,692	1,981	1,989	1,992	1,979	1,957	2%	2%
Impairment of PPE	7	0	0	0	0	0	0	0		
Impairment of Product Intangibles										
COGS	11,892	11,631	11,036	11,246	11,235	11,370	11,520	11,621	0%	0%
Gross profit	36,720	36,842	37,839	39,304	40,925	42,810	44,585	46,319	4%	3%
Gross margin	78.5%	79.8%	80.7%	81.2%	81.9%	82.5%	83.0%	83.5%		
Marketing & Distribution	8,241	7,793	7,895	8,125	8,260	8,460	8,670	8,950	2%	1%
% Sales	17.6%	16.9%	16.8%	16.8%	16.5%	16.3%	16.1%	16.1%		
Corporate	315	388	345	355	365	375	385	395	0%	3%
Administration	1,515	1,389	1,445	1,545	1,565	1,585	1,605	1,625	3%	1%
Other general items	340	280	295	315	335	355	375	395		
Pensions - Past Service Income	(301)									
General & Administration	1,875	2,059	2,085	2,215	2,265	2,315	2,365	2,415	3%	4%
% Sales	4.0%	4.5%	4.4%	4.6%	4.5%	4.5%	4.4%	4.4%		
Total SG&A	10,116	9,852	9,980	10,340	10,525	10,775	11,035	11,365	2%	2%
% Sales	21.6%	21.3%	21.3%	21.4%	21.1%	20.8%	20.5%	20.5%		
R&D expenses excluding non-cash items	8,700	8,815	8,925	9,125	9,200	9,300	9,400	9,500	1%	1%
R&D	8,700	8,815	8,925	9,125	9,200	9,300	9,400	9,500	1%	1%
% Sales	18.6%	19.1%	19.0%	18.8%	18.4%	17.9%	17.5%	17.1%		
Operating Expenses	18,816	18,667	18,905	19,465	19,725	20,075	20,435	20,865	2%	1%
% Sales	40.2%	40.4%	40.3%	40.2%	39.5%	38.7%	38.0%	37.6%		
Operating Income	17,904	18,175	18,934	19,839	21,200	22,735	24,150	25,454	6%	5%
% Sales	38.3%	39.4%	40.4%	41.0%	42.4%	43.8%	45.0%	45.9%		
Financial income	(119)	77	95	105	115	125	135	145		
Financing costs	(1,580)	(1,370)	(1,575)	(1,475)	(1,375)	(1,275)	(1,175)	(1,075)		
Net financial income/loss	(1699)	(1,293)	(1,480)	(1,370)	(1,260)	(1,150)	(1,040)	(930)		
Profit before tax	16,205	16,882	17,454	18,469	19,940	21,585	23,110	24,524	6%	6%
% Sales	34.6%	36.6%	37.2%	38.1%	39.9%	41.6%	43.0%	44.2%		
Tax	3,679	3,981	4,014	4,248	4,586	4,965	5,315	5,641	6%	6%
Tax rate	22.7%	23.6%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%		
Net Income	12,526	12,901	13,439	14,221	15,354	16,621	17,795	18,884	7%	6%
Roche shareholders	12,316	12,688	13,204	13,976	15,099	16,356	17,520	18,599	7%	6%
Non-controlling interests	210	213	235	245	255	265	275	285	5%	4%
Core Net Income	12,316	12,688	13,204	13,976	15,099	16,356	17,520	18,599	7%	6%
Net Income used to calculate diluted EPS	12,316	12,688	13,204	13,976	15,099	16,356	17,520	18,599	7%	6%
Core EPS (Diluted)	14.26	14.70	15.30	16.20	17.50	18.95	20.30	21.55	7%	6%
Share count (MM)	865	863	863	863	863	863	863	863	0%	0%

Source: Company data, Cowen and Company

Oncology

Roche currently has 20 NMEs in its oncology pipeline including 3 immune oncology compounds in clinical trials and another 6 expected to be in clinicals within the next 12 months. The company believes its oncology portfolio is differentiated by its breadth of compounds with which it can evaluate numerous combinations, and its in-house diagnostics capabilities which help target the optimal patients for each therapy.

Kadcyla Strengthens HER2 Franchise

In February 2013, the FDA approved T-DM1 (commercial name Kadcyla) for the treatment of HER2-positive metastatic breast cancer. Kadcyla is priced at \$9,800/month. Trastuzumab-DM1 is a first-in-class HER2 antibody drug conjugate (ADC) comprised of Herceptin linked to ImmunoGen's cell-killing agent, DM1 (emtansine), a maytansine derivative and anti-microtubule agent. Kadcyla was approved in Switzerland in May 2013, Japan in September 2013, and in the E.U. in November 2013. Kadcyla has been launched in Germany and Denmark with launches in most remaining EU countries in Q3:14. According to management, Kadcyla has captured 40-45% share of the 2nd line treatment U.S. market as of Q2:14.

Kadcyla's label allows for use in front-line HER-2 positive metastatic breast cancer. This was not a major surprise, since EMILIA included about 12% front-line mBC patients (about 60 1st-line mBC patients in the T-DM1 arm of the EMILIA trial). The label contains a black box warning for hepatotoxicity, cardiac and embryo-fetal toxicity; however, Herceptin, Tykerb (GSK), and Perjeta all carry similar black box warnings.

IMGN is entitled to 3% royalty on Kadcyla sales <\$250MM, 3.5% on sales \$250-400MM, 4% on sales \$400-700MM, and 5% on sales >\$700MM. In the E.U., Kadcyla has 10-years of exclusivity. We estimate Kadcyla sales of CHF560MM (+139%) in 2014, CHF1,020MM in 2015, CHF1,500MM in 2016, CHF2,400MM in 2018, and CHF3,300MM in 2020.

MARIANNE: A Phase III Trial Of Kadcyla And Perjeta In 1st-Line mBC

In June 2010, based on early signs of efficacy observed in the 137-patient Phase II trial in the 1st-line metastatic breast cancer setting, Roche advanced Kadcyla to Phase III testing for the treatment of 1st-line metastatic breast cancer. The Phase III MARIANNE study was initiated in July 2010, with the goal of testing the efficacy and safety of Kadcyla, alone or in combination with pertuzumab (Perjeta), for the treatment of 1st-line metastatic breast cancer. The data (PFS) from this trial are expected by year end, followed by BLA/MAA filings in 2015.

Study design: This is a randomized, open-label, multicenter, international, Phase III three-arm trial of Kadcyla in "*patients with HER2-positive, progressive or recurrent, locally advanced or chemotherapy-naïve metastatic breast cancer*". The trial enrolled 1095 patients who are randomized into three arms:

Arm-1) Kadcyla (3.6 mg/kg IV every 3 weeks) (n=364),

Arm-2) Kadcyla (3.6 mg/kg IV every 3 weeks) in combination with pertuzumab (840 mg IV on day 1 of cycle 1, followed by 420 mg IV every 3 weeks in subsequent cycles) (n=364), and

Arm-3) Herceptin in combination with a taxane (either docetaxel or paclitaxel) (n=364).

Endpoints: The primary endpoint of the trial is progression-free survival (PFS), with overall survival (O/S), 1-year survival rate, time-to-treatment failure, overall or objective response rate (ORR), clinical benefit rate (CBR), duration of response (DOR), and PFS by investigator review as secondary endpoints.

Trial statistics: The trial is 80% powered to test the superiority of the Kadcyla arms over the control arm, with a hazard ratio of 0.75 or a 33% improvement in median PFS. The trial will also test for non-inferiority of each of the Kadcyla arms, compared with control: the trial is 80% powered to detect a hazard ratio between 0.88 and 1.18 or a result ranging between a 14% increase and a 15% decrease in median PFS.

T-DM1 More Effective And Less Toxic Than Lapatinib + Capecitabine In EMILIA; OS Endpoint Met

The EMILIA study compared T-DM1 to Lapatinib plus Capecitabine in second-line Her2+ metastatic breast cancer. T-DM1 met its co-primary PFS endpoint in EMELIA (PFS for T-DM1 of 9.6 vs. 6.4 for Lapatinib plus capecitabine (XL), (HR=0.65, p<0.0001). PFS curves were consistent across investigator and independent reviews. The interim OS analysis (HR of 0.621, p= 0.0005) did not meet the Lan-DeMets alpha spending function/O'Brien-Flemming stoppage criteria. Had a single more patient died in the XL treatment arm, the study would have met the interim efficacy stopping criteria for OS. The difference in survival at 1- and 2-years is the largest absolute difference in OS that has ever been observed in mBC. In August 2012, Roche announced that T-DM1 met the OS endpoint in EMILIA. Patients treated with T-DM1 lived an average of 5.8 months longer than patients treated with second-line SOC Tykerb + Xeloda (30.9 vs. 25.1 months, HR=0.68, p= 0.0006). A detailed summary of T-DM1's efficacy in EMILIA is shown on the next page:

Efficacy Of T-DM1 In EMILIA

	T-DM1	Cap + Lap
PFS, mo	9.6	6.4
OS, % (95% CI)		
1-year	84.7 (80.76-88.55)	77.0 (72.40-81.50)
2-year	65.4 (58.65-72.15)	47.5 (39.20-55.89)
Objective Response (OR) %, (95% CI)	43.6 (38.6-48.6)	30.8 (26.3-35.7)
Duration of response in pts with OR, med mo (95% CI)	12.6 (8.38-20.76)	6.5 (5.45-7.16)
Dose reduction, %	16.3	Cap- 53.4 Lap- 27.3
Aes ≥3, %	40.8	57

Source: ASCO

T-DM1 uses a stable MCC linker to bind DM1 to trastuzumab. Trastuzumab binding to HER2 overexpressing cells allows for the selective delivery of DM1 and limits chemotherapy-mediated toxicities. In EMILIA, T-DM1 limited a majority of non-hematologic adverse events compared to Xeloda/lapatinib, with the exception of AST/ALT, which was increased in patients treated with T-DM1. Consistent with the administration of trastuzumab, significantly more anemia and thrombocytopenia was observed with T-DM1 treatment; however, the number of transfusions and serious bleeding was similar between treatment arms. A detailed summary of adverse event profile of T-DM1 in EMILIA is detailed below:

Non-Hematologic Adverse Events in EMILIA

Adverse Event	Cap + Lap (n=488)		T-DM1	
	All Grades, %	Grade ≥3, %	All Grades, %	Grade ≥3, %
Diarrhea	79.7	20.7	23.3	1.6
Hand-foot syndrome	58	16.4	1.2	0
Vomiting	29.3	4.5	19	0.8
Hypokalemia	8.6	4.1	8.6	2.2
Fatigue	27.9	3.5	35.1	2.4
Nausea	44.7	2.5	39.2	0.8
Mucosal Inflammation	19.3	2.3	6.7	0.2
Increased AST	9.4	0.8	22.4	4.3
Increased ALT	8.8	1.4	18.9	2.9

Source: ASCO 2012

Hematologic Adverse Events in EMILIA

Adverse Event	Cap + Lap (n=488)			T-DM1		
	All Grades, %	Grade 3, %	Grade 4, %	All Grades, %	Grade 3, %	Grade 4, %
Neutropenia	8.6	3.5	0.8	5.9	1.6	0.4
Febrile Neutropenia	1	0.4	0.6	0	0	0
Anemia	8	1.6	0	10.4	2.7	0
Thrombocytopenia	2.5	3.5	0.2	28	10.4	2.4

Source: ASCO 2012

TH3RESA Phase III Trial In 3rd-Line mBC Meets PFS Co-Primary Endpoint

In August 2013, Roche reported that Kadcyla met the co-primary endpoint of PFS in the Phase III TH3RESA trial in 3rd-line mBC. Data are not yet mature for the other co-primary endpoint of O/S. TH3RESA is a randomized (1:1), open-label, two-arm, multicenter, international, Phase III trial of Kadcyla in patients with HER2-positive metastatic breast cancer who have received at least two prior regimens of HER2-directed therapy. The trial enrolled 600 patients, who were randomized to receive either Kadcyla as a single agent or Physician's choice of treatment.

TH3RESA PFS, ORR, Safety Results

	Comparison	Kadcyla	Physician's Treatment of Choice*
Median PFS	2.9 mos difference HR=0.528 (95% CI, 0.422, 0.661) p<0.0001	6.2mos median PFS	3.3 mos median PFS
Overall survival	OS endpoint not yet been reached	Median OS not yet reached	14.9 mos median OS
ORR	27.7% difference (95% CI, 16.2, 29.2) p<0.0001	31.3%	8.6%
Safety profile grade 3 or higher AEs		32.3%	43.5%
Most common AEs grade 3 or higher in more than 2% of pts		Inc. liver/other enzymes 2.2%, dyspnea 2.0%, neutropenia 2.5%, fatigue 2.0%, low BRC 2.7%, thrombocytopenia 4.7%	Diarrhea 4.3%, abdominal pain 2.7%, inc. liver/other enzymes 2.2%, fatigue 2.2%, asthenia 2.2%, cellulitis 2.2%, blood clot in lung 2.2%, neutropenia 15.8%, fever w/ neutropenia 3.8%, low WBC 2.7%, low RBC 2.7%

*Options included chemo and Herceptin, single agent chemo, lapatinib and Herceptin, chemo and lapatinib, hormonal therapy and Herceptin

Source: Company data

Other Indications Under Evaluation

Roche has two Phase III trials ongoing with Kadcyla in adjuvant (KAITLIN) and neo-adjuvant (KATHERINE) breast cancer. Kadcyla is also in a Phase II/III trial (GATSBY) in 2nd-line/metastatic HER2+ gastric cancer.

Perjeta Momentum Building

Perjeta (pertuzumab) is a humanized antibody and the first-in-class HER dimerization inhibitor (HDI). HDIs block the ability of the HER2 receptor to collaborate with other HER receptor family members (HER1/EGFR, HER3, and HER4). In cancer cells, interfering with HER2's ability to collaborate with other HER family receptors blocks cell signaling and may ultimately lead to cancer cell growth inhibition and death of the cancer cell. HDIs, because of their unique mode of action, have the potential to work in a wide variety of tumors, including those that do not overexpress HER2 but thus far pertuzumab appears most effective in breast and ovarian cancers. A Phase II study in hormone refractory prostate cancer failed.

Perjeta was approved by the FDA in June, 2012 for the treatment of first-line mBC in Herceptin-naïve patients. In March 2013, Roche received E.U. approval for patients with previously untreated HER2+ mBC. Meaningful efficacy and a benign side-effect profile are expected to drive the rapid adoption of Perjeta. In September 2013, the FDA approved neoadjuvant use of Perjeta in HER2-positive early-stage breast cancer. The company estimates that, in the U.S. market, Perjeta has 60% share in the 1st-line setting and 70% in the neoadjuvant setting. Perjeta was filed for neoadjuvant use in the EU in Q3:14. We estimate Perjeta sales of CHF885MM in 2014, CHF1,390MM in 2015, CHF1,850MM in 2016, CHF3,100MM in 2018, and CHF4,300MM in 2020.

CLEOPATRA: Median OS Data For Perjeta Impressive

At ESMO 2014, final OS data for Perjeta in 1st line HER2+ mBC (CLEOPATRA) was presented which showed that adding Perjeta to Herceptin and docetaxel extended OS by 15.7 months compared to Herceptin and chemotherapy (median OS: 56.5 vs 40.8

months). Death was reduced by 32% for Perjeta compared to Herceptin and chemotherapy (HR=0.68). No new safety signals were observed. Neutropenia was the most common Grade 3-4 AE.

PFS data was released in 2011 and showed 18.4 months for the combination of Perjeta plus Herceptin vs. 12.4 months for Herceptin alone. In December 2012, Roche announced updated survival data, stating that the risk of death was reduced by 34% in people who received Perjeta plus Herceptin vs. Herceptin alone ($p=0.0008$). At that time, median OS had not been reached in people receiving Perjeta; median OS was 37.6 months in people who received Herceptin. At ESMO, we will see final OS data. The final data is later than originally expected, and given that it is an event-driven trial, the delay suggests a longer time to achieve the necessary events (death), which should be favorable for Perjeta.

Addition Of Perjeta To Herceptin In Adjuvant Setting In Phase III

The APHINITY Phase III trial ($n=4808$) is evaluating the addition of Perjeta to Herceptin plus chemo for one year in the adjuvant setting for HER2+ breast cancer. Data is expected in-house late 2015/early 2016 (primary completion date is December 2023 per clinicaltrials.com). If positive, this combination might decrease the need for a second year of adjuvant treatment.

Phase II/III Data Supporting Perjeta + Herceptin Use

Phase II breast cancer data presented at ASCO 2008 demonstrated pertuzumab plus Herceptin resulted in a CR 7.6%, PR 16.7% and the SD $\geq 6/12$ was 25.8%. The combination of pertuzumab and Herceptin was well tolerated, and no patients were withdrawn from the trial with treatment-related adverse events. As an extension to this study, data evaluating pertuzumab monotherapy in patients who had progressed on Herceptin were presented at ASCO 2009. Fourteen patients have received trastuzumab plus pertuzumab following inadequate response (or response then relapse) on pertuzumab monotherapy. Of these 14, 2 having progressed during trastuzumab failed to respond to pertuzumab monotherapy but underwent confirmed response when trastuzumab was added to the pertuzumab, possibly the first report of such a phenomenon and providing good evidence of an enhanced effect when the antibodies are combined.

Herceptin Near-Term Growth Keyed To Emerging Markets As Transition To Kadcyla/Perjeta Progresses

Herceptin, approved in 1998, has almost fully penetrated its initial market of HER2-positive metastatic breast cancer patients (approximately 25-30% of the estimated 50,000 new cases each year). Herceptin received FDA approval for adjuvant breast cancer therapy in February 2006. Although Herceptin is associated with a 3-4% incidence of serious cardiotoxicity including heart failure, the strong survival data for Herceptin supports its use even with this risk. The incidence of this toxicity may have been subset-driven, as analysis of the NSABP trial showed that women either >50 years of age or with pre-existing heart disease had a much higher risk for this adverse effect. Our consultants note that approximately 10% of their patients have experienced reductions in ejection fraction, this has usually been resolved by withholding two to three cycles of Herceptin. Estimates for the number of women with breast cancer starting adjuvant therapy annually are that roughly one-half to two-thirds of all women (100,000-140,000 in the U.S) might receive some sort of adjuvant chemotherapy (in addition to either tamoxifen or an aromatase inhibitor). It is estimated that 50% of patients initiating adjuvant therapy are node negative and 50% node positive. Of patients with early-stage breast cancer, 20%, or 20,000-28,000 of

those on adjuvant therapy, might overexpress HER2 and be candidates for Herceptin therapy.

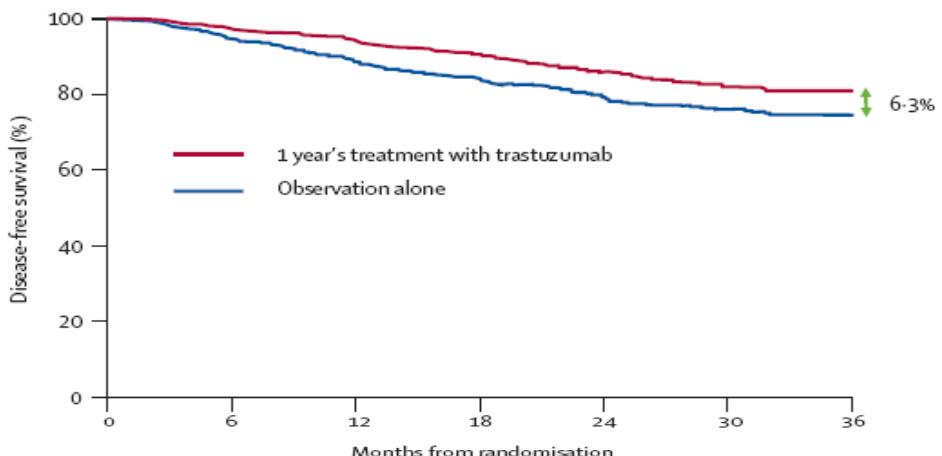
In the U.S., Herceptin is currently priced at \$3,500 per month or \$40-45K per year. The price is similar in most other Western markets and in the E-7, within 95% of the price. Herceptin's penetration in first-line in the U.S. and E.U. is 90% and in the adjuvant setting, 90% and 75%, respectively. However, penetration is much less in the rest of the world and emerging markets, and therefore much of Herceptin's growth will depend on Roche's ability to commercialize in these markets. Roche has employed several strategies to extend Herceptin's exclusivity. A novel subQ formulation of Herceptin received E.U. approval in September 2013, expanding Herceptin's label and providing additional IP. The second strategy is the combination of Kadcyla and pertuzumab that could improve Herceptin's effectiveness. Pertuzumab (Perjeta) was approved in June 2012 and Kadcyla was approved in February 2013. Roche anticipates the first Herceptin biosimilars outside the U.S. to enter the market in 2016. We estimate Herceptin sales of CHF6.065B (flat) in 2014 and CHF5.87B in 2015, and declining to CHF4.285B in 2018 and CHF3.145B in 2020, as Herceptin is replaced by the newer therapies.

HERA Study Shows 12 Months Equal To 24 Months Of Adjuvant Treatment

A key question for adjuvant Herceptin therapy had been the duration of treatment and whether today's standard (12 months) was optimal. Roche's HERA study in adjuvant HER2-positive breast cancer evaluated chemotherapy +/- Herceptin (12 or 24 months' duration). HERA enrolled 5,102 HER2-positive breast cancer patients between December 2001 and March 2005. Patients were randomized 1:1:1 to receive standard adjuvant chemotherapy followed by 1) Herceptin for 1 year, 2) Herceptin for 2 years, or 3) supportive care.

At ESMO 2012, Roche announced that 1 year of Herceptin remains the standard of care for people with early-stage HER2-positive breast cancer. The results showed that there was no difference in the time women lived without their disease returning (disease-free survival, DFS) when they received Herceptin for 1 year versus 2 years. The final analysis also showed that after 8 years of median follow-up, the improvements in the primary endpoint of DFS and secondary endpoint of overall survival for women who received Herceptin for 1 year remained statistically significant compared to the patients in the control arm.

1-Year Herceptin Dosing Is Superior To Placebo



Source: Cowen and Company, Roche

Several studies are ongoing evaluating much shorter Herceptin therapy. The SOLD study is evaluating 9 weeks versus one year, and PERSEPHONE and a British trial, are comparing 6 months versus one year. Data from the PHARE trial, also comparing 6 months to one year, was presented at ESMO 2012. PHARE's primary endpoint was time to recurrence with overall survival data many years away. According to the design of this trial, which allowed for a noninferiority hazard ratio margin of 1.15, the 6-month trastuzumab arm was not demonstrated to be significantly inferior to 12-month trastuzumab, since the confidence interval contains the 1.15 non inferiority margin ($HR=1.28, 95\% CI: 1.04 - 1.56, p=0.29$). A HR of 1.28 suggests a trend favoring 12-months of treatment. A HR of 1.28 translates into a 28% increase in risk of relapse or death for patients randomized to the 6 month duration arm, which is clinically relevant.

Given the small size of short-course Herceptin trials, physicians are unlikely to adopt regimens less than 12-months even if shorter duration trials are successful. However, the success of short-course Herceptin trials could increase physicians' willingness to discontinue Herceptin therapy early if patients are not able to tolerate therapy.

SubQ Formulation Launched In 18 Countries OUS

In 2009, in agreement with regulatory authorities, Roche initiated the Phase III HannaH study comparing a novel subQ formulation versus the standard I.V. formulation. The open-label neo-adjuvant study enrolled 500 patients with operable or locally advanced breast cancer. Patients were randomized to pre-operative treatment with eight cycles of chemotherapy (docetaxel followed by 5-fluorouracil/epirubicin/ cyclophosphamide) concurrent with either subQ Herceptin or I.V. Herceptin. After surgery, patients received a further 10 cycles of Herceptin subQ or IV as per randomization to complete 1 year of treatment. Patients were followed for up to 2 years after the end of treatment for safety and efficacy. In October 2011 Roche announced that HannaH demonstrated comparable efficacy between the I.V. and SQ formulations of Herceptin. The SQ formulation took, on average, 5 minutes to administer compared to a 30 minute I.V. infusion. Similarly, results from the international PrefHer study, released September 2013, showed the SC formulation preferred over the intravenous form by 92% of patients and also reduced the time required by doctors and pharmacists to treat patients. Roche received E.U. approval for Herceptin SQ in October 2013. The SQ formulation will not be pursued in the U.S.

as the endpoints of the HannaH trial (pCR/cTrough) are not considered valid trial endpoints by FDA.

Roche licensed the IP from Halozyme for hyaluronidase, the co-formulated enzyme needed to break down the matrix under the skin to open up for the volume of antibody solution being injected. Roche believes that the subQ formulation will provide much longer IP to protect against biosimilars. The IP on Herceptin cannot be extended, but Roche can protect Herceptin subQ.

Gastric Cancer Likely A Modest Opportunity

In January 2010, Roche received EMEA approval for Herceptin in HER2-positive advanced gastric cancers based on the ToGA study that was presented at ASCO 2009. Approximately 16% of all gastric cancers are HER2-positive, less than the 22% reported in ToGA. In addition, Roche is pursuing an indication for the IHC3+ and IHC2+/ISH patients and not the IHC1+ patients. ToGA compared Xeloda or 5-FU and cisplatin \pm Herceptin. For overall survival, the Hazard Ratio was 0.74 (CI 0.60, 0.91) with a p-value of p=0.0046. Herceptin increased the median overall survival time by 2.7 months to 13.8 months. The response rate was increased with Herceptin from 34.5% to 47.3%. Patients with tumors exhibiting high levels of HER2 experienced even greater benefit from the addition of Herceptin. No new or unexpected side effects were observed. In October 2010, the FDA approved Herceptin for HER-2 positive gastric cancers, and Japanese approval was gained in March 2011.

Herceptin Opportunity In HER2-Negative Breast Cancer A Wild Card

Re-analysis of the Phase III NSABP B-31 study suggested that nearly 10% of the women enrolled as HER2-positive patients should have been classified as HER2-negative, yet experienced the same benefit from Herceptin as those who were correctly identified as HER-2 positive. Based on these unexpected results, the NCI is enrolling a 3,620 patient Phase III trial (NSABP B-47) to evaluate the role of post-surgery Herceptin in the treatment of HER2-negative breast cancer. The trial is expected to complete in 2017.

Avastin Growth Driven By New Indications

Avastin (bevacizumab) is an anti-VEGF (vascular endothelial growth factor) humanized antibody. Avastin is the first-in-class antiangiogenesis agent and currently approved for eight indications: 1) in combination with i.v. 5-fluorouracil for patients with first- or second-line metastatic colorectal cancer; 2) in combination with carboplatin and paclitaxel for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC); 3) in combination with paclitaxel for treatment naïve metastatic HER2-negative breast cancer (rescinded in U.S., remains in E.U.); 4) treatment of recurrent glioblastoma; 5) in combination with interferon alpha for metastatic renal cell carcinoma, 6) newly diagnosed and recurrent ovarian cancer (E.U. only, 7) persistent, recurrent, or metastatic carcinoma of the cervix, in combination with chemotherapy (FDA approved August 2014, 1 month after receiving Priority Review), and 8) platinum-resistant recurrent ovarian cancer in combination with chemotherapy approved in EU August 2014 (Priority Review granted by the FDA in July 2014).

Neither Avastin's side-effect profile (including hypertension, bleeding, and GI perforation) nor its price has capped its use, but the failed NSABP and AVANT trials (adjuvant colorectal cancer) and the misses in prostate, melanoma and stomach cancers limit upside. Nonetheless, future Avastin growth is keyed to the ongoing studies in lung (ECOG 1505, adjuvant lung, read out 2018), additional indications in

breast cancer, and new indications in ovarian cancer and cervical cancer. Simultaneous with Avastin's approval in NSCLC cancer in October 2006, the company announced a program that caps the overall expense of Avastin at \$55,000 per year per eligible patient for any FDA-approved indication. This has largely alleviated pricing concerns given the 2X higher dose of Avastin used in lung, breast, and renal cancers (\$8,800 per month) versus colorectal cancer (\$4,400 per month). We estimate Avastin sales of CHF6.305B (+1%) in 2014, CHF6.525B in 2015, CHF6.775B in 2016, CHF6.825B in 2018, and CHF6.1B in 2020.

Avastin Remains Dominant In Stage IV Colorectal Cancer

Our oncology consultants employ Avastin in the majority (90%) of first-line colorectal cancer patients and are comfortable combining the drug with any background chemotherapy. Patients not receiving Avastin are typically contraindicated for therapy (uncontrolled hypertension, recent arterial thrombosis, MI, or recent surgery). Phase III data from Roche's NO16966 study demonstrated that Avastin in combination with FOLFOX (FOLinic acid, 5-FU, and OXaliplatin; the most commonly used first-line chemotherapy regimen in the U.S.) produced somewhat disappointing results in first-line disease. While certain findings from this study, such as the underwhelming PFS benefit, can be explained by trial-specific issues, others, such as the lack of a response rate benefit, cannot. Nonetheless, experts report that study NO16966 results, which were presented at ASCO GI in early 2007, have hardly impacted Avastin's first-line market share. This reflects Avastin's ease of use, entrenched status, and physician comfort with an earlier first-line study that demonstrated a very significant (4+ month) overall survival benefit.

CALGB Study Shows No Difference Between Avastin and Erbitux in mCRC

A Phase III randomized study (CALGB/SWOG 80405) comparing Avastin to Erbitux (Lilly) when used with combination chemo in mCRC KRAS wild-type CRC was presented at ASCO 2014. The study showed no significant difference between the two arms. Median OS for the Avastin arm was 29.0 months vs 29.9 months for Erbitux (HR=0.925, p= 0.34). Median PFS was 10.8 months for Avastin vs. 10.4 months for Erbitux (HR = 1.04, p=0.55). No new adverse events were seen with either agent. Colorectal cancer represents roughly 50% of Avastin sales, so this study is expected to at least support this current level of use.

Avastin Demonstrated Efficacy In Second Line mCRC

In January 2012, Roche announced that Avastin's AIO/ML18147/TML trial succeeded. This study evaluated the efficacy of second-line Avastin in Avastin-experienced metastatic colorectal cancer patients with a primary endpoint of overall survival. Complete TML data was presented at ASCO 2012. Regeneron and Sanofi's Zaltrap, which works by the same mechanism as Avastin, succeeded in its pivotal Phase III trial in the second-line setting. Zaltrap was approved in combination with FOLFIRI for the treatment of second-line mCRC in August 2012. The ML 18147 trial enrolled approximately 800 European mCRC patients who had received Avastin plus chemotherapy in the first line, and randomized them to receive Avastin plus chemotherapy, or chemotherapy alone, upon disease progression. A significant benefit was observed on the primary endpoint of OS, and no new or unexpected safety findings were observed (OS of 11.2 months on Avastin vs. 9.8 months on chemotherapy, HR=0.81, p=0.0062). Patients who continued with Avastin plus second-line chemotherapy also experienced a significant improvement in PFS (PFS on Avastin of 5.7 months vs. 4.1 months on chemotherapy). Both Avastin (December 2012) and Zaltrap (February 2013) have been approved in the E.U. for second-line

mCRC. In January 2013, FDA approved Avastin for continued use in Avastin failures (second-line treatment) in patients with mCRC.

Details of Avastin's efficacy in TML and a comparison to Zaltrap's efficacy in VELOUR are below:

Avastin Efficacy In TML; Comparison To Zaltrap In VELOUR

	Avastin	Chemotherapy	HR	p-value	Zaltrap in VELOUR	Chemotherapy in VELOUR
Overall Survival, mo	11.2	9.8	0.81	0.0062	13.5	12.1
Progression Free Survival, mo	5.7	4.1	0.68	<0.0001	6.9	4.7
Best Overall Response, %	5.4	3.9		0.3113		

Source: Cowen and Company

Avastin Has Penetrated Its Eligible Lung Cancer Market

Avastin has penetrated approximately 50% of all first-line NSCLC patients in the U.S. and 10% in the E.U. Contraindications include patients with tumors of squamous cell histology, patients on anti-coagulants, patients with prior MI, patients with brain metastases, and patients with a history of hemoptysis.

It is estimated that there were 225K new cases of lung cancer in the U.S. in 2012, of which about 80% were of the non-small cell variety. NSCLC is further sub-divided into adenocarcinoma (40-45% of the total), squamous cell (25-30%) and large cell (10%). A minority of NSCLC are diagnosed when the disease is still localized, and therefore are amenable to potentially curative (surgery, radiation) therapy. The majority of NSCLC patients present with either metastatic (40%) or stage IIIb/IV (30-40%) disease. Of those patients presenting with metastatic disease, approximately 80% might be candidates for chemotherapy (prognostic scores 0, 1, or 2) and 40-50% may be eligible for treatment with Avastin.

Using these market assumptions (220K new patients, 50-55% adenocarcinoma or large cell histology, 70-80% stage IIIb/IV, 80% candidates for chemo, 40-50% candidates for Avastin), the front-line U.S. NSCLC market opportunity ranges from 20K to 31K patients per year. Disqualifying an additional 10-15% of patients due to brain metastases, treatment with anticoagulants, or prior history of hemoptysis, 26-43K patients would still be eligible. At a price of \$8,800/month and assumed treatment duration of six months, this equates to a potential U.S. Avastin market opportunity of \$1.3-2.3B.

AVAiL Data Leads To 1st Line Approval For Non-Squamous NSCLC In Europe

In 2007, Roche announced that the ex-U.S. 1,000 patient AVAiL study comparing chemotherapy (gemcitabine + cisplatin) +/- Avastin in first-line non-squamous, non-small cell lung cancer met its primary endpoint of improved progression-free survival for Avastin. Both doses of Avastin (7.5 mg/kg and 15 mg/kg every three weeks) had a similar and statistically significant benefit on progression-free survival versus cisplatin/gemcitabine alone. Patients receiving 15mg/kg of Avastin + chemotherapy experienced a 22% improvement in risk of progression based on a hazard ratio of 0.82 ($p=0.03$) vs. patients receiving chemotherapy alone. Patients receiving 7.5 mg/kg Avastin + chemotherapy experienced a 33% improvement in PFS based on a hazard ratio of 0.75 ($p=0.002$). The confidence intervals of the two Avastin arms broadly overlapped, indicating the two Avastin arms had a similar effect on PFS. No safety differences between arms were observed. Based on these data, in August 2007 Genentech's partner Roche received European approval for both doses of Avastin in

first-line NSCLC. In May 2008, Genentech announced that neither Avastin dose was associated with an improvement in overall survival vs. chemotherapy alone.

AVAiL Has Had Little Impact On Dosing In The U.S.

AVAiL has enticed few U.S. physicians to switch to lower dosing of Avastin in lung cancer. Use of the higher dose (15mg/kg) has held roughly steady in the 70% area. Reasons to explain why a majority of U.S. physicians have stuck with the higher dose of Avastin in lung cancer include: 1) 15 mg/kg is still the labeled U.S. dose and regulatory implications of AVAiL are unclear, 2) the majority of U.S. physicians use a carboplatin-based regimen, the regimen that was proven to work in combination with 15 mg/kg Avastin, 3) many future trials on Avastin in lung cancer employ the 15mg/kg dose, making it likely more difficult in the future for doctors to move away from the body of clinical experience, and 4) many physicians have accepted 15mg/kg as the standard in lung and see no reason to alter what has been working, especially while financial incentives continue to favor higher dosing.

In addition, consultants do not expect the lack of a survival advantage in AVAiL to have a significant impact on Avastin's market share in the U.S. This reflects the solid survival advantage associated with Avastin in the U.S. ECOG 4599 study. The future of Avastin in lung cancer may be similar to that of Avastin in colorectal cancer, where subsequent studies might not live up to the initial clinical observation but are also unlikely to derail adoption.

AVAPERL Supports NSCLC Use

AVAPERL, a 362 patient Phase III study evaluating the combination of Avastin and chemotherapy for patients with previously untreated, advanced non-squamous non-small cell lung cancer was presented at EMCC 2011. Avastin met its primary endpoint, increasing PFS in combination with pemetrexed and cisplatin. The addition of Avastin to chemotherapy increased PFS to 10.2 months versus 6.6 months with chemotherapy alone (HR=0.50, p>0.01).

Avastin Front-Line Breast Cancer Claim Upheld In E.U.; Pulled In U.S.

In 2005, Genentech announced that a Phase III trial of Avastin plus chemotherapy had met its primary endpoint (progression-free survival) versus chemotherapy alone in front-line metastatic breast cancer patients (the ECOG 2100 trial). This open-label randomized, controlled trial enrolled 722 metastatic breast cancer patients to receive paclitaxel plus or minus Avastin. The physician-reported progression-free survival (PFS) difference in ECOG 2100 was 13.3 months for Avastin plus chemotherapy vs. 6.7 months for chemotherapy alone. Avastin also doubled the response rate attributable to chemotherapy from 14% to 28%. A non-statistically significant trend favoring the Avastin arm had been observed in ECOG 2100. Avastin in breast cancer patients has been very well tolerated, and unlike the drug's profile in colorectal cancer or lung cancer, not associated with any serious drug-related adverse events. Hypertension (13% vs. 0%) was the most notable side effect of the Avastin arm.

In February 2008, Avastin's front-line breast cancer indication was granted accelerated approval under Subpart H guidelines. A full approval was contingent on the submission of the AVADO and RIBBON-1 studies. The accelerated approval was a surprise to some, given that a December 2007 ODAC panel had voted 5-4 against approval. The panel asserted that ECOG 2100 demonstrated Avastin to be associated with a benefit in PFS; however, it deemed that this benefit was less than robust when weighed against Avastin's toxicity and lack of improvement in overall survival.

In support of the ECOG 2100 data, in February 2008, Genentech announced that AVADO, a Roche-sponsored Phase III study evaluating docetaxel +/- Avastin in first-line metastatic breast cancer, met its primary endpoint of a significant improvement in progression-free survival (PFS). AVADO was a 736-patient study that evaluated the addition of one of two doses of Avastin (7.5 mg/kg or 15 mg/kg) every three weeks, to docetaxel chemotherapy. After a median follow-up of 11 months, the AVADO trial showed a statistically significant difference in progression-free survival between women taking either dose of Avastin plus docetaxel and those taking docetaxel alone; stratified HR was 0.69 ($P = .0035$) for the low dose and 0.61 ($P = .0001$) for the high dose. The median time to disease progression was 8.0 months with docetaxel alone, compared with 8.7 months with docetaxel plus low-dose Avastin, and 8.8 months with docetaxel plus high-dose Avastin. The overall response rate, a secondary end point, was 44% with docetaxel alone, 55% with low-dose Avastin ($P = .0295$), and 63% with high-dose Avastin ($P = .0001$). At the median follow-up of 11 months, 80% of the patients were still alive.

In November 2009, Genentech filed two sBLA's based on the AVADO and RIBBON-1 studies. These submissions were in support of ECOG 2100. RIBBON-1, which evaluated Avastin plus several chemo regimens (Xeloda, anthracyclines or taxanes) in HER2-negative front-line metastatic breast cancer, met its primary endpoint of PFS in late 2008. The RIBBON-1 data presented at ASCO 2009 demonstrated that Avastin plus Xeloda resulted in 45% improvement in PFS versus Xeloda alone (Group 1) and Avastin plus anthracyclines or taxanes resulted in a 55% improvement in PFS (Group 2). Neither group demonstrated an overall survival (OS).

An FDA Oncology Drugs Advisory Committee met on July 20, 2010 and voted to remove metastatic breast cancer in combination with paclitaxel from Avastin's label, and voted not to expand the label to usage with docetaxel, anthracyclines or capecitabine. The FDA withdrew its approval of Avastin for the first line treatment of metastatic breast cancer on the December 16, 2010 PDUFA date.

On January 11, 2011 Roche submitted its response to FDA's Notice of Opportunity for a Hearing, which was issued following the recommendation to rescind Avastin's first line mBC claim. FDA granted a hearing, which took place on June 28-29, 2011. Following the hearing, the FDA committee recommended removing the first-line breast cancer claim. On November 18, 2011 the FDA pulled the first-line mBC claim from Avastin's label. In September 2011, Japan approved an additional indication for Avastin for use in inoperable or recurrent breast cancer in combination with paclitaxel.

European Commission Continues To Support Avastin In First Line mBC

In March 2011, the European Commission confirmed the CHMP recommendation to allow Avastin in combination with paclitaxel to remain a treatment option for mBC in Europe. The committee did however remove the first line combination with docetaxel from the label.

Avastin Fails In TBNC Beatrice Trial

Roche evaluated the safety and efficacy of adding Avastin to standard adjuvant therapy (anthracycline +/- taxane or taxane alone) in 2,581 triple-negative breast cancer (TBNC) patients in the BEATRICE study. Approximately 20% of the total breast cancer population has triple negative disease. In July 2012, Roche announced that Avastin failed to meet its primary endpoint of a significant improvement in invasive disease free survival versus chemotherapy alone.

Avastin Approved In Recurrent Glioblastoma, But Data Mixed On First Line Use

Avastin was granted provisional (accelerated) approval in May 2009 for recurrent GBM. We estimate 8,000 patients/year seek treatment for recurrent GBM. At an assumed cost of \$8,800/month (10 mg/kg every 2 weeks) and a duration of treatment of 4-6 months, recurrent GBM represents a \$300-400MM opportunity for Avastin. In August 2012, Roche announced that Avastin's Phase III AVAglio study in first-line glioblastoma met its co-primary endpoint of a significant improvement in PFS. When added to chemotherapy, Avastin reduced the risk of cancer progression by 36% (HR=0.64, p<0.0001). However, OS did not reach statistical significance. No new safety findings were observed in AVAglio and adverse events were consistent with previous trials of Avastin in other tumor types. Another Phase III study (from the Radiation Therapy Oncology Group), released in February 2014, reported similar results. Avastin again did not demonstrate improved survival for newly diagnosed GBM patients. OS was 15.7 months for the Avastin group, and 16.1 months for placebo group; but PFS was greater with Avastin (10.7 months vs. 7.3 months for placebo). However, quality-of-life data between the two studies was very different, suggesting a potential role in the first-line setting. Avastin was filed in the E.U. in Q1:2013, but received a negative CHMP opinion and re-examination is ongoing. Avastin was approved in June 2013 in Japan for newly diagnosed GBM patients.

Kidney Cancer Is A Niche Indication For Avastin

In August 2009, FDA-approved Avastin in combination with interferon-alpha for metastatic renal cell carcinoma (RCC). The FDA approval was based on data from a global, randomized, double-blind, placebo-controlled Phase III study (AVOREN) of 649 patients with previously untreated metastatic RCC. The study showed patients who received Avastin plus interferon-alfa had a 67% increase in PFS, compared to those who received interferon-alfa alone (HR=0.60, 95% CI=0.49, 0.72). In AVOREN, median PFS was 10.2 months for patients who received Avastin plus interferon-alfa compared to 5.4 months for patients who received interferon-alfa alone, corresponding to an 89% improvement in median PFS. The study was originally designed to measure an improvement in overall survival (OS). However, in prior consultation with the FDA and European regulatory authorities, the primary analysis endpoint was revised to assess improvement in PFS. Secondary analysis endpoints included objective response rate and OS. Tumor size decreased in 30% of patients in the Avastin plus interferon-alfa group, compared to 12% of patients who received interferon-alfa alone. There was no improvement in OS based on the final analysis after 444 deaths, with a median OS of 23 months in the Avastin plus interferon-alfa arm and 21 months in the interferon-alfa plus placebo arm (HR ratio=0.86, 95 percent CI=0.72, 1.04).

The approval has had only limited impact on Avastin sales. This reflects the fact that: 1) interferon therapy is no longer the standard of care due to its poor tolerability, and 2) newer therapies including Pfizer's Sutent and Torisel, Onyx/Bayer's Nexavar, GSK's Votrient, and Novartis' Afinito dominate the RCC market.

Avastin Meets Primary Endpoint In Ovarian Cancer, But Only As Maintenance

In February 2010, Roche announced top-line data from the GOG-0218 study (front-line metastatic ovarian cancer). In the three-arm study, women with newly diagnosed advanced ovarian cancer who already had surgery to remove as much of the tumor as possible were randomized to receive one of the following: 1) standard of care + placebo + placebo maintenance; 2) standard of care + Avastin + placebo maintenance; or 3) standard of care + Avastin + Avastin maintenance. The women who continued maintenance use of Avastin alone, after receiving Avastin in

combination with chemotherapy (Arm 3), lived longer without the disease worsening compared to those who received chemotherapy alone. There was no difference between Arms 1 and 2. The COG-240 trial (relapsed platinum-sensitive) met its primary endpoint of improving overall survival, demonstrating a 29% reduction in the risk of death ($HR=0.71$, $p=0.0035$). Women who received Avastin lived a median of 3.7 months longer compared to those who received chemotherapy alone (17 months on Avastin vs. 13.3 months for chemo alone).

ICON7 Did Not Demonstrate Improved OS For Avastin In High-Risk Ovarian Cancer

ICON7 is a Phase III placebo-controlled study (front-line metastatic ovarian cancer) comparing the addition of Avastin (7.5mg/kg Q3 weeks) to 6 months of carboplatin and paclitaxel (CP) followed by 6 months of Avastin as monotherapy compared to 6 months of CP alone in women with newly diagnosed ovarian cancer. At ESMO 2010, the addition of Avastin to CP-based therapy significantly improved PFS (19.0 months for Avastin + CP vs. 17.3 months for CP alone) and demonstrated a trend towards OS (based on 34% of required events) at 18 months. Based on these data, regulators requested an interim analysis on OS be performed once 50% of required events had been reached. At the time of presentation, 53% of events had matured and a non-significant trend towards OS persisted across the entire study population; however, the addition of Avastin in a pre-defined analysis of high risk patients (stage IV or stage III with tumors >1cm, 89–71% of patients in ICON7) showed a significant OS benefit (36.6 months for Avastin + CP vs. 28.8 months for CP alone, $HR=0.64$, $p=0.002$). Updated PFS data across all patients remained consistent with that presented at ESMO 2010 (19.8 months for Avastin +CP vs. 17.4 months for CP alone).

Final OS data was released in September 2013 which showed that Avastin with carboplatin and paclitaxel did not improve survival by a clinically important magnitude (median OS was 58 months with RMST improvement of 0.9 months from 44.6 to 45.5 months). However, a benefit of 4.8 months was observed in a pre-specified subgroup of women at high risk for progression.

OCEANS Prompts E.U. Approval Based On PFS Benefit; OS Data Not Yet Mature

OCEANS was a placebo-controlled Phase III study in 484 women with recurrent, platinum-sensitive, ovarian, primary peritoneal or fallopian tube cancer comparing Avastin (15mg/kg Q 3 weeks) in combination with GC followed by continued Avastin for an additional 6 months as maintenance therapy or until disease progression or unacceptable toxicity to GC alone. The study met its primary endpoint of PFS, extending PFS by 3 months (12.4 month PFS for Avastin vs. 8.4 months for GC alone). The PFS endpoint was verified by an independent review committee and the data found to be consistent with internal results. The overall response rate for Avastin was 78.5% compared to 57.4% for GC alone ($p<0.001$). While the data to measure OS has not yet matured (40% of necessary events have occurred), OS at the time of presentation was 35.5 months for Avastin patients compared to 29.9 months for GC alone. Patients remained on Avastin containing regimens for an average of 10.4 months compared to 7.4 months on GC alone, possibly reflecting the decreased rate of disease progression. In November 2012, the EMA approved Avastin in combination with chemotherapy for women with recurrent, platinum-sensitive ovarian cancer.

Avastin Misses In Gastric Cancer

In February 2010, Roche announced the top-line results from a global Phase III trial investigating Avastin plus Xeloda or fluorouracil and cisplatin chemotherapy in patients with inoperable, advanced or metastatic gastric cancer (stomach cancer). The study, known as AVAGAST, did not meet its primary endpoint of extending overall

survival in patients treated with Avastin in combination with chemotherapy compared to the same chemotherapy plus placebo.

Avastin Misses In Prostate Cancer

In March 2010, Roche announced that the CALGB sponsored Phase III trial, CALGB 90401, in first-line hormone refractory prostate cancer failed to meet its primary endpoint of overall survival. CALGB compared docetaxel plus prednisone with or without Avastin (15mg/kg q3 weeks).

Seragon Acquisition Bolsters Breast Cancer Pipeline

In August 2014, Roche acquired Seragon Pharmaceuticals (private) for \$725MM upfront cash and a potential \$1B in milestone payments. Seragon's portfolio consists of next-generation oral selective estrogen receptor degraders (SERDs), for potential treatment of HR+ breast cancer. SERDs are designed to both block estradiol action at the estrogen receptor and also eliminate the estrogen receptor from the cell altogether. It is believed SERDs change the shape of the estrogen receptor in a manner that targets it for elimination by the cell. Seragon's lead candidate is ARN-810 which is in Phase I for HR+ breast cancer patients who have failed current hormonal agents.

Numerous Antibody Drug Conjugates In Development

Roche is currently developing 25 different molecules targeting 9 different disease states using an antibody-linker-drug delivery system, similar to what has been done in the development of T-DM1. Roche believes this strategy reduces the toxicity associated with traditional chemotherapy by directing drugs directly to the tumor and reducing systemic exposure. Roche has 9 ADC's in clinical development. The targeted delivery of chemotherapy may allow for increased concentration of drug to reach a tumor, thus increasing the efficacy of drugs which may have failed in previous trials. This strategy may therefore give new life to old drugs in 2nd and 3rd line therapy.

Roche Oncology ADCs In Development

Agent	Indication	Phase	Comments
polatuzumab vedotin (RG7596)	Hematologic malignancies	II	Data presented 2013
	NHL	II	+ Rituxan vs RG7593 + Rituxan (ROMULUS); data ASCO 2014 Data in 2014; safety, anti-tumor activity primary endpoints
pinatuzumab vedotin (RG7593)	Hematologic malignancies	II	Data presented 2013
anti-STEAP1 (RG7450)	Prostate	I	Data presented 2013
anti-MUC16 (RG7458)	Ovarian, pancreatic	I	Data presented 2013
NME (RG7598)	Multiple myeloma	I	Trial initiated Q3:11
anti-NaPi2b (RG7599)	NSCLC, ovarian	I	Data presented 2013
	Pt-sensitive ovarian	Ib	Trial initiated Q4:13
	Pt-resistant ovarian	II	Trial (HERAEA) initiated Q1:14; PFS primary endpoint
NME (RG7600)	Pancreatic, ovarian	I	Trial initiated Q4:11
anti-ETBR (RG7636)	mMelanoma	I	Data presented 2014
ADC (RG7841)	Solid tumors	I	FPI Q2:14

Source: Company data

PD-L1 Competitive, Lags Leaders But Data Compelling

The efficacy of PD-L1 (RG7446/MPDL3280A) appears competitive with Bristol's nivolumab and Merck's pembrolizumab, but different patient populations, prior treatment differences, and small study size make a direct comparison difficult. Tumor responses correlated with low IL-17 expression in tumors and PD-L1 status. Positive responses were also correlated with a T-cell gene signature that included CD8, INFg, and Granzyme-A. A comparison of the Phase I efficacy of nivolumab and MPDL3280A is below.

Comparison Of MPDL3280A vs. Nivolumab ORRs

Tumor Type	MPDL3280A	Nivolumab
Melanoma	29%	28%
NSCLC	23%	18%
RCC	13%	27%

Source: ASCO 2013, Company data

In data released to date, MPDL3280A has demonstrated ORRs in a range of 13-29%, with an overall ORR of 21%.

What We Have Seen To Date For Anti-PDL1

mNSCLC	23%	RECIST 1.1
	46%	PDL1 IHC2/3*
	83%	PDL1 IHC3
mMelanoma	29%	27% in PDL1-positive
	58%	ORR + stable disease (disease control rate)
	87%	ORR + stable disease (PDL1 positive)
mRCC	13%	20% in PDL1 positive
	73%	ORR + stable disease (disease control rate)
	80%	ORR + stable disease (PDL1 positive)
Overall	21%	36% in PDL1-positive
	61%	ORR + stable disease (disease control rate)
	86%	ORR + stable disease (PDL1 positive)

* IHC3 ≥ 10% PD-L1-positive tumor cells; IHC2/3 ≥ 5%; IHC1/2/3 ≥ 1%

Source: Company data

MPDL Shows Benefit In Bladder Cancer

At ASCO 2014, Roche presented a Phase I, single-arm, open-label study of MPDL3280A (anti-PDL1) showing it delivered an ORR in 43% (13/30) of previously treated, PD-L1 positive metastatic urothelial bladder cancer patients. This is the first time we have seen data in this tumor type. A CR was observed in 7% of PD-L1-positive people (2/30). The ORR was 11% (4/35) in PD-L1-negative patients. The median time to response was 42 days. Grade 3 AEs occurred in 4% (3/68) of people in the study and included asthenia 2%, thrombocytopenia 2% and low phosphate levels 2%. The most common AEs were decreased appetite (12%), fatigue (12%), nausea (12%), fever (9%) and asthenia (7%). Roche has been awarded breakthrough designation by FDA in bladder, and will begin Phase III in 2014. The company expects filing for the bladder cancer indication in 2016 (post Phase III trial), although we believe an earlier filing might be possible assuming strong Phase II results.

Many Trials In Progress

MPDL3280A is in numerous monotherapy and combination trials as shown below, in July 2014, Roche announced a clinical trial agreement (non-exclusive, terms not provided) with Incyte to evaluate MPDL3280A in combination with INCB24360, Incyte's IDO1 inhibitor in NSCLC. The company has also indicated that it will announce another new tumor type by year end. In addition, Roche believes its biomarker approach is more specific, selective and reproducible than that of competitors. We estimate sales of MPDL3280A at CHF250MM in 2018 and CHF1000MM in 2020.

Data from combo trial with MPDL3280A plus Avastin and /or chemotherapy in advanced or metastatic solid tumors was presented at ESMO 2014. The combination was well tolerated and resulted in a 40% ORR in 1st line renal cancer and 8% in CRC. A combo of MPDL3280A plus Avastin plus FOLFOX resulted in a 44% ORR in 1st line CRC and a 36% ORR in previously treated CRC.

PD-L1 Trial Overview

Indication	Trial	Phase	n	Design	Endpoint	Status
mNSCLC (PD-L1 pos.)	BIRCH	II	300	Single arm, open label 1200mg q 3 wks. up to 16 cycles	ORR	Started 2/2014; Primary completion 2018
mNSCLC; platinum-failure	OAK	III	850	1200mg q 3 wks. up to 16 cycles vs. docetaxel; open label; includes biomarker subgroups	OS	Started 3/2014; Primary completion June 2017
mNSCLC (PD-L1 pos.)	FIR	II	130	Single arm; open label; 1200mg q 3 wks. up to 16 cycles	ORR	Started 5/2013; Primary completion 5/2015; potentially registrational; Data in-house end 2014
mNSCLC (2nd/3rd Line)	POPLAR	II	287	1200mg q 3 wks. up to 16 cycles vs. docetaxel	OS	FPI Q3:2013; enrollment complete; primary completion Mar 2016
NSCLC w/Tarceva	--	II	32		Safety	FPI Q1:2014; Primary completion Sept 2015
Bladder cancer	--	II	330	2 cohorts: Tx naïve or plat-intolerant; Tx experienced w/plat.; 1200 mg q 3 wks.	ORR	Starts 5/2014; Primary completion Nov 2015
Solid tumors w/Avastin	--	I	154	5 Arms: PD-L1 + Avastin Avastin + FOLFOX Avastin + carbo + pac Avastin + carbo + pemetrex Avastin + carbo + nab-pac	Safety, PK	Data ESMO 2104: PD-L1 + Avastin 40% ORR in 1st -line RCC and 8% ORR in CRC; PD-L1+Avastin +FOLFOX 44% ORR in 1st-line CRC and 36% ORR in Tx-naïve CRC
mMelanoma, BRAF +, Tx naïve w/ Zelboraf	--	I	44	3 arms w/different doses	Safety, PK	Data 2014; FPI Q3:12; Primary completion Feb 2015
RCC, Tx-naïve w/Avastin	--	II	150	3 arms: PD-L1 + Avastin PD-L1 followed by PD-L1 + Avastin Sutent; followed by PD-L1 + Avastin	PFS	FPI Q1:2014; Primary completion Jan 2016
mTumors w/cobimetinib	--	I	90	2 arms: dose finding dose expansion	Safety	FPI Q4:13; Primary completion Oct 2016

Source: Company data

OX-40 Under Evaluation

At ASCO 2014, Roche announced work on an OX40, for which an IND was just filed and the first patient is expected to be treated in 2014. OX40 has multiple mechanisms; it co-stimulates effector T cells and inhibits regulatory T cells. It also has both single agent activity and the ability to be used in combination, and combinations may prove to be safer than immune combinations tested to date. Our physician

experts share enthusiasm for OX40. In total, Roche stated that it has 20 IO candidates, many in preclinical.

CSF1R Unique And Promising Early Stage Compound

CSF1R is a macrophage inhibitor. Phase I data was presented at ASCO 2014. This compound offers a unique mechanism that could work well in combo with other agents: it reduces tumor-associated macrophages in the tumor microenvironment. Local action in the tumor microenvironment is key to the limitation of side effects.

MabThera/Rituxan Entrenched In NHL/CLL Markets

Rituxan's success is due to its high penetration of the non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL) markets. Rituxan is also approved for rheumatoid arthritis; an indication that now contributes more than \$1B in sales. In February 2009, Roche received E.U. approval for MabThera in combination with chemotherapy for previously untreated CLL, the most common form of adult leukemia. In Q3:09 MabThera received E.U. approval for relapsed or refractory CLL, based on results of the REACH trial. In May 2009, Genentech and Biogen Idec submitted two sBLAs to the FDA for approval of Rituxan plus standard chemotherapy in previously untreated or treated CLL. After the companies addressed one CRL, the FDA approved the CLL indication in February 2010.

The key drivers for Rituxan's growth are expanded use in follicular lymphoma (indolent NHL), maintenance (PRIMA), and indolent NHL refractory maintenance (NHL 2013). PRIMA demonstrated that continuing Rituxan for two years in patients who responded to initial treatment with Rituxan plus chemotherapy, doubled the likelihood of them living without their disease worsening (PFS) compared to those who stopped treatment (based on a hazard ratio of 0.50, 95% CI, 0.39; 0.64; p=<0.0001). Roche received approval from the European Commission in October 2010 in 1st line maintenance treatment of follicular (or indolent) non-Hodgkin's lymphoma. The FDA approved the follicular NHL indication in January, 2011. In February 2011, Roche initiated a Phase III trial evaluating the SQ administration of MabThera, which can be delivered in a 10 minute bolus. The primary endpoint for the SQ trial (SABRINA) is a PD/PK endpoint, which is not sufficient for a U.S. filing. The Stage 1 primary endpoint was achieved. Roche received EU approval for the SC formulation in March 2014.

Roche anticipates the first MabThera biosimilars outside the U.S. to enter the market in 2016. Rituxan is also being evaluated in combo with Infinity's PI3K inhibitor duvelisib in follicular lymphoma, with a Phase III study (DYNAMO+R) expected to start in 2014. We estimate Rituxan/MabThera sales, inclusive of sales in RA, of CHF6.94B (flat) in 2014, CHF6.855B in 2015, CHF6.44B in 2016, CHF5.48B in 2018, and CHF4.72B in 2020.

Rituxan U.S. And E.U. Oncology Indications

		U.S.	E.U.
NHL	Maintenance Second Line	Not approved	As maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera
	First Line	Previously untreated diffuse large B-cell, CD20-positive, NHL in combination with CHOP or other anthracycline-based chemotherapy regimens	For the treatment of patients with CD20 positive diffuse large B cell NHL in combination with CHOP chemotherapy
	Second Line	Non-progressing (including stable disease), low-grade, CD20 positive, B-cell NHL as monotherapy, after first-line CVP chemotherapy	As monotherapy for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy
		Treatment of relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a monotherapy	
CLL	First Line	Rituxan plus FC for first-line or relapsed/ refractory CD20-positive CLL	For the treatment of patients with previously untreated or relapsed/refractory CLL in combination with chemotherapy

Source: Company data

An estimated 575K people in the U.S. suffer from NHL, of which 60-70% are considered to have aggressive NHL and 20-30% follicular/indolent NHL. Each year, an additional 66K new cases of NHL develop in the U.S. Powered by the results of the GELA, ECOG4494, and MInT studies, an sBLA was approved in February 2006 for front-line diffuse large B-Cell NHL (the most common subtype of aggressive NHL) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy. In addition, Rituxan was approved in November 2006 for first-line use in combination with chemotherapy in low-grade NHL. These approvals had a modest impact on Rituxan's penetration, given significant off-label use in an estimated 85% of patients with aggressive NHL, and 87% of low-grade NHL prior to approval. Rituxan has also deeply penetrated the CLL market with an estimated market share of approximately 70%.

PRIMA Data Presented At ASCO 2010 Support Maintenance Use

The use of maintenance therapy following a first-line regimen for low grade NHL should be supported by data from the PRIMA study. PRIMA was an international, multicenter, randomized, Phase III clinical study that enrolled 1,217 patients with previously untreated advanced follicular lymphoma (indolent NHL). The study evaluated the efficacy and safety profile of maintenance Rituxan in patients who responded to initial treatment with Rituxan plus chemotherapy (induction treatment). In the study, Rituxan plus either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CVP (cyclophosphamide, vincristine, prednisone) or FCM (fludarabine, cyclophosphamide, mitoxantrone) chemotherapy was used as initial treatment. Patients who responded (1,018/1,217) were randomized to receive Rituxan alone, given once every two months for two years (maintenance), or observation alone. The

data showed that continuing Rituxan for two years in patients who responded to initial treatment with Rituxan plus chemotherapy, doubled the likelihood of them living without their disease worsening (progression-free survival or PFS) compared to those who stopped treatment (based on a hazard ratio of 0.50, 95% CI, 0.39; 0.64; $p < 0.0001$). After two-years of follow-up, 82% of patients who received Rituxan maintenance were in remission compared to 66% of patients who did not (HR:0.50, $p < 0.001$). No new safety signals were observed in this study. Serious adverse events (Grade 3 or 4) were reported in 23% of patients who received Rituxan maintenance compared to 16% who did not, including low white blood cell (neutrophil) counts (4% vs. 1%) and infections (4% vs. 1%). Our physician consultants note that the majority of community oncologists and up to 50% of academic oncologists had already adopted first-line maintenance Rituxan into their treatment paradigms.

Physicians Believe Competitive Threats To Rituxan Are Modest In Scope

According to consultants, six or seven monoclonal antibodies in development for NHL and CLL have intriguing profiles, including several that target the same anti-CD20 antigen as Rituxan. Consultants are most interested in drugs with differentiation, either via novel properties (such as ADCC recruitment or complement activation) or novel mechanisms, but acknowledge that it is hard to predict which drugs might fail or succeed. Although hundreds of clinical studies and 10+ years of experience support Rituxan's core franchise, physicians believe newer antibodies could chip away at Rituxan's use in more fringe indications. Rituxan's main patents expire in the U.S. between 2015 and 2018 and in the rest of the world in 2014.

Rituxan Battling For Share In Refractory RA Market

In 2006, Biogen Idec and Genentech received approval for the use of Rituxan in TNF refractory moderate to severe rheumatoid arthritis (RA). Approval was supported by data from the Phase III REFLEX trial. The study evaluated Rituxan in 520 patients with active RA refractory to anti-TNF therapy. Patients were randomized to receive Rituxan ($n=201$) or placebo ($n=298$) on days 1 and 15, and a stable dose of methotrexate plus two weeks of corticosteroids during the study. The study met its primary endpoint of ACR20 response rate at 24 weeks (51% Rituxan vs. 18% placebo). ACR 50 (27% Rituxan vs. 5% placebo) and ACR70 (12% Rituxan vs. 1% placebo) response rates were also achieved with statistical significance ($p < 0.0001$). In 2006, positive results were reported from another analysis of REFLEX that looked at the ability of Rituxan to impact joint erosion and joint space narrowing. The study investigated the effect at one year of Rituxan plus methotrexate on joint structural damage, compared with methotrexate alone. At week 56, the mean change in the total Genant-modified Sharp score in the placebo arm was 2.31 compared with 1.00 in the Rituxan group ($p=0.0043$). Significant differences were also observed in changes of erosion score and joint space narrowing score. In addition, the proportion of patients with no change in erosion score was significantly higher in the Rituxan arm compared to placebo: 61% vs. 52%, respectively ($p=0.0445$).

Rituxan Phase III REFLEX Data In Rheumatoid Arthritis

	Placebo + Methotrexate (n=184)	Rituxan + methotrexate (n=272)	p-value
Mean change in total Sharp/Genant score (SD)	2.31 (5.28)	1.00 (2.76)	p=0.0043
Mean change in erosion score (SD)	1.32 (3.16)	0.59 (1.85)	p=0.0106
Mean change in Joint Space Narrowing (SD)	0.99 (2.57)	0.41 (1.33)	p=0.0007
% of patients with no change in erosion score	52	61	P=0.0445

Source: EULAR

Rituxan is competing against Bristol-Myers' Orencia and Roche's Actemra for share in the TNF-refractory market. Consultants project that perhaps as many as 10-15% of their moderate to severe RA patients might be treated with either Rituxan/Orencia/Actemra. Orencia and Rituxan are viewed as having generally comparable efficacy and on-treatment safety profiles, but physicians have voiced concern over the safety of switching patients from Rituxan to Orencia during a period of prolonged B-cell suppression. Rather, non-responding patients would face a six-month or longer washout period following Rituxan in order to avoid potentially immunosuppressive therapy with two concurrent biologics. Rituxan's competitive positioning in RA may also be encumbered by the label, which reflects the risk of PML.

Rituxan's Move Into Earlier Lines Blocked Due To PML Risk

In January 2008, Genentech and Biogen Idec announced that the Phase III SERENE trial, comparing Rituxan versus placebo in biologic-naïve, methotrexate-inadequate responder patients, achieved its primary endpoint of a statistically significant reduction in ACR20 at week 24. The study enrolled 509 patients with moderate to severe RA randomized to receive either Rituxan (500mg or 1000mg) + MTX, or placebo + MTX. Patients in both Rituxan dose arms achieved a statistically significant reduction in ACR20 scores as compared to the placebo group. While the study was not powered to show a difference between the two Rituxan arms, Genentech noted similar efficacy for both Rituxan doses. While these data are positive, few were surprised by the results given Rituxan's demonstrated efficacy in other RA populations. The companies filed an sBLA in Q4:08 but in October 2009 received a complete response letter from FDA. The FDA indicated that an approval for Rituxan (in people with RA who have not previously received MTX or those who were MTX inadequate responders) cannot be supported due to the rare risk of progressive multifocal leukoencephalopathy (PML) in light of the number of effective RA treatments currently available to patients in earlier stages of the disease. The incidence of PML in RA patients treated with Rituxan is rare (as of November 2012, eight reports out of approximately 228,000+ patients).

At the time of the October 2009 complete response letter, FDA updated Rituxan's label to include safety and efficacy data in the label that provides guidance on how later-stage patients, those who have inadequately responded to anti-TNF therapies, can be retreated with Rituxan. The prescribing information includes language that subsequent courses of the standard Rituxan regimen (two doses at 1000 mg each) can be administered every 24 weeks or based on clinical evaluation. Subsequent courses should not be administered sooner than 16 weeks. Rituxan's ability to improve physical function and slow joint damage for up to two years as demonstrated in clinical studies was also included.

Rituxan In Autoimmune Disease Less Promising

SLE And Lupus Nephritis Data Disappoint

Top-line data from the Genentech/Biogen Idec's pivotal EXPLORER trial on Rituxan in lupus were reported in April 2008. Rituxan failed to meet its primary endpoint in this study (proportion of Rituxan-treated patients achieving a clinical response, as measured by BILAG scores at 52 weeks) or any of its six secondary endpoints. This news was disappointing, as our physician consultants who have used Rituxan (both in trials and off-label) believed the drug to be active in lupus patients. We believe the trial likely failed due to the general difficulties in conducting lupus trials (waxing/waning nature of disease, untested rating scale endpoints, heterogeneity of the disease). Data from the Phase III LUNAR trial (evaluating Cellcept +/- Rituxan in lupus nephritis) were announced in March 2009 and showed failure to achieve statistical significance on the primary endpoint of improved renal function over Cellcept.

PPMS Too High A Hurdle For Rituxan

In April 2008, Biogen Idec and Genentech announced that a Phase II/III trial of Rituxan in primary progressive multiple sclerosis (PPMS) missed its primary endpoint. The U.S. and Canadian OLYMPUS trial randomized 439 patients 2:1 to receive either four doses of Rituxan or placebo six months apart, with a primary endpoint of time to confirmed disease progression during the 96-week treatment period. Physicians generally held low expectations for this study, and noted that PPMS represents a particularly high hurdle, owing to the unchanging nature of these patients.

Rituxan Promising In Relapsing-Remitting MS But Development Efforts Shifted To More Promising Ocrelizumab

In February 2008, Biogen Idec and Genentech published 48-week data on a Phase II double-blind study that randomized 104 patients to either a single treatment course of Rituxan (two infusions separated by two weeks) or placebo. The trial met its primary endpoint, with Rituxan producing a statistically significant decrease in total number of gadolinium-enhancing lesions (as measured by MRI) at all time points (weeks 12, 16, 20, and 24) versus placebo ($p < 0.0001$). At 24 weeks, the Rituxan arm demonstrated an impressive 91% decrease in gadolinium lesions and a 58% relative reduction in relapse rate ($p = 0.02$). These benefits were generally sustained through 48 weeks despite no additional treatment with Rituxan. Adverse event profile was similar between the two groups. Although Rituxan's Phase II RRMS trial was of modest size ($n = 104$), its efficacy data was viewed as compelling. However, partners Biogen Idec and Genentech disagreed over decision making rights on the Rituxan in RRMS program, and an arbitrator finally sided with Biogen in 2009. By this time, development of Rituxan for MS had been terminated as a Phase II trial on ocrelizumab (a humanized anti-CD20 antibody) was showing greater potential for this indication.

Generic Rituxan Risk May Be Overstated

There are a number of companies with Rituxan biosimilars in development, but none appear imminent and several initiatives have been curtailed over the past year. Teva and Celltrion/Hospira terminated their trials and have at least delayed development efforts in this area. Sandoz, Pfizer, Merck, and Boehringer Ingelheim all have rituximab biosimilars in development, but all early stage. The eventual arrival of biosimilars is highly likely, but market dynamics are significantly different from that of small-molecule generics. Developing a biosimilar requires a \$250–500MM investment in facilities, \$200–400MM for clinical trials, and a significant investment in a sales force. Given that biosimilars may only be viable in the E.U. for the foreseeable future

and competition is likely from at least a few generic competitors, the appeal of developing a biosimilar may be limited. Furthermore, in Roche's biologic contract manufacturing agreements with Lonza and Samsung, Roche does not allow these companies to manufacture a biosimilar in the same plant.

Reditux Very Different From Rituxan; Patient Safety Could Be At Risk

Reditux is a biosimilar version of Rituxan that is marketed in Mexico. Because there is no clinical data detailing the safety and efficacy of Reditux, the two agents are difficult to compare. Roche has performed side-by-side mass spectrometry on Reditux and Rituxan and has determined that the agents are structurally dissimilar. In fact, the spectra are so different that Reditux may place patient safety at risk.

Ocrelizumab Now In Phase III For RMS and PPMS

Ocrelizumab is a next-generation humanized anti-CD20 monoclonal antibody partnered with Biogen. Ocrelizumab carries potential benefits over Rituxan, which is a chimeric antibody, including: 1) lower association with serum sickness; 2) HACA (human anti-chimeric antibodies); 3) potential to mediate enhanced antibody-mediated cytotoxicity (ADCC) and 4) reduce complement-dependent cytotoxicity (CDC). While in theory anti-Rituxan antibodies have the potential to impact Rituxan's longer-term efficacy, data to support this hypothesis (including subset data from EXPLORER) are not available. Ocrelizumab is one of several second-generation anti-CD20 mAbs including Glaxo's Azerra (approved) and Immunomedics' Veltuzumab (Phase II). Roche is focusing its development in RRMS, especially after the positive Phase IIb data announced in 2009 and Q4:11. Ocrelizumab is in three Phase III trials, two for RMS (OPERA I and II), and one in PPMS (ORATORIO). Enrollment for all three trials was completed in Q1:13. The RMS trials evaluate ocrelizumab vs. Rebif with relapse rate at 96 weeks the primary endpoint. In the PPMS trial, ocrelizumab is compared to placebo with sustained disability progression the primary endpoint.

Trial data and filing is anticipated in 2015. We forecast ocrelizumab sales of CHF200MM in 2016, CHF400MM in 2018, and CHF600MM in 2020.

Phase IIb Studies Positive In RRMS

A 220-patient, 6 month Phase II study in patients with RRMS reported in December 2009. Ocrelizumab showed a strong effect with a highly statistically significant reduction in signs of disease activity as measured by brain lesions versus placebo, the primary endpoint (Gd-enhancing T1 lesions at 12,16, 20, and 24 weeks). The study evaluated a 2,000mg and 600mg dose regimen given twice daily. Avonex was an active comparator. Ocrelizumab reduced MRI activity by 90% and the annual relapse rate by greater than 80%.

An additional 24 week Phase III trial reported in October 2010 and showed similar results to the 6 month study. Ocrelizumab demonstrated a significant reduction in disease activity as measured by brain lesions and relapse rate. Reductions in total number of brain lesions detected by MRI (the primary endpoint of the study) were highly significant at 96% for 2,000mg ocrelizumab and 89% for 600mg ocrelizumab compared to placebo. Disease activity was also measured by reduction in annualized relapse rate (ARR), the rate of attacks or flare-ups per patient-year. At week 24, ARR was significantly lowered versus placebo with a reduction of 73% for ocrelizumab 2000mg and 80% for ocrelizumab 600mg.

In a 72-week Phase II study, ocrelizumab was evaluated in 220 patients with RRMS who were randomized 1:1:1:1 to receive, at days 1 and 15, placebo, intravenous

ocrelizumab 600 mg, 2000 mg, or weekly interferon beta-1a at a dose of 30 µg in cycle 1 for 24 weeks. For cycles 2 and 3 until week 72, all groups received ocrelizumab at a dose of 600 mg, except for the 2000-mg ocrelizumab group, which received a subsequent 1000-mg dose. After 72 weeks, 86.8% of patients were still enrolled in the trial. Ocrelizumab effectiveness was maintained through week 72 as demonstrated by annual relapse rates. No patients dropped out of the study due to adverse events from weeks 48 to 72. The proportion of relapse-free patients at week 72 was 84% for the 600-mg group and 82% for the 2000/1000-mg ocrelizumab groups. One patient in the high-dose group died at week 12 of treatment in an earlier phase of this trial; however, no deaths were observed throughout the remainder of the trial.

At ECTRIMS 2011, Roche announced that ocrelizumab showed significant reduction in RRMS disease activity as measured by the total number of active brain lesions and relapses previously reported for 24 weeks, was maintained through 96 weeks in a 220 patient Phase II trial. ARR was significantly reduced by 80% ($p=0.0005$) with ocrelizumab 2 x 300mg and by 73% ($p=0.0014$) with ocrelizumab 2 x 1000 mg versus placebo at week 24. Overall, at week 96, there were no gadolinium-enhancing T1 lesions observed by magnetic resonance imaging (MRI) scans of the brain in any patient in either of the ocrelizumab 600mg or 1000mg groups. The ARR for Weeks 0–96 was 0.18 (95% CI: 0.11–0.31) for the ocrelizumab 600mg group and 0.22 (0.13–0.35) for the ocrelizumab 1000mg group. Serious infection rates were similar for ocrelizumab 600mg (1.97 events/100 patient/years [95% CI: 0.49–7.98]) and ocrelizumab 1000 mg (1.93 events/100 patient/years [95% CI: 0.48–7.71]) and did not increase with time on ocrelizumab treatment. No opportunistic infections were reported and the rate of infections (and serious infections) did not increase over the treatment period.

Gazyva (GA101) Clinical Development Continues, Although Initial Rollout Tepid

Gazyva (GA101/obinutuzumab) is a glycoengineered, humanized, type II anti-CD20 monoclonal antibody. Glycoengineering is designed to increase antibody-dependent cell-mediated cytotoxicity (ADCC) when compared to Rituxan. GA101 binds with high affinity to a type II epitope on CD20 and is characterized by reduced complement-dependent cytotoxicity (CDC) and strongly enhanced direct cell death. In January 2013, Roche announced positive results from the first stage of CLL11. An improvement in PFS and OS was achieved with GA101 plus chlorambucil vs. chlorambucil alone. A filing based on the first stage of CLL11 took place in Q2:13 and Breakthrough Therapy designation was received at the same time. FDA approval was granted on November 1, 2013 (well ahead of the scheduled December 20, 2013 PDUFA date) for use with chlorambucil in previously untreated CLL patients. EU approval was granted in July 2014.

A Phase III study in untreated or relapsed CLL (GREEN, n=800) with Gazyva + alternative chemotherapy backbones (other than chlorambucil) will be presented at ASH in December 2014. Chlorambucil is used less commonly in the U.S. so this trial is aimed at replicating benefits when combined with different chemotherapeutic agents. We estimate Gazyva sales of CHF55MM in 2014, CHF130MM in 2015, CHF200MM in 2016, CHF400MM in 2018, and CHF600MM in 2020.

Gazyva To Be Studied In Combo With PI3K Inhibitor

In September 2014, Roche entered into a master clinical supply agreement with Infinity in which Roche will supply Gazyva to Infinity for use in studies with PI3K inhibitor duvelisib (IPI-145) in hematologic malignancies. Duvelisib inhibits both PI3K-

delta and PI3K-gamma. Infinity will also supply duvelisib to Roche for use in preclinical/translational research. In 2014, Infinity will initiate a Phase Ib/II study of the combo in treatment-naïve iNHL and a Phase Ib in CLL patients who have failed a BTK inhibitor.

Stage 2 Data Impressive

In November 2013, Roche released data from the Stage 2 Phase III study comparing GA101 plus chlorambucil to Rituxan plus chlorambucil in untreated CLL patients. Final data was presented at ASH in December 2013. The patients in the GA101 arm reported a median PFS of almost 27 months, a year better than the Rituxan arm. Side effect profile was similar to previous studies. The higher rate of infusion reactions was evidenced in initial infusions. Use of steroids and splitting of the dose resolved the local reaction.

Stage 2 Data for GA 101*

	GA101 + chlorambucil	Rituxan + chlorambucil
Number patients	336	321
ORR %	78%	65%
CR%	21%	7%
Median PFS (months)	26.7	15.2
HR (p-value)	0.39 (<0.0001)	
Grade 3-5 AEs (%)	70%	55%
Grade 3-5 Infusion-related AEs (%)	20%	4%
Grade 3-5 Neutropenia (%)	33%	28%
Grade 3-5 Thrombocytopenia (%)	10%	3%
Grade 3-5 Infections (%)	12%	14%

*Investigator assessed

Source: Company data

Data for Stage 1 of GA101's CLL11 trial versus chlorambucil was impressive. GA101 + chlorambucil demonstrated a 23-month PFS compared to 10.9-months and 15.7 months of PFS for chlorambucil alone and Rituxan + chlorambucil, respectively. Response rates for the GA-101 arm were also significantly higher than comparators. A summary of Stage 1 data from CLL11 is below:

GA 101 Efficacy Data For Stage 1 Of CLL11

	Chlor	GA-101 + Chlor	Chlor	Rituxan + Chlor
Median observation time	13.6	14.5	14.2	15.3
ORR (%)	30.2	75.5	30	65.9
CR (%)	0	22.2	0	8.3
Median PFS(months)	10.9	23	10.8	15.7
HR (p-value)		0.14 (<0.001)		0.32 (<0.001)
Grade 3-5 AEs (%)	41	67	41	46

Source: ASCO 2013, Cowen and Company

Several Phase II NHL studies for GA101 were presented at ASH 2010. In the first Phase II study in aggressive NHL, patients had received a median of 3 prior therapies and 63% had not responded to or had disease progression within 6 months of

Rituxan/MabThera. Nearly a third of patients responded to treatment with GA101 (11 of 40 patients, 24% in the 400 mg cohort, 32% in the 1600/800 mg cohort). For patients no longer responding to Rituxan/MabThera, response rate was 25% in the 1600/800 mg cohort.

In the second Phase II study in relapsed/refractory indolent NHL, patients had received a median of 3 prior treatments and 55% had not responded to or had disease progression within 6 months of Rituxan/MabThera. In the overall indolent NHL population, which was heavily pre-treated, 55% of patients responded to treatment with GA101 with a promising median progression-free survival (PFS) of 11.3 months in the 1600/800 mg cohort (in the 400 mg cohort, there was a 17% response rate with 6 months of median PFS). For patients no longer responding to Rituxan/MabThera, response rate in the 1600/800 mg cohort was 50%.

Roche has three ongoing studies evaluating GA101 to Rituxan/MabThera in iNHL and DLBCL. Data readouts for these trials is expected in 2015 and beyond.

GA101 Studies Vs. Rituxan/MabThera In NHL

	Indication	Treatment	Maintenance	Primary Endpoint	Expected Data
GADOLIN	Rituxan-refractory iNHL (n=410)	Arm 1: GA101 + bendamustine x 6 cycles	GA101 q2months x 2 yrs	PFS	H2:14
		Arm 2: bendamustine x 6 cycles	none		
GOYA	Previously untreated DLBCL (n=1,400)	Arm 1: GA101 x 8 cycles + CHOP x 6 or 8 cycles	none	PFS	2016
		Arm 2: Rituxan x 8 cycles + CHOP x 6 or 8 cycles	none		
GALLIUM	Firstline NHL (n=1,400)	Arm 1: GA101 x 8 cycles + CHOP x 6 or GA101 x 8 cycles + CVP x 8 or GA101 x 6 cycles + bendamustine x 6 ARM 2: Rituxan x 8 cycles + CHOP x 6 or Rituxan q2months x 2 yrs Rituxan x 8 cycles + CVP x 8 or Rituxan x 6 cycles + bendamustine x6	GA101 q2months x 2 yrs	PFS	2017

Source: Company data

MetMab Failed In Lung; Other Indications On Hold

Since the up-regulation of Met is believed to be a primary mechanism of resistance to EGFR inhibitors, Roche developed MetMab (onartuzumab) to inhibit Met signaling to the MEK/ERK pathways. In a Phase II study, patients with stage IIIB/IV NSCLC and archived tumor samples available for histological analysis were randomized to MetMab (15mg/kg Q3weeks) + erlotinib (15mg/kg QD) (n=68) or erlotinib + placebo (n=68). The primary endpoint of the study was PFS in the total population and PFS in Met diagnostic positive patients (50% of tumor cells stain positive for moderate or high expression of Met by IHC). While no difference was observed across the entire study population for either PFS or OS (PFS HR=1.09, OS HR=0.8), the addition of MetMab resulted in significant increases in both PFS and OS in the Met diagnostic positive group (PFS of 2.9 months for MetMab + erlotinib vs. 1.5 months for erlotinib alone, HR=0.53, p=0.04; OS of 12.6 months for MetMab + erlotinib vs. 3.8 months for erlotinib alone, HR=0.37, p=0.002). However, the addition of MetMab to erlotinib resulted in significantly worse PFS and OS in Met diagnostic negative patients (PFS HR=1.82, OS HR=1.72). However, MetMab did not reach its

endpoint in a study of 2nd/3rd line NSCLC. Post that, all other clinical trials were put on hold. MetMab sales forecasts of CHF25MM in 2017, CHF50MM in 2018, and CHF100MM in 2020 are now at risk.

MetMab Development Program

MetMab Development Program				
Indication	Trial Phase	# patients	Status	
NSCLC- 2nd/3rd line	III	490	Terminated Q1:14; endpoint not met	
NSCLC- advanced w/EGFR	III	300	Terminated Q1:14	
NSCLC- 1st line squamous	II	260	Terminated Q1:14	
NCSCL- 1st line non-squamous	II	110	Terminated Q1:14	
mGastric (Mett+)	III	800	On hold as of Q1:14; FPI Q4:12	
mGastric (all comers)	II	120	On hold as of Q1:14; FPI Q3:12	
mCRC	II	188	On hold as of Q1:14; Expect data 2014	
Hepatocellular	I	54	On hold as of Q1:14; FPI Q3:13	
Advanced solid tumors	I	96	On hold as of Q1:14; FPI Q4:13	

Source: Company data

Xeloda Under Generic Pressures

Xeloda (capecitabine) is an oral pro-drug, and it only becomes active once it comes into contact with a tumor, forming 5-fluorouracil (5-FU). Xeloda is indicated for first-line therapy in metastatic colorectal cancer, adjuvant colon cancer in combination with oxaliplatin (XELOXA trial; approved in E.U. 2/10), combination therapy with docetaxel in metastatic breast cancer after anthracycline treatment, and monotherapy in metastatic breast cancer resistant to anthracycline and paclitaxel. Xeloda is also approved in Europe in combination with platinum-based chemotherapy in gastric cancer and in combination with Herceptin+cisplatin for HER2+ gastric cancer. Xeloda's growth is keyed to expansion into adjuvant breast and colon cancer. Xeloda's market exclusivity expired in the U.S. in Q1:14 and in the E.U. in 12/13; the company anticipates rapid genericization. We forecast Xeloda sales of CHF805MM (-47%) in 2014 (post the 12/13 patent expiration), CHF555MM in 2015, CHF545MM in 2016, CHF540MM in 2018, and CHF565MM in 2020.

Tarceva Is Standard Of Care In EGFR-Mutant NSCLC; Failed In Adjuvant Trial

In 2004, the FDA-approved OSI Pharmaceuticals/Genentech's Tarceva as a monotherapy for treatment of refractory non-small cell lung cancer (NSCLC). Approval was based on a demonstrated improvement in median survival (6.7 months versus 4.7 months for best supportive care, p<0.001) from the BR.21 study in patients who had failed one or more lines of chemotherapy. Shortly afterwards, the failure of AstraZeneca's Iressa in a similar study allowed Tarceva to capture essentially the entire U.S. EGFR inhibitor market. A series of price hikes and moderate adoption in pancreatic cancer (U.S. approval granted in 2005) have supported sales growth in the U.S. Virtually all EGFR-mutant patients will be given Tarceva as first line therapy. In April 2010, FDA approved Tarceva for the first-line maintenance treatment of locally advanced or metastatic NSCLC in patients whose disease had not progressed after four cycles of platinum-based first-line chemotherapy. While this is a positive, approval in maintenance does not seem to be aiding Tarceva's growth. In December

2013, Roche announced that Tarceva did not meet its primary endpoint (of Disease Free Survival) in the Phase III (RADIANT) trial for adjuvant use in NSCLC. We estimate Tarceva sales of CHF1,275MM (-5%) in 2014, CHF1,270MM in 2015, CHF1,255MM in 2016, CHF1,220 in 2018 and CHF805MM in 2020.

Tarceva has fared well in ex-U.S. geographies where the brand has posted steady and significant growth. Factors that have supported ex-U.S. sales trends include a more favorable reimbursement environment for oral therapies, a differentiated label that includes claims for improved quality of life, and more recent launches in several new geographies.

EURTAC Supports Tarceva Use In First-Line EGFR-Mutated NSCLC

It is known that patients with activating EGFR mutations respond particularly well to EGFR inhibitors including Tarceva and Iressa. The Phase III EURTAC study (European Randomized Trial of Tarceva vs. Chemotherapy), carried out by the Spanish Lung Cancer Group, was designed to better clarify the prognostic and predictive relevance of EGFR mutations, and compare Tarceva's efficacy to conventional doublet chemotherapy in the front-line setting. Of 1,227 patients screened, 174 patients were EGFR mutation positive and randomized to receive either erlotinib or platinum-based chemotherapy. EURTAC was stopped early after a successful pre-defined interim analysis. Erlotinib met its primary PFS endpoint (9.7 months for erlotinib vs. 5.2 months for chemotherapy, HR=0.37, p<0.0001) with no differences with regard to age, gender, performance status 0 and 1, or in patients with exon 19 deletions; however, a significant treatment effect was not observed in patients with a performance status of 2 or in current/former smokers. The ORR was 58% for erlotinib compared to 15% in the chemotherapy arm. At the time of evaluation, a significant difference in OS was not observed (22.9 months for erlotinib vs. 18.8 months for chemotherapy, HR=0.8, p=0.42), but the data was immature and a high-level of known crossover to erlotinib was observed. Hematologic adverse events were significantly more common in the chemotherapy arm compared to the erlotinib arm, while rash was only observed with erlotinib treatment. While the PFS for erlotinib in EURTAC is less than has been observed in previous studies (13-14 months), a PFS of 9.7 months is similar to the PFS in the pivotal registration trial for gefitinib (IPASS PFS=9.3 months).

A similar Phase 3 trial, OPTIMAL, evaluated Tarceva vs. chemotherapy in treatment naive patients in China. Efficacy results for this study showed a tripling of PFS with Tarceva therapy (13.1 months) compared to gemcitabine/carboplatin (4.6 months). Additionally, only 17.1% of Tarceva patients experienced adverse events compared to 65% of patients on chemotherapy. 40-60% of Asian patients have been shown to possess activating EGFR mutations, which may explain such dramatic differences in response.

Subset data from several prior studies have demonstrated the utility of EGFR TKI's in NSCLC patients whose tumors harbor EGFR mutations. The SATURN study (Tarceva's pivotal study in maintenance NSCLC) associated Tarceva with a hazard ratio of 0.10 for PFS in these patients (vs. a HR of 0.71 for all patients). Furthermore, competitor Iressa received a European label for use in all lines of therapy in patients with EGFR mutations based on data from two Phase III studies demonstrating a strong benefit in these patients.

Tarceva Receives Paragraph IV Challenge; Indian Generics Unstoppable

In February 2009, Teva and Mylan submitted ANDAs to the FDA to market a generic version of Tarceva. In March 2009, OSI filed lawsuits in the U.S. District Court in

Delaware against Teva and Mylan for infringement of three patents associated with Tarceva: U.S. Patent Nos. 5,747,498, 6,900,221 and 7,087,613. The filing of these lawsuits restricts the FDA from approving the ANDAs for either company until seven and a half years have elapsed from the date of Tarceva's initial approval (i.e., May 18, 2012). On the other hand, if OSI were to prevail in an infringement action, the ANDAs filed cannot be approved until the patent held to be infringed expires. In July 2013, Mylan entered into a settlement agreement with OSI, Pfizer, and Genentech involving the erlotinib 25mg, 100mg, and 150mg tablets, under which pending litigation will be dismissed. Other terms of the contract are confidential. The agreement is subject to DoJ and FTC review.

Tarceva is protected by three Orange Book-listed patents. The drug's key patent ('498) covers Tarceva's composition of matter and certain methods of use; this patent expires in 2018. In February 2008, OSI filed for a re-issuance of this patent, the basis for which was that several compounds claimed in Claims 8 and 10 of the patent were outside the genus of compounds defined in the broadest claim of the patent (Claim 1). OSI requested cancellation of all compounds in Claim 8, except for that covering Tarceva's structural composition, and a cancellation of Claim 10. The U.S. PTO reissued the '498 patent under a new number, U.S. RE41,065.

Separately, Roche and OSI sought to enforce the composition-of-matter patent against Cipla with respect to a generic form of Tarceva launched by Cipla in India in January 2008. A lawsuit against Cipla was filed in India in January 2008; a request for a preliminary injunction was denied in March 2008 and upheld upon appeal. In September 2012, the Delhi high Court dismissed Roche's patent infringement suit, ruling in favor of Cipla. On December 15, 2009 and January 19, 2010, OSI filed lawsuits against Natco and Dr. Reddy's, respectively, in the High Court of Delhi to enforce the composition of matter patent with respect to additional generic forms of Tarceva. On March 6, 2010, OSI filed a lawsuit against Glenmark in the High Court of Delhi to enforce the composition-of-matter patent.

Zelboraf Fully Penetrated In U.S.; Competition May Pressure

Zelboraf (vemurafenib, R7204/PLX4032) is an oral small molecule for melanoma harboring the BRAF mutation. Vemurafenib was co-developed under a 2006 license and collaboration agreement between Plexxikon and Roche. A DNA-based companion diagnostic to identify patients whose tumors carry the BRAF mutation was co-developed by Plexxikon and Roche Molecular Systems, in parallel with the therapeutic development of vemurafenib. In August 2011, Zelboraf was concurrently approved with its companion diagnostic, the Cobas 4800 V600 Mutation Test.

More than 80% of metastatic melanoma patients are tested for BRAF mutations in the U.S. Post testing, Roche believes it is relatively easy to follow patients and determine their course of therapy. Roche believes that Zelboraf is nearly fully penetrated in the U.S. market. Growth is likely ex-U.S. where only 50% of patients are tested for BRAF mutations, although in December 2013 U.K.'s NICE decided to not recommend Zelboraf and Germany's IQWiG indicated they found no significant value-add for the drug. Zelboraf is available in the U.S. at a cost of \$9,400 per month. We estimate Zelboraf sales of CHF295MM (-17%) in 2014, CHF360MM in 2015, CHF420MM in 2016, CHF540MM in 2018, and CHF660MM in 2020.

Zelboraf was approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutations and was not recommended for use in patients with wild-type BRAF melanoma. The label warns against the potential for developing

cutaneous squamous cell carcinomas, hypersensitivity reactions, dermatologic reactions, QT prolongation, liver abnormalities, ophthalmologic reactions, and new primary malignant melanomas; these warnings are in line with the adverse event profile for vemurafenib in clinical trials. Instructions for dose adjustments and recommendations for discontinuation are provided in label. Zelboraf was approved with a Medication Guide to inform health care professionals and patients of potential risks. Our physician consultants note that their real world experience with Zelboraf is generally in line with reports from clinical trials. Zelboraf appears to be fairly well tolerated with ~25% of patients experiencing trouble with fatigue or skin lesions that require intervention.

Zelboraf is also being evaluated (Phase III BRIM8) for adjuvant use in BRAF-positive melanoma and is in Phase II trials for use in BRAF-positive papillary thyroid cancer and BRAF-positive melanoma patients with brain metastases. Updated BRIM-3 data (33 month follow-up) on brain metastases was presented in November 2013 and showed an OS for Zelboraf of 13.6 months (95% CI 12.0-15.3) vs 9.7 months for chemo (95% CI 7.9-12.8).

Broad Adoption Of Mutation Testing And Ease Of Use Favor Zelboraf

Our academic physician consultants currently perform BRAF mutational analysis in all newly diagnosed patients of whom ~50% are positive for activating BRAF mutations. The oral formulation and tolerability of BRAF inhibitors are viewed as positives and are expected to drive adoption by community oncologists. Many of our physician consultants believe all patients with BRAF V600 mutations should receive Zelboraf first-line; however, this view is not shared by all physicians, some of who believe early stage/relatively healthy BRAF positive patients should be treated first with Yervoy (ipilimumab; BMY) with the hope of achieving a sustained response and then treated with Zelboraf upon progression. All physicians agree that BRAF positive patients with late stage disease or high tumor burden should be treated with Zelboraf prior to Yervoy. Regardless of Zelboraf's staging in an oncologist's armamentarium, we expect the majority of BRAF V600E patients to receive Zelboraf during the course of their disease. Our physician experts have noted that tumors appear to be significantly more aggressive when Zelboraf is withdrawn after progression on drug. Additionally, our melanoma experts noted that they have not seen any patient respond to ipilimumab therapy post Zelboraf failure. If such data is replicated, this may impact how Zelboraf use is staged relative to immunotherapy.

Phase III BRIM3 Data The Basis For Approval

In January 2011, Roche announced that BRIM3, a Phase III clinical study of vemurafenib, met its co-primary endpoints showing a significant survival benefit in people with previously untreated BRAF V600 mutation-positive metastatic melanoma. BRIM3 is a Phase III study comparing vemurafenib to dacarbazine chemotherapy (DTIC) in 675 patients with previously untreated BRAF V600 mutation-positive (47% of patients screened were positive for V600 mutations), unresected locally advanced or metastatic melanoma. Co-primary endpoints were OS and PFS. Secondary endpoints included response rate, response duration and safety profile. Vemurafenib met the overall survival endpoint with 84% of patients alive at 6 months compared to 64% of patients on DTIC (HR=0.37, p<0.0001). Median OS was not evaluable in this study because of the small number of patients alive at the later time points. Median OS estimates when BRIM3 met this co-primary endpoint in January 2011 were 9.2 months in patients receiving vemurafenib and 7.8 months in those receiving chemotherapy; an additional two months of follow-up showed an estimated median OS of 10.5 months for patients receiving vemurafenib, while the median OS estimate for patients receiving chemotherapy remained at 7.8 months. The overall survival

endpoint was consistently improved in the vemurafenib arm across age, sex, and EGOC status; however, a statistically significant treatment effect did not exist in patients with stage IIIC disease or M1a and M1b disease status. PFS was statistically superior in vemurafenib treated patients compared to DTIC (5.3 months for vemurafenib vs. 1.6 months in DTIC, HR=0.26, p<0.0001). The PFS treatment effect was consistent across all pre-specified subgroups. The ORR rate for vemurafenib was 48.4% compared to 5.5% for DTIC (CR of 0.9% for vemurafenib vs. 0% for DTIC; PR of 47% for vemurafenib vs. 5.5% for DTIC, p<0.0001). Arthralgia, rash, fatigue, photosensitivity, and increased liver function tests were the ADRs most frequently associated with vemurafenib dose reduction. Cutaneous lesions including keratoacanthoma and skin papillomas were also observed in the vemurafenib arm; all were easily excised by dermatologists with no evidence of metastases. Treatment discontinuation was 6% in the vemurafenib arm compared to 4% in the DTIC arm.

MEK And Other Pathways Identified As Mechanisms For BRAF Inhibitor Resistance; Justifies BRAF/MEK Inhibitor Combination

Biopsies were isolated from 51 patients in the Phase I PLX06-02 study of vemurafenib in V600 mutant melanoma. Tissue samples were acquired before starting vemurafenib, after 15 days of therapy, and at the time of disease progression. 56% of patients in this trial responded to vemurafenib. In responders, p-ERK and p-MEK were significantly decreased after 15 days of vemurafenib therapy, correlating with a reduction in the expression of markers of cell proliferation (Cyclin D1 and Ki67) and 66% of samples stained positive for increased markers of apoptosis. The PTEN/PI3K pathway was unaffected at day 15. At progression, pERK and pMEK expression increased in some samples, and Cyclin D1 and Ki67 expression returned to baseline. MassARRAY gene analysis identified 3 compensatory mutations (1 NRAS, 1 MEK1, and 1 PTEN deletion) out of 11 patients who had progressed and had evaluable tissue. All three of these mutations were associated with survival which was significantly lower than the median survival for the overall population. Our consultants note that resistance does develop against BRAF inhibitors and therefore BRAF inhibitors are ideal candidates for combination therapy either with another mechanism for example ipilimumab, a MEK inhibitor, or an antiangiogenesis agent (Roche's Avastin). A January 2012 publication in NEJM suggests that squamous cell carcinomas and other secondary tumors are most commonly observed in patients with RAS mutations who are subjected to BRAF inhibition. The authors suggest that RAS status and diagnostic testing for RAS mutations cofactors in determining who receives a BRAF inhibitor.

New BRAF/MEK Combination Competition, But Roche's Own Zelboraf/MEK Combo Meets Primary Endpoint In Phase III

GSK (soon to be Novartis) markets both a BRAF inhibitor (dabrafenib/Tafinlar) and a MEK inhibitor (trametinib/Mekinist), both of which were approved in the U.S. in May, 2013 and a label for combination therapy in the treatment of melanoma was approved in January 2014. Roche has its own MEK-inhibitor cobimetinib+Zelboraf combo in Phase III BRAF-positive, treatment naïve, melanoma trials. In May 2014, final data from a Phase Ib study (BRIM7) of cobimetinib + Zelboraf in BRAF+ metastatic melanoma patients were reported which showed a median PFS of 13.7 months for the combo in inhibitor-naïve patients (n=63). For patients who had failed Zelboraf, the PFS was 2.8 months. While the study showed the two drugs were able to be given in combination at their individual single-agent maximum dose, a sizable number of side effects were reported (across entire study) including diarrhea (64%), rash (60%), fatigue (48%), nausea (45%), abnormal liver tests (40%); the most frequent Grade 3+ AEs included abnormal liver tests (10%), cutaneous squamous cell carcinoma (9%), rash (8%).

In July 2014, Roche announced that a Phase III confirmatory trial (coBRIM, 500 patients) evaluating the combo versus Zelboraf alone in treatment-naïve BRAFV600 metastatic melanoma patients met its primary PFS endpoint. Full data revealed a 3.7 month median PFS benefit (9.9 months vs 6.2 months) for cobimetinib/Zelboraf combo compared to Zelboraf alone. The ORR was higher with the combi vs, the control arm (68% vs 45%, p<0.0001). OS data are not yet mature. The most common AE's reported in the combo arm included diarrhea, nausea, rash, photosensitivity, and lab abnormalities. The combo was filed for 1st-line BRAF+ melanoma in the EU in Q3:14; a U.S. filing is expected by year end.

Dabrafenib was well tolerated in BREAK3 with only 3% of patients discontinuing treatment as the result of adverse events. Interestingly, the side effect profile of dabrafenib is distinctly different than that of Zelboraf. Only 7% of patients on dabrafenib developed keratoacanthoma (KA) or squamous cell carcinoma (SCC) compared to 11% and 19% of patients on Zelboraf in BRIM3. Additionally, only 3% of patients on dabrafenib experienced photosensitivity compared to 41% of patients on Zelboraf in BRIM3. Dabrafenib has previously shown intracranial disease control in >80% of patients with a median OS of >31 weeks, which may further differentiate dabrafenib from Zelboraf.

Erivedge Marketed For Basal Cell Carcinoma; Additional Indications In Development

Erivedge (vismodegib/GDC-0449/RG3616), a novel small molecule hedgehog signaling pathway inhibitor, was approved for the treatment of advanced basal cell carcinoma in January 2012 and remains in Phase II for several other indications including operable BCC, basal cell nevus syndrome, advanced stomach or gastroesophageal junction cancer, pancreatic ductal adenocarcinoma, refractory medulloblastoma, and extensive-stage small cell lung cancer. In October 2013, Roche initiated a Phase Ib/II trial in relapsed/refractory AML and relapsed/refractory, high-risk myelodysplastic syndrome. We estimate Erivedge sales of CHF140MM (+87%) in 2014, CHF210MM in 2015, CHF270MM in 2016, CHF390MM in 2018, and CHF520MM in 2020.

Mircera May Enter U.S. Market With A Partner

Mircera (formerly CERA for Continuous Erythropoiesis Receptor Activator) is a native erythropoietin (Roche's NeoRecormon, marketed in Europe) that has been engineered through PEGylation technology to exhibit an extended serum half-life. Mircera's primary amino acid sequence (165 amino acids) and glycosylation pattern are believed to be identical to Amgen's erythropoietin. The E.U.'s EPAR documents indicate that Mircera differs from Aranesp only by the addition of a PEG group, without any change to the amino acid sequence of the protein backbone. The addition of a large PEG chain provides Mircera with a half-life that is 5-15x longer than native erythropoietin and 3-5x longer than Aranesp. In addition, Roche asserts that PEGylation appears to allow Mircera to "continuously" stimulate the EPO receptor through repeated attachment and rapid detachment. In contrast, Roche believes native EPO stimulates its receptor only once. Phase III data on Mircera encompassing more than 2,000 ESRD patients suggest Mircera is more potent gram for gram than EPO and capable of driving rapid increases in hemoglobin levels in patients treated every third week. No antibodies to Mircera have been observed in clinical trials.

Mircera Approved In Europe...

Roche gained EMEA approval of Mircera for the treatment of anemia associated with chronic kidney disease patients in 2007. Mircera was launched into a competitive ESA

environment that included Roche's NeoRecormon, JNJ's Eprex, Amgen's Aranesp, and biosimilars. Mircera's modest market share gains have come at the expense of NeoRecormon as opposed to extending Roche's overall market share.

...But Roche Loses U.S. Patent Battle...

In October 2005, Amgen filed a patent infringement lawsuit against Roche in the U.S. District Court related to PEGylated EPO derivatives. This suit alleged infringement of six of Amgen's U.S. patents that claim EPO products and compositions, as well as processes for making EPO. In its complaint against Roche, Amgen asserted that Mircera contains erythropoietin as claimed by three of its U.S. patents, and that Mircera would not be functional but for its erythropoietin component. Amgen also claimed that Roche produces the glycosylated human EPO in PEG-EPO by means of processes covered by Amgen's patents.

In August 2007, Judge Young of the U.S. Federal District Court of Boston issued a surprisingly early and favorable decision for Amgen in the company's erythropoietin patent dispute versus Roche. Judge Young granted Amgen's motion for a summary judgment that Roche's PEG-Epo (Mircera) infringes Amgen's U.S. patent 5,955,422 (covering pharmaceutical compositions of erythropoietin purified from mammalian cells). Subsequently, in October 2007, a jury of the U.S. District Court in Massachusetts issued a verdict in favor of Amgen. The jury ruled that Mircera infringes 11 valid Amgen patent claims.

...And Finally "Settled"

In December 2009, Amgen announced that the United States (U.S.) District Court in Boston entered final judgment and a permanent injunction against Roche prohibiting Roche from infringing Amgen's patents on recombinant erythropoietin (EPO), thus bringing the five-year patent infringement dispute to an end. The judgment was accompanied by Roche's admission that the five Amgen EPO patents involved in the lawsuit are valid, enforceable and infringed by Mircera and by Amgen allowing Roche to begin selling Mircera in the U.S. in mid-2014 under terms of a limited license agreement. Roche has not commented on whether or not it intends to pursue a U.S. launch but a partnership to market the product in the U.S. may be likely. The settlement terms do not include any financial payments between the parties. Mircera was approved by the FDA in 2007 for use in ESRD patients.

NeoRecormon Sales Declining

Roche's NeoRecormon (erythropoietin beta) is approved for sale in Europe while Epogin is the brand name marketed in Japan. The franchise has struggled in the face of greater competition from Aranesp, biosimilars and cannibalization from Mircera (PEGylated erythropoietin beta). Mircera is not available in the U.S. due to Amgen's patents. In Japan, Epogin had suffered from price cuts, as well as competition from Aranesp, but appears to be stabilizing. We expect NeoRecormon/Mircera/Epogin sales will continue to decline driven by biosimilar competition, and contraction of the overall market. We estimate NeoRecormon sales of CHF455MM (-13%) in 2014, CHF415MM in 2015, CHF375MM in 2016, CHF295MM in 2018, and CHF220MM in 2020.

Infectious Diseases

Pegasys/Copegus Has Been The Backbone Of HCV Therapy, But Interferon Free Regimens Dampening Prospects

Roche and Schering-Plough (now Merck) dominate the pegylated alpha-interferon market. In October 2002, Pegasys (pegylated interferon α -2a) received approval as monotherapy treatment for chronic hepatitis C infection and in December 2002 Pegasys was approved in combination with Copegus (Roche's proprietary ribavirin). Roche launched the combination in January 2003 almost two years after Schering's PEG-Intron's market entry. The Pegasys/Copegus combination now captures 80+% share of the hepatitis C treatment market. Several head-to-head studies including Schering's IDEAL study (and the Laguna et al study) suggest that Pegasys is more effective than PEG-Intron. While Pegasys is likely to retain its market dominance, the outlook for the pegylated-interferons is capped given the recent success of interferon free regimens. The new targeted-antivirals reduce and may remove the need for interferon therapy by improving on efficacy and shortening the duration of therapy, thereby limiting the interferons' side effects (high rate of flu-like symptoms). Roche will not pursue HCV research beyond existing pipeline agents. We estimate Pegasys sales of CHF1065MM (-19%) in 2014, CHF720MM in 2015, CHF595MM in 2016, CHF435MM in 2018, and CHF280MM in 2020.

Danoprevir, Mericitabine May Have A Role In Combo HCV Therapy

RG7227/R05190519/ITMN-191 (danoprevir) is a macrocyclic inhibitor of HCV NS3/4A protease activity (PI). In October 2010, Roche purchased development and commercialization rights to RG7227/R05190519 for \$175MM in cash. R7128 (mericitabine), a pro-drug of PS-6130, is a nucleoside-based (active site) HCV polymerase inhibitor, for which a large Phase IIb study (DYNAMO) was initiated in April 2009 which included mercitabine in combo with telaprevir, PEG-interferon , and ribavirin in prior null-responders. SVR24 rates of 71% were achieved with 12 week treatment, but jumped to 96% with 24 weeks of treatment.

However, with the evolving HCV treatment landscape, Danoprevir and Mericitabine are being evaluated in various combo settings. The two agents are currently in a 3 DAA, Phase II trial (ANNAPURNA) with setrobovir (a Roche agent), ritonavir, and ribavirin. Results presented in March 2014 showed much more favorable results in GT-1b patients with an SVR12 of 96% in a 14-week regimen while a 26-week regimen in GT-1a patients showed an SVR12 of 70%. The two drugs are also in a Phase IIb study evaluating 3DAA regimens with ribavirin and with/without interferon (Matterhorn) in a 24 week treatment regimen. Preliminary results showed SVRs of 84-86%. We estimate danoprevir and mercitabine with sales for each of CHF25MM in 2018, and CHF75MM in 2020.

Tamiflu Sales Forecast To Be Flat

Tamiflu is a neuraminidase inhibitor that is indicated for the treatment and prevention of influenza types A and B. Tamiflu has also demonstrated efficacy in treatment of the H1N1 strain. Roche built capacity to manufacture 400MM doses of Tamiflu per year. Much of the Tamiflu sales are through government stock piling and the rest are from seasonal flu requirements. Tamiflu generally has a seven-year shelf life. In March 2014, Natco Pharma received tentative approval from the FDA to launch a generic Tamiflu and may have first-to-file approval for the ANDA, contingent upon successful

litigation of the original patent. We forecast Tamiflu sales of CHF550MM (-13%) in 2014, and CHF400MM in each year from 2015-20.

In March 2008, the FDA gave Tamiflu a stronger warning for rare reports of delirium and abnormal behavior leading to self-injury, and, in some cases, death. Tamiflu's label continues to stress the importance of watching flu patients for signs of unusual behavior and seeking immediate care if any such signs are observed. Since November 2006, Tamiflu's warning information has noted post-marketing reports, mainly from Japan, of self-injury and delirium in flu patients, and that it is not clear if Tamiflu caused those problems. Now, Tamiflu's warning information also includes more details, including reports of "some cases" of fatal injuries from delirium and abnormal behavior in patients taking Tamiflu. Tamiflu's updated label also states that those reports appear to be "uncommon," and that the reported cases may happen abruptly. The drug's label also points out that flu itself can cause neurological and psychiatric problems.

In 1996, Gilead out licensed worldwide rights to Tamiflu to Roche, but in June 2005 Gilead delivered a licensing agreement termination notice to Roche, contending that Roche had materially breached its obligations by not launching Tamiflu in 43 of 64 territories in which it is approved. In November 2005, the two parties announced an end to the dispute. Under the amended agreement, Gilead now receives a tiered royalty on end user sales (14% on the first \$200MM, 18% on the next \$200MM, and 22% above \$400MM during the calendar year), and will no longer incur COGS adjustments to those royalties. Gilead will have an increased say in the manufacturing, commercial, and pandemic planning for Tamiflu, and will reserve the right to co-promote Tamiflu in specialized areas of the U.S. Should Gilead choose to co-promote, it would receive the same royalty on Tamiflu sales in addition to a per-detail reimbursement for its sales force. Gilead does not co-promote Tamiflu and has not decided whether it will opt-in for co-promotion in future years.

Valcyte Dominates The CMV Market

Valcyte (valganciclovir) is an antiviral agent that is highly active against human herpes virus 5, also known as cytomegalovirus (CMV). It is a highly bioavailable orally administered prodrug of ganciclovir. Valcyte is used in immunocompromised patients to prevent CMV disease in kidney, heart and kidney-pancreas solid organ transplant (SOT) recipients at high risk and to treat CMV retinitis in people with acquired immunodeficiency syndrome (AIDS). There are several vaccines in development (Vical, Sanofi, Novartis) attempting to prevent CMV infection although progress of these vaccines has been slow. In October 2012, Merck acquired exclusive global rights to AiCuris' portfolio of CMV-targeting candidates, including the orally administered drug letermovir (AIC246), which has successfully completed a Phase II trial for treating and preventing CMV infection in transplant patients. IMPACT, which was presented at ATC 2009, demonstrated that 100 days of additional Valcyte (200 total days) reduces the proportion of patients with CMV disease within the first year post-transplant to 16%, compared to 37% with 100-day Valcyte prophylaxis ($p < 0.0001$). We forecast Valcyte sales of CHF705MM (+2%) in 2014, CHF630MM in 2015 (9/15 patent expiration), CHF550MM in 2016, CHF390MM in 2018, and CHF230MM in 2020.

Arthritis/Inflammation

Actemra Growth Driven By SQ Formulation And Superiority To Humira In Methotrexate-Free Regimen

Actemra (Roche and Chugai) is an injectable humanized monoclonal antibody against IL-6 receptor (membrane bound and soluble forms). IL-6 production by B and T lymphocytes, macrophages, and fibroblasts is stimulated by TNF- α and IL-1. IL-6 in turn accelerates the inflammatory cascade by mediating T lymphocyte activation, maturation of megakaryocytes, B cell autoantibody and immunoglobulin production, hepatocyte production of acute phase reactants, and osteoclast activation.

Actemra was approved by the EMEA and FDA in January 2010, based on multiple Phase III trials (SAMARUI, TOWARD, OPTION, RADIATE, AMBITION, and LITHE) that enrolled over 4,000 patients and tested the drug as monotherapy or in combination with traditional DMARDs, in naïve and refractory methotrexate and anti-TNF patients. All studies have demonstrated that Actemra (4mg/kg and 8mg/kg) is effective in treating the signs and symptoms of RA, including radiographic progression of structural damage. Adverse events noted in the trials include an increased risk of infection, increase in total cholesterol, LDL, triglycerides, and blood pressure, transient increases in liver function tests, transient neutropenia, infusion reactions (7% reactions, mostly mild to moderate), and GI perforations.

In March 2010, Roche submitted an sBLA to extend the Actemra label to cover slowing joint damage in RA based on two-year data from the LITHE trial. Supplemental FDA approval for this indication was granted in January 2011. A similar submission to the EMA in 2009 was approved in June 2010. Actemra was approved for first line use in October 2012. In July 2014, Actemra received a positive CHMP opinion for use in patients with early RA, not previously treated with methotrexate.

Our physician consultants are excited about the SQ formulation which was approved in Japan in June 2013, the U.S. in October 2013 and in the EU in March 2014, given that the i.v. formulation requires a 1hr+ infusion and is associated with a higher incidence of infusion site reactions compared to Orencia. Roche estimates that almost 80% of new patients in the U.S. start on SQ Actemra. The SQ formulation is in Phase III studies for giant cell arteritis (GiACTA) and Phase II for systemic sclerosis (faSScinate). We estimate Actemra sales of CHF1,195MM (+15%) in 2014, CHF1,435MM in 2015, CHF1,685MM in 2016, CHF2,185MM in 2018, and CHF2,535MM in 2020.

Actemra Efficacy Data

Response Rate Week 24	Percent of Patients												
	Study I		Study II			Study III			Study IV		Study V		
	MTX	ACTEMRA 8 mg/kg	Placebo + MTX	ACTEMRA 4 mg/kg + MTX	ACTEMRA 8 mg/kg + MTX	Placebo + MTX	ACTEMRA 4 mg/kg + MTX	ACTEMRA 8 mg/kg + MTX	Placebo + DMARDs	ACTEMRA 8 mg/kg + DMARDs	Placebo + MTX	ACTEMRA 4 mg/kg + MTX	ACTEMRA 8 mg/kg + MTX
ACR20													
Responders	53%	70%	27%	51%	56%	27%	48%	59%	25%	61%	10%	30%	50%
Weighted Difference % ^a (95% CI) ^b			19 (11, 27)	23 (17, 29)	29 (23, 35)		23 (15, 32)	32 (23, 41)		35 (30, 40)		25 (15, 36)	46 (36, 56)
ACR50													
Responders	34%	44%	10%	25%	32%	11%	32%	44%	9%	38%	4%	17%	29%
Weighted Difference % ^a (95% CI) ^b			12 (4, 20)	15 (9, 20)	22 (16, 28)		21 (13, 29)	33 (25, 41)		28 (23, 33)		15 (5, 25)	31 (21, 41)
ACR70													
Responders	15%	28%	2%	11%	13%	2%	12%	22%	3%	21%	1%	5%	12%
Weighted Difference % ^a (95% CI) ^b			14 (7, 22)	8 (3, 13)	10 (5, 15)		11 (4, 18)	20 (12, 27)		17 (13, 21)		4 (-6, 13)	12 (3, 22)

^a The weighted difference is the difference between ACTEMRA and Placebo response rates, adjusted for site (and disease duration for Study I only).

^b CI: 95% confidence interval of the weighted difference

Source: Cowen and Company, FDA

In terms of monitoring, physicians are required to check neutrophils, platelets, LFTs, and lipids every four to eight weeks (after an unspecified period of time, lipids can then be checked every 6 months). Depending on the blood test results, FDA has provided dosing recommendations in Actemra's label (see below). We believe these monitoring issues are a modest negative compared to methotrexate, anti-TNFs, and Orencia, which require less frequent monitoring. Roche is also mandated by the Agency to conduct a randomized controlled clinical trial to assess Actemra's impact on serious CV complications (e.g. stroke, heart attack, death) based on the drug's ability to increase LDL and blood pressure.

Monitoring Requirements For Actemra

Liver Enzyme Abnormalities [see Warnings and Precautions (5.3)]:

Lab Value	Recommendation
> 1 to 3x ULN	Dose modify concomitant DMARDs if appropriate For persistent increases in this range, reduce ACTEMRA dose to 4 mg/kg or interrupt ACTEMRA until ALT/AST have normalized
> 3 to 5x ULN (confirmed by repeat testing)	Interrupt ACTEMRA dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN, discontinue ACTEMRA
> 5x ULN	Discontinue ACTEMRA

Low Absolute Neutrophil Count (ANC) [see Warnings and Precautions (5.3)]:

Lab Value (cells/mm ³)	Recommendation
ANC > 1000	Maintain dose
ANC 500 to 1000	Interrupt ACTEMRA dosing When ANC > 1000 cells/mm ³ resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 500	Discontinue ACTEMRA

Low Platelet Count [see Warnings and Precautions (5.3)]:

Lab Value (cells/mm ³)	Recommendation
50,000 to 100,000	Interrupt ACTEMRA dosing When platelet count is > 100,000 cells/mm ³ resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 50,000	Discontinue ACTEMRA

Source: Cowen and Company, FDA Label

ADACTA A Success; Actemra Delivers Impressive Efficacy Versus Humira

Roche presented data from the ADACTA trial, comparing Actemra to AbbVie's Humira as monotherapy for the treatment of RA, at EULAR 2012. ADACTA was a Phase IV parallel group study designed to compare the safety and efficacy of Actemra to Humira as monotherapy in adult biologic-naïve patients with severe RA who could not tolerate methotrexate. 326 patients were randomized (1:1) to receive Actemra (8mg/kg IV, Q 4-weeks) or Humira 40mg SQ, Q 2-weeks) for 24-weeks.

In ADACTA, Actemra met its primary endpoint of a significant reduction in the mean change in DAS28 at 24-weeks compared to Humira (3.3 point reduction for Actemra vs. 1.8 point reduction for Humira). The percentage of patients achieving DAS28 remission was significantly higher in the Actemra group compared to those treated with Humira (DAS28 remission rate for Actemra of 40% vs. 11% for Humira).

Additionally, Actemra demonstrated significant improvements in joint tenderness and swelling compared to Humira as measured by ACR response rates (ACR20/50/70 for Actemra of 65%/47%/33% vs. 49%/28%/18% for Humira). The comparative efficacy of Actemra and Humira in ADACTA is summarized on the next page:

ADACTA Efficacy Summary

	Actemra	Humira
DAS28 (absolute reduction)	3.3	1.8
DAS28 (% achieving remission)	40%	11%
ACR20	65%	49%
ACR50	47%	28%
ACR 70	33%	18%

All listed differences between Actemra and Humira are statistically significant ($p < 0.05$)

Source: Company data

While Humira labeling states that “some patients with RA not receiving methotrexate may benefit from increasing the frequency of dosing to 40mg every week,” our physician consultants use the 40mg every two week dosing schedule in >90% of their patients. In Humira’s registration CD-III study, the group that received Humira every week did not demonstrate significantly higher remission rates compared to the group that received Humira every other week. We believe Humira dosing in ADACTA was sufficient, consistent with the Humira label and clinical practice, and that once-weekly Humira dosing in ADACTA would be unlikely to change the outcome of the study.

Safety Profile In ADACTA As Expected

The safety profiles of Actemra and Humira were comparable and consistent with previous clinical trial data. The frequency of adverse and serious adverse events was similar between Actemra and Humira treatment groups. Two deaths occurred in the Actemra group compared to none in the Humira group; one death was unrelated to Actemra, the second death was considered possibly related to study drug. Liver enzymes and LDL-C were elevated to a greater extent in patients treated with Actemra compared to Humira. A summary of the safety data from ADACTA is below:

ADACTA Safety Summary

	Actemra (n=162)	Humira (n=162)
AEs, n (%)	133 (82)	134 (83)
SAEs, n (%)	19 (12)	16 (10)
Infection AEs, n (%)	77 (48)	68 (42)
Infection SAEs, n (%)	5 (3)	5 (3)
Deaths, n (%)	0 (0)	2 (1)
Liver Function (%)		
Normal ALT	62.3	72.2
>2.5x ULN	30.9	24.7
>2.5-5x ULN	5.6	1.9
>5-20x ULN	1.2	1.2
Sustained elevation of 15- LDL-C		
	20mg/dL over 24-weeks	Constant over 24-weeks

Source: Company data

SQ Approval Supported By SUMMECTA And BREVACTA

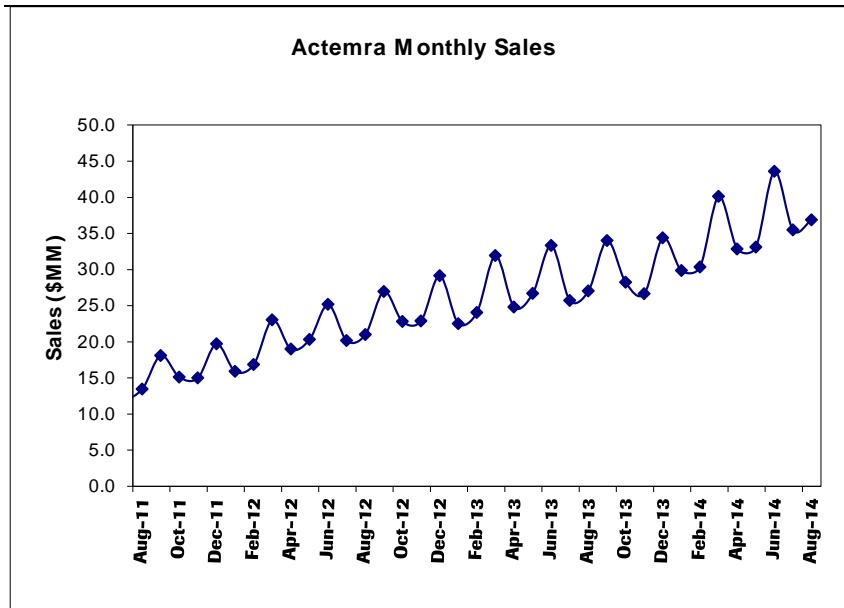
In May 2012, Roche announced that the SUMMECTA study met its primary endpoint, showing efficacy of the SQ formulation of Actemra compared to the i.v. formulation. A similar portion of patients in each treatment arm achieved ACR20 at 24-weeks. In July 2012, Roche announced that a second study of SQ Actemra, BREVACTA, met its primary ACR20 endpoint in patients with RA. In BREVACTA, patients on Actemra were also significantly less likely to experience worsening joint damage (by x-ray) at 24 weeks compare to placebo. A summary of the SQ Actemra program is provided below:

SQ Actemra

Patient population	Rheumatoid arthritis DMARD inadequate responders	Moderate-to-severe rheumatoid arthritis	Moderate-to-severe rheumatoid arthritis
Phase/study	Phase III ADACTA Head-to-head study	Phase III SUMMECTA Subcutaneous study	Phase III BREVACTA Subcutaneous study
# of patients	N=326	N=1,200	N=600
Design	<p>24 week treatment</p> <ul style="list-style-type: none"> • ARM A: Actemra IV 8mg/kg q4w plus pbo Adalimumab • ARM B: Adalimumab 40mg sc q2w plus pbo Actemra 	<ul style="list-style-type: none"> • Add-on to DMARD therapy • Weekly dosing for 104 weeks • ARM A: Actemra sc 162mg weekly plus placebo IV q4w • ARM B: Actemra IV 8mg/kg q4w plus placebo sc weekly 	<ul style="list-style-type: none"> • Add-on to DMARD therapy • Dosing every two weeks for 104 weeks • ARM A: Actemra sc 162mg q2w • ARM B: Placebo sc q2w
Primary endpoint	<ul style="list-style-type: none"> • DAS28 at 24 weeks 	<ul style="list-style-type: none"> • ACR 20 at week 24 	<ul style="list-style-type: none"> • ACR 20 at week 24

Source: Company data

Actemra Monthly Sales



Source: Cowen and Company and IMS Data

Xolair Looking Beyond Respiratory Indications; Approved In U.S. For CIU

In March 2014, Xolair (omalizumab; anti-IgE antibody) received U.S. approval (subcutaneous delivery) for chronic idiopathic/spontaneous urticarial (CIU/CSU), which is a skin condition causing hives and severe itching. According to Roche, nearly 50% of CIU patients have an inadequate response to anti-histamines, the only previously approved treatment. In February 2013, Roche reported that Xolair met its primary endpoint of improved disease control versus placebo at 12-months in the Phase III ASTERIA II trial in CIU patients. At the end of the 12-week treatment period, 66% of patients on Xolair had well controlled disease versus 19% of patients on placebo. In January 2014, Xolair received a positive CHMP opinion for use in CIU. We estimate Xolair sales of CHF877MM (+11%) in 2014, CHF965MM in 2015, CHF1,050MM in 2016, CHF1,200MM in 2018, and CHF1,350MM in 2020.

Xolair was approved in June 2003 for the treatment of moderate to severe allergic asthma in adolescent and adult patients (12 years of age and above). Our consultants believe that Xolair's price and subQ formulation have constrained the drug's use to the most refractory of asthma patients (approximately 10% of patients). In November 2009, FDA's advisory panel voted against recommending Xolair for approval for children between six and eleven years.

Lebrikizumab Showing Significant Promise In Asthma

Lebrikizumab (RG3637), which targets IL13, in tandem with a biomarker, is being evaluated for use in severe asthma. Results from the Phase IIb LUTE/VERSE trials, released in March 2014, showed that lebrikizumab appears most effective in a sub-population of asthma patients who have high levels of periostin. Asthma attacks in this sub-group were reduced by 60% compared to 5% in those with low periostin levels. Lung function, as measured by FEV1, was also improved in the periostin group. Immune-based adverse events are the main concern, but thus far, it appears none have been seen. This project is unique in that earlier studies were halted due to a manufacturing-related impurity, and those shortened studies provided further validation of what was seen in Phase II. Lebrikizumab is now in Phase III studies (LAVOLTA I and LAVOLTA II) in severe asthma patients and will also be studied in idiopathic pulmonary fibrosis. We forecast lebrikizumab sales of CHF25MM in 2018, and CHF100MM in 2020.

InterMune A Good Bolt-On Acquisition

In August 2014, Roche announced that it will be acquiring InterMune (ITMN) for \$74 per share in an all-cash transaction totaling \$8.3B. The transaction will be financed with a combination of available funds, commercial paper line, and newly issued bonds. InterMune expands Roche's existing respiratory portfolio portfolio of Pulmozyne (for cystic fibrosis), Xolair (asthma, chronic urticaria), and lebrikizumab (Phase III asthma). The transaction is expected to be neutral to core EPS in 2015 and accretive starting in 2016. Closing is expected by year end 2014.

Esbriet Could Be Leader In IPF

InterMune's lead product is pirfenidone (Esbriet), an oral TGF-beta inhibitor used for treatment of Idiopathic Pulmonary Fibrosis (IPF). IPF is a chronic disease characterized by progressive decline in lung function. Esbriet was the first drug approved for IPF: in the EU in 2011 and in Canada in 2012. The NDA was re-

submitted in the U.S. in May 2014 (the FDA had previously requested an additional study) after the release of positive data from a Phase III trial (ASCEND). Breakthrough Therapy designation was granted in July; the PDUFA date is November 23, 2014. We estimate Esbriet sales of \$280MM in 2015, \$550MM in 2016, \$1,375MM in 2018, and \$1,825MM in 2020.

Esbriet Approval Expected By November PDUFA

We see Esbriet's safety and efficacy data package as very strong in regards to US approval (Nov. 23, 2014 PDUFA). We think ASCEND met FDA requirements for efficacy in IPF, despite older controversies around appropriate pivotal endpoints. We expect no major safety warning and think there is a good chance the final label could include ASCEND/CAPACITY meta-analysis showing statistically significant mortality benefit.

Competition Expected, But Esbriet Profile May Be More Compelling

Boehringer Ingelheim's pan-kinase inhibitor nintedanib is also under FDA review with an estimated Q1/15 PDUFA date and priority review. While we view BI's drug as approvable, we think it may prove to be less tolerable than pirfenidone with real-world use. Most KOLs we have spoken to believe the 2 drugs have equal efficacy although differences in trial design make head-to-head comparisons difficult. We think that managing the drug's 60% diarrhea rate could prove to be a high enough practice burden at community pulmonologists' offices (where most IPF patients are treated) to relegate the drug to de facto second line use.

We see tolerability as one of Esbriet's major advantages. The drug's most frequent side effects are photosensitivity and upper GI side effects (mainly nausea). However, our conversations with KOLs in Europe where the drug is already approved suggest these can be relatively easily managed especially compared to BI's drug. As a result we model peak US sales of \$1.4B driven by a conservative 45% peak market share. We model EU peak sales of \$700M driven by 45-50% peak market share.

ASCEND Data Should Support Approval

ASCEND met its primary endpoint of reduction of percentage of patients that experience a 10% drop in forced vital capacity (clinically meaningful deterioration) versus placebo over 52 weeks of treatment. Data showed a highly statistically significant 47.9% reduction in percentage of patients that deteriorated (only 16.5% versus 31.8% for placebo) and a 132% increase in patients with stable disease versus placebo ($p < 0.000001$ for both measures). We believe the primary endpoint (essentially a responder analysis) is very acceptable to FDA as every IPF KOL we have spoken to regards it as clinically meaningful. While in the past there has been controversy over the acceptability of an FVC-based pivotal trial endpoint in a disease where FDA has stated they prefer a mortality endpoint, we think more recent KOL opinion has led FDA to acknowledge that for 1st generation drugs like pirfenidone, trials with mortality based primary endpoints are not feasible: FVC will have to do for now.

Ophthalmology

Competition Pressuring Lucentis Despite DME Approval

Lucentis is a pan anti-VEGF antibody fragment. While the VEGF165 isoform is thought to account for most VEGF activity in AMD, blocking all VEGF activity in the retina appears to translate into superior clinical activity. In June 2003, Genentech licensed ex-North American rights for Lucentis to Novartis. The BLA for Lucentis was filed in

December 2005 and final approval was received on June 30, 2006. Lucentis is priced at \$1,950 per vial. Lucentis had an impressive launch: in its first year on the U.S. market, the drug achieved \$800MM in sales. Despite competition from less expensive Avastin, Lucentis has grown, driven by new indications, particularly, diabetic macular edema (DME) and retinal vein occlusion (RVO). Lucentis was approved by FDA for RVO in June 2010 and was approved for DME in the E.U. in January 2012 and in the U.S. in August 2012 based on the positive results of the Phase III RIDE trial. The BRAVO and CRUISE pivotal studies in RVO, and the Phase III DME trial, RISE and RIDE trials met their primary endpoints. RISE showed that a significantly higher percentage of patients receiving monthly Lucentis achieved an improvement in vision (BCVA) of at least 15 letters on the eye chart at 24 months, compared to those in a control group who received a placebo (sham) injection. In RIDE, 45.7% of patients on Lucentis were able to read at least 15 more letters on the eye chart than at baseline, compared to 12.3% of patients on placebo. In September 2011, five cases of blindness associated with Avastin-related infections highlighted the risk of infection with repackaged intravitreal injections of Avastin. As a result of perceived safety concerns, U.S. V.A. hospitals have stopped using Avastin to treat AMD.

Our physician consultants believe there is a perception in the community of increased efficacy for Eylea in AMD, although there is no data to support this conclusion. The possibility to inject less frequently with Eylea has resulted in its rapid adoption at the expense of Lucentis. The likely approval of Eylea in mid-2014 for DME will add further pressure (DME represented ~15% of 2013 Lucentis sales). Despite likely approvals for additional indications, we anticipate stable sales for Lucentis through 2018, before declining post 2019 U.S. patent expiration. We estimate Lucentis sales of CHF1,710MM (+1%) in 2014, CHF1,740MM in 2015, CHF1,770MM in 2016, CHF1,830MM in 2018, and CHF1,250MM in 2020.

CATT Data As Expected; Has Not Changed Clinical Practice

Full 12-month data from CATT were presented at the 2011 ARVO conference, following publication of data in the *New England Journal of Medicine*. In CATT, Avastin and Lucentis looked similar in terms of efficacy in the monthly arms at one year; however, Avastin was not as effective as Lucentis at reducing retinal thickness, a secondary endpoint of the study. Additionally, Avastin PRN dosing was similar to Lucentis PRN. While a higher rate of SAE's occurred in the Avastin arm (24% vs. 19%), this does not concern our physician consultants as there were similar rates of typical anti-VEGF SAE's, diversity of SAE types and hospitalization causes, and the lack of a dose relationship to Avastin.

Two-Year CATT Data Support 12-Month Observations

In May 2012, two-year CATT data comparing Lucentis to Avastin for the treatment of age-related macular degeneration (AMD) were published in the journal *Ophthalmology*. Visual acuity was similar between Lucentis and Avastin. While the mean gain was largest on monthly compared to as-needed treatments, patients receiving monthly injections were more likely to experience endophthalmitis. Rates of serious systemic events were higher with Avastin than Lucentis, although the majority of the excess events in the Avastin group have not previously been associated with systemic anti-VEGF therapy. Two-year data are similar to what was observed with 12-months of treatment, in-line with our consultants' expectations, and unlikely to dramatically change the share of Avastin, Lucentis, or Eylea (REGN) for the treatment of AMD.

There are three key findings in the two-year results:

- Mean visual acuity gain was similar for Avastin and Lucentis through year two (Avastin-Lucentis difference of -1.4 letters, p=0.21).
- The mean gain was greater for monthly treatment than for as-needed treatment (difference -2.4 letters, p=0.046), although the magnitude of the difference at 2.4 letters was less than what our consultants have in the past said was borderline clinical significance.
- The proportion of patients who had SAEs was again higher for Avastin than Lucentis (39.9% vs. 31.7%, p=0.009), although similar to the one year data, the excess events have not been associated previously with systemic anti-VEGF therapy. Moreover, while the cumulative incidence of SAEs on Avastin compared to Lucentis increased, the annualized frequency difference actually decreased in year 2 compared to year 1.

Meningitis Compounding Scare Could Benefit Lucentis/Eylea

According to our physician experts, the 2012 deadly outbreak of meningitis associated with steroid injections traced to a Framingham, MA compounding pharmacy may have prompted some physicians to forego the use of compounded Avastin. Patients on Avastin may have switched to Lucentis or Eylea.

Lampalizumab Now In Phase III In Geographic Atrophy

Lampalizumab is an antigen-binding fragment of a humanized, monoclonal antibody directed against complement factor D, a rate-limiting enzyme involved in the activation of the alternative complement pathway (ACP) of the immune system. Genetic factors as well as hyperactivity of the ACP have been implicated in the development of AMD, including Geographic Atrophy (GA). Phase II trials were very encouraging, especially in patients with the complement factor I (CFI) biomarker. Phase III trials began in September 2014. We estimate lampalizumab sales of CHF200MM in 2019, and CHF400MM in 2020.

Phase II Results Demonstrated Impressive Results In Biomarker Positive Patients

Phase II results were presented in September 2013 at the American Society of Retina Specialists from MAHALO, a 143-patient study on the safety, tolerability and activity of lampalizumab, Roche's anti-factor D for the treatment of geographic atrophy secondary to age-related macular degeneration. Participants received an injection of lampalizumab in one eye either monthly or every other month for 18 months. The primary endpoint was change of GA area from baseline to month 18 as assessed via fundus autofluorescence (FAF). Efficacy as measured by FAF was observed beginning in month 6 and maintained through month 18. Lampalizumab showed an overall 20.4% reduction rate of GA at 18 months in monthly dosing. In a subpopulation of patients identified as having exploratory biomarkers, the GA progression rate was reduced by 44%; in a subset of these patients with better vision (20/50 to 20/100), progression was reduced by 54%. Fifty-seven percent of the patient sample was positive for the exploratory biomarkers; more information on these biomarkers will be revealed at a future medical conference. The data showed no unexpected or unmanageable serious adverse events associated with lampalizumab. The most frequently reported AE's were associated with the injection procedure. There were no AE's suspected to be caused by lampalizumab and no treatment discontinuations attributable to AE's.

In November 2013 at AAO, Roche presented the biomarker data for this trial. The data showed that in patients who tested positive for the genetic biomarker Complement Factor I (CFI), the reduction rate was 44% at 18 months in monthly dosing and 18% for every other month dosing. In the trial, 57% (of 93 patients sampled) tested positive for CFI; given the small trial size, it is unclear if this is a representative percentage of the overall population. Most interestingly, only the CFI-positive patients showed a treatment effect with lampalizumab. The pCR-based companion diagnostic represents an incremental revenue opportunity for Roche Diagnostics. Our consultant was extremely positive about the study results, having expected a 10-15% benefit going into the trial; so the 20% all-in reduction rate was considered highly successful. The biomarker potential was viewed as even more exciting, with the potential to identify patients that could gain a 40-50% slowing of GA, which would translate into perhaps 5-6 additional years of vision.

Phase III Trials Underway

In September of 2014, Roche initiated Phase III trials for lampalizumab in geographic atrophy. Chroma (GX29176) and Spectri (GX29185) are identically-designed, double-masked, randomized studies comparing 10mg dose lampalizumab administered every 4 or 6 weeks by intravitreal injection to sham injections. 936 patients will be enrolled in each study (188 biomarker-positive patients and 124 biomarker-negative patients each for the sham, lampalizumab q4w, and lampalizumab q6w treatment groups in each study). Key inclusion criteria are similar to that of the Phase II MAHALO study and include the presence of GA in both eyes with no history of wet AMD. The primary efficacy endpoint, a reduction in the rate of GA disease progression, will be evaluated at one year (week 48). It will be defined as the mean change in the GA lesion area of the chosen study eye from baseline and will be measured by fundus autofluorescence (FAF). Secondary objectives looking at the impact of lampalizumab treatment on patients' visual function will be assessed at 2 years (96 weeks). If successful, long-term follow patients will be enrolled into an open-label safety extension study.

Geographic Atrophy A Significant Unmet Need

According to our consultant, the prevalence of dry AMD is 8-9MM in the U.S. and 2-3MM with the advanced form, geographic atrophy (GA). Incidence of GA is estimated at 100-150,000/yr. The WW market is estimated to be 3x the U.S. market. GA is a slow, wearing-away of the retina, with the affected area exhibiting various shapes and patterns (hence the name), and the disease progresses over time (could be 10-12 years until complete loss of vision). There is also a genetic component to the disease. GA and Wet AMD can occur at the same time, but patients usually have one or the other. A bit more than half of GA patients may test positive for the biomarker, thus be candidates for treatment. The only treatment today is specialized vitamins, which at best provide a modest (5%) slowing in disease progression, thus providing a significant opportunity for better therapies. In addition, lampalizumab will be a good complement to Lucentis from a detailing perspective.

Neuroscience

Gantenerumab In Phase III For Alzheimer's; Crenezumab Misses Endpoints In Phase II Trial But Subgroup Trends Positive

Gantenerumab (anti-amyloid-beta) is being moved to Phase III trials in early AD patients (MARGUERITE RoAD) based on an interim look at the SCARLETT RoAD trial (prodromal patients). We estimate sales of gantenerumab of CHF25MM in 2018, and CHF75MM in 2020.

In July 2014, Roche presented Phase II crenezumab (anti-amyloid-beta) data in mild/moderate Alzheimer's patients (ABBY – cognition study, and BLAZE – biomarker study) at the AAIC meeting. In the larger study, ABBY, crenezumab did not meet the co-primary endpoints of ADA-cog12 (although a trend of slowing cognitive decline was seen) and CDR-SOB. In an analysis of patients with milder disease receiving the high dose of IV crenezumab, there was a trend toward slowing cognitive decline. In the BLAZE trials, a trend in slowing of cognitive decline was also seen in mild patients with high dose IV crenezumab. No significant adverse events were reported although there was one asymptomatic ARIA case. Biomarker results (change in brain amyloid) will be presented at a future meeting. Roche is evaluating this data to inform next steps, but has reiterated commitment to the Alzheimer's area. We estimate sales of crenezumab of CHF25MM in 2018, and CHF75MM in 2020.

Bitoperin Misses Endpoint In First Two Schizophrenia Studies; Four Other Trials Ongoing

Based on data suggesting that suprapharmacological doses of glycine improve the negative symptoms of schizophrenia, Roche developed the glycine reuptake inhibitor, bitoperin (RG1678). There are currently no approved drugs for the treatment of the negative symptoms of schizophrenia. Current therapies for schizophrenia increase dopamine in the striatum, where they impact positive symptoms. RG1678 mediates activation of NMDA receptors on GABA and dopaminergic neurons, increasing dopamine in both the nucleus accumbens and the prefrontal cortex to activate reward-centers and benefit negative symptoms.

In Phase II studies, RG1678 (10 and 30mg) improved negative symptoms after 8 weeks of treatment as assessed by both the PANSS negative symptom factor score and CGI-S/I clinical assessment score. There was also a trend towards improvements in function as assessed by PSP. Interestingly the 60mg dose did not show a benefit. Improvements in the positive symptoms of schizophrenia were improved at all doses tested.

In late 2010, Roche initiated six Phase III studies with Bitoperin: 3 in patients with negative symptoms and 3 in patients with sub-optimally controlled symptoms of schizophrenia. Change in PANNS negative or positive symptoms factor score at 12 or 24 weeks is the primary endpoint. The study design will allow for clinicians to choose which study a patient will be enrolled in and has been agreed to by the regulatory authorities in the U.S., E.U., and Japan. In January 2014, Roche announced that Bitoperin did not meet its primary endpoint in two of the studies in patients with negative symptoms of schizophrenia. The third study in negative symptoms as well as the 3 trials in sub-optimally controlled symptoms remain ongoing. We estimate bitoperin sales of CHF10MM in 2017, CHF20MM in 2018, and CHF40MM in 2020.

Diagnostics Division Well Positioned For Evolving Environment

In-Vitro Diagnostics (IVD) is a \$50B dollar industry. Roche has 20% of the IVD market with its next largest competitor holding only 12% market share. The IVD market is driven by labs' willingness to invest to address costs and improve efficiencies and payors' support for documented solutions that improve health economics and increase medical value. Additionally, emerging markets adopting western standards of care is expected to continue to drive expansion of the IVD market. New drug approvals are increasingly linked to companion diagnostics and are expected to increase the need for developing novel molecular diagnostics.

The Roche Diagnostics Division has four business units: Professional Diagnostics, Diabetes Care, Molecular Diagnostics, and Tissue Diagnostics. The former Applied Sciences group was largely incorporated into Molecular Diagnostics. Professional Diagnostics is the largest revenue-generating unit (almost 55% of total Diagnostic sales) with its growth fueled by the Cobas franchise. Diabetes Care is the second largest unit but has the slowest growth. The Accu-Chek franchise is the single biggest product line in the Diagnostic division. Molecular Diagnostics is benefitting from recent test approvals. Tissue Diagnostics is the smallest unit (6% of total Diagnostic sales) but has the fastest growth. The U.S. contributes roughly 25% of the division's sales; Europe/Middle East/Africa account for more than 50% of the business. Reimbursement pressures (E.U. austerity, Medicare cuts) and low-cost OUS competition have dampened overall industry growth. While pricing pressure (estimated at -2-3%) remains an overhang, offsetting volume gains powered by Affordable Care Act mandates in the U.S., further inroads in Emerging Markets, and an array of innovative new products improve the overall Roche Diagnostic picture and fuel at least modest top-line gains over the next few years. We estimate total Diagnostic division sales of CHF10,525MM (flat) in 2014, CHF10,955MM in 2015, CHF11,440MM in 2016, CHF12,290MM in 2018, and CHF13,140MM in 2020.

Professional Diagnostics: Leader In Immunoassay And Clinical Chem

Roche is in a leading position in all fast-growing professional market segments, including clinical chemistry, immunoassays, hematology, coagulation, urinalysis, point of care and automation, and covers the full spectrum of end-users (commercial labs, hospitals, physician offices, rapid clinics, and home use). Immunoassays are the largest growth driver within Roche Professional Diagnostics (RPD) and the company is committed to increasing medical value by adding improved and innovative immunoassays. For example, the sensitivity for detection of ovarian cancer has been improved to 89% from 43% with the addition of a new biomarker, HE4, to CA125. Roche also added a total vitamin D assay to complete its bone marker offering. Roche believes that tests with significant medical value will be reimbursed at a premium price (as much as 10-20x). RPD is focused on improving customer-specific efficiencies by integrating pre-analytics and IT systems with Cobas and other systems by offering IT solutions and consulting services.

In 2014, Roche will be rolling out its next-generation Cobas 6800/800 system which will have up to 3x higher throughput than the closest competitive systems and will enable very high volume (up to 1,000 samples in 8 hours) testing in Virology (HIV, HCV, HBV viral load), Blood Screening (viral panel), and Women's Health (CT/NG and HPV). The Virology and Blood Screening assays will be available on the 6800/8800 outside the US this year. We estimate RPD sales of CHF5,945MM (+4%) in 2014, CHF6,255MM in 2015, CHF6,600MM in 2016, CHF7,150MM in 2018 and CHF7,700MM in 2020.

IQuum Acquisition Brings POC Molecular to Roche

On April 7, 2014, Roche announced the acquisition of IQuum, a company focused on the development of a fast turnaround time (as fast as 20 minutes) POC molecular platform. This will give Roche platforms that address the extremes of the market. Strategically, IQuum reflects Roche's view that certain segments of molecular testing "make sense" being as close to the patient as possible, and IQuum's technology was described as uniquely well suited for this with its ease of use and turn-around time. Currently, only a flu A/B test is FDA cleared in the US. The near term plan is to seek FDA clearance of tests in the broader respiratory disease testing category including Strep A and RSV. The company will seek CLIA waiver on the platform, but will sell into the hospital segment in the meantime. Further along, tests for hospital acquired

infections MRSA and C. difficile will be developed. Interestingly, while prior to the acquisition IQuum was focusing development efforts on HIV viral load testing with an eye on the developing world, Roche noted that this market application is not a priority for them. Roche believes IQuum brings significant capabilities for a broad range of sensitivity and sample type requirements, and pointed to its pipeline as evidence of this.

Molecular Diagnostics: Expanding Test Menu Key To Growth; Companion Testing Also A Large Opportunity

Roche is the clear market leader (32% share) in the \$3B U.S. molecular diagnostics market (estimated to be growing +4%) with a strong presence in virology, blood screening, HPV, CT/NG, microbiology, and genomics and oncology. Virology and blood screening are the fastest growing segments with Roche committed to expanding its comprehensive virology test menu and offering the most complete blood screening menu in the industry. Examples include a highly sensitive and specific *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) screening kit for the Cobas 4800 leveraging its large installed base for the ~\$500MM CT/NG screening market, a primary DNA-based HPV screening test which was recently recommended an FDA Adcom, and a comprehensive HCV menu (11 different tests), to take advantage of the anticipated acceleration in HCV testing and treatment subsequent to the recent approval of next-generation therapies. Roche has also been successful in developing diagnostics for use in identifying specific oncology targets used to direct therapy, including BRAF-V600, KRAS, EGFR, P13KCA, and p53. We estimate Molecular Dynamics sales of CHF1,555MM in 2014 (-4%), CHF1,615MM in 2015, CHF1,665MM in 2016, CHF1,785MM in 2018, and CHF1,905MM in 2020.

Roche Molecules Start Development With Companion Diagnostics

Roche believes that developing companion diagnostics is a critical component of de-risking Phase III development. Therefore, all of Roche's drugs in development start out with a potential companion diagnostic. Some of these diagnostics do not progress, but of those that do, the benefits of development under one roof include lower costs and no IP concerns. Most therapies have been historically developed based on disease and not on the underlying molecular cause. Roche's approach to target therapies to well-defined populations requires matching a drug's mechanism of action to a diagnostic signature. Roche's combination of drug development and diagnostic divisions leverages technologies and regulatory expertise across five business areas that encompass the most relevant companion diagnostic platforms. Roche is working on the development of an optimal biomarker for PD-1. Difference that are still being refined include: use of stored versus fresh tissue samples, location of sample, and timing of sample collections.

Roche's lebrikizumab (asthma) and Zelboraf (melanoma) are examples of the successful collaboration between pharma and diagnostics. Early studies identified IL-13 as a gene of interest in asthmatics, resulting in the development of lebrikizumab (anti-IL13 antibody) for the treatment of asthma. As patients were treated with lebrikizumab, efficacy was stratified by blood periostin levels in asthmatics with patients with high periostin levels showing an improved response to anti-IL13 therapy. Several other key products in development with companion diagnostics are:

Molecules In Development With Companion Diagnostics

Compound	Potential Companion Diagnostic	Assay
Lebrikizumab (RG3637)	Periostin	ELISA
Navitoclax (RG7423)	Bcl-XL, MCL1	IHC
PI3K Inh (RG7231, RG7604) and PI3K/mTOR Inh (RG7422)	PI3KCA mutations	PCR, CNA
Anti-FGFR3 (RG7444)	FGFR3 expression	IHC/FACS
AKT Inhibitor (RG7440)	PTEN loss, PIK3CA mutation	IHC/PCR
MEK Inh (RG7420, RG7421)	KRAS, BRAF, NRAS mutation	PCR, CNA
Gantenerumab	Amyloid-beta	

Source: Company data

Roche is also involved in developing companion diagnostics for a number of external partners. With companion diagnostics becoming a critical component of the regulatory pathway for many drugs, partners have become increasingly willing to pay a premium for a reliable partner. Roche now partners with 40+ pharma companies, including: Pfizer (Crizotinib - ALK IHC), Syndax (Entinostat- E-cadherin), Aeterna Zentaris (AEZS 108- LHRH), Bayer (antibody-drug conjugate), Seattle Genetics & Millennium Pharma (ADCETRIS – CD30) and AstraZeneca (AZD9291, identify EGFR mutations).

HPV Approved As Primary Cervical Cancer Screen But Significant Adoption May Take Time

In April 2014, FDA approved Roche's HPV test to become the primary screening tool for cervical cancer. Management acknowledges that gaining FDA clearance is just one step in the process towards changing clinical practice; clearly, a bigger catalyst to primary screen adoption is the inclusion of this protocol into clinical guidelines. On this pursuit, management acknowledged that changing clinical behavior will "take quite a while" but believes the clinical and economic rationale in favor of this paradigm are compelling. A number of pilot studies in Europe (Sweden, Netherlands, UK and Italy) are ongoing and it is clear that testing practices vary greatly from country to country. Roche believes it will be able to continue to differentiate its HPV test offering through its test format which uniquely provides three results (genotype 16, 18, high risk genotype pool) in one test, the quality of its platforms, and the unparalleled clinical dossier based on the 47K patient ATHENA study.

Still Committed to Sequencing

Subsequent to the failed takeover attempt of Illumina, Roche has remained committed to sequencing in both research and clinical settings. In clinical, Roche continues to define its potential future role as one addressed through the IVD, not lab-developed test (LDT) channel. In September 2013, Roche entered into an agreement with Pacific Biosciences to develop sequencing products based on its "long-read" Single Molecule, Real-Time (SMRT) technology. Pacific Biosciences will develop and manufacture products for which Roche will have exclusive rights to worldwide distribution for their use in human in vitro diagnostics. Roche paid \$35MM upfront with an additional \$40MM payable tied to development milestones. The partnership with Pacific Biosciences reflects Roche's view that longer reads, fast runs, and fewer sample preparation requirements, are important characteristics of a IVD sequencing platform. Roche continues to support R&D efforts both internally and externally and continues to evaluate innovative sequencing technologies.

Roche expanded its sequencing efforts with the June 2014 acquisition of Genia, a privately-held next-generation sequencing company for \$125MM upfront cash and potential \$225MM in milestone payments. Genia's focus appears to be the leveraging of the long read capabilities of nanopores, with the scalability of semiconductor detection.

Tissue Diagnostics Focused On Oncology

Roche Tissue Diagnostics (RTD) generates >\$500MM in annual revenue (high-double digit growth rate) with more than 3,000 labs around the world and registered products in 63 countries. Roche is the leader in the tissue diagnostics space with 50% share of the \$800MM immunohistochemistry (IHC) market and 15% share of the \$250MM *in situ* hybridization (ISH) market. RTD is focused on advanced anatomic pathology in oncology. RTD markets several platforms to manage workflow and connectivity, including VANTAGE (pre-analytical), SYMPHONY (primary staining, H&E), NexES and BenchMark ULTRA (advanced staining), and Digital Pathology (imaging/reporting).

Novel companion diagnostics are expected to be a significant driver of growth. For example, the INFORM HER2 Dual ISH assay has been approved as a fully automated alternative to HER2 FISH. This assay improves efficiencies and ease of use for the pathologist to determine who is likely to benefit from anti-HER2 therapy. Similarly, the cMET assay is critical to guiding therapy in NSCLC patients. Roche is also partnering with and acquiring innovative companies to build its tissue diagnostics portfolio. Partnering with Clovis Oncology has given Roche a hENT1 assay to use as a companion diagnostic for CO-101 in pancreatic cancer, while the University of Michigan has contributed to developing an assay to define ERG status and predict outcomes in prostate cancer patients. The acquisition of MTM Labs expanded RTD's portfolio by adding assays for the detection of p16 and Ki-67 in cervical cancer. We estimate Tissue Diagnostic sales of CHF695MM (+5%) in 2014, CHF740MM in 2015, CHF785MM in 2016, CHF875MM in 2018, and CHF965MM in 2020.

Diabetes Trends Disappointing But Company Remains Optimistic On Future

The diabetes testing market has been particularly difficult reflecting E.U. austerity measures, and Medicare reimbursement cuts on diabetes testing products (strips, lancets, etc.). Despite these pricing issues, Roche remains committed to the business (good CF and margins) and believes that there are two opportunities: 1) for innovative products, which will garner premium pricing for a documented feature/benefit (e.g. CGMs, unique GMs, insulin pumps, etc.) and 2) a low-cost market for "no-frills" monitors and test strips (especially appealing to emerging markets). As an example, the new Accu-Chek Mobile glucose monitor is currently growing at a 20%+ pace. Management is also highly focused on streamlining costs, citing the recent consolidation of three R&D centers to two and more targeted efforts such as closing of the 24 hour U.S. call center which is no longer feasible given recent Medicare reimbursement cuts. We estimate Diabetes sales of CHF2,330MM (-5%) in 2014, CHF2,345MM in 2015, CHF2,390MM in 2016, CHF2,480MM in 2018, and CHF2,570MM in 2020.

Emerging Markets Offer Potential For Diagnostics Growth

In 2013, only 25% of Roche Diagnostics sales were generated in North America with 46% in EMEA, 5% in Japan, 16% in Asia Pacific, and 8% in Latin America. Growth in Asia Pacific (+14%) and Latin America (+13%) is substantially outpacing growth for

the diagnostics division as a whole (+4%). Within Asia, Roche is focused on placing instruments, improving reagent flow through and differentiating themselves through superior service. In China, growth will likely be driven by a rapidly aging population, urbanization and rising affluence, and improving access to healthcare. Roche is currently leading the IVD market in China (\$18B in 2010) with 17% market share and is outgrowing the market with a 2005-2010 CAGR of 32%. Roche's early-comer advantage, focus on immunochemistry, and best-in-class service are expected to continue to increase share in IVD, blood screening, life sciences, and diabetes care as they expand to tier 2 hospitals, tier 3-4 cities, and commercial labs.

Roche 2013-20 Balance Sheet Analysis (CHF MM)

	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Assets:								
Cash and Cash Equivalents	4,000	2,540	5,045	9,118	13,843	19,336	25,584	32,331
Inventories	5,906	6,450	6,150	6,250	6,250	6,300	6,400	6,450
Accounts Receivable	8,808	8,600	8,750	9,000	9,300	9,650	10,000	10,350
Marketable Securities	7,935	6,000	6,000	6,000	6,000	6,000	6,000	6,000
Current Income Tax Assets	218	200	200	200	200	200	200	200
Other Current Assets	2,297	2,400	2,100	2,200	2,250	2,350	2,400	2,500
Total Current Assets	29,164	26,190	28,245	32,768	37,843	43,836	50,584	57,831
Property, Plant & Equipment - Net	15,760	16,150	16,400	16,950	17,500	18,150	18,800	19,400
Goodwill	7,145	7,300	7,300	7,250	7,250	7,200	7,200	7,150
Intangibles	3,944	3,900	3,900	3,800	3,800	3,700	3,700	3,700
Deferred Income Tax Assets	4,707	5,200	5,200	5,200	5,200	5,200	5,200	5,200
Other Long-Term Assets	811	800	800	800	800	800	800	800
Post-employment Benefit Assets	636	650	650	650	650	650	650	650
Total Non-Current Assets	33,003	34,000	34,250	34,650	35,200	35,700	36,350	36,900
Total Assets	62,167	60,190	62,495	67,418	73,043	79,536	86,934	94,731
Liabilities:								
Short-Term Debt	2,220	5,500	5,000	5,000	5,000	5,000	5,000	5,000
Current Income Tax Liabilities	1,805	2,500	2,500	2,500	2,500	2,500	2,500	2,500
Provisions	2,148	2,000	2,000	2,000	2,000	2,000	2,000	2,000
Accounts Payable	2,162	2,050	1,950	2,000	2,000	2,000	2,050	2,050
Other Current Liabilities	7,425	6,750	6,400	6,500	6,500	6,600	6,700	6,750
Total Current Liabilities	15,760	18,800	17,850	18,000	18,000	18,100	18,250	18,300
Long-term Debt	16,423	19,000	17,000	16,000	15,500	15,000	14,500	14,000
Deferred Income Tax Liabilities	1,282	1,300	1,300	1,400	1,400	1,500	1,500	1,500
Post-employment Benefit Liabilities	6,062	7,000	7,000	7,000	7,000	7,000	7,000	7,000
Provisions	1,097	1,500	1,500	1,500	1,500	1,500	1,500	1,500
Other Long-Term Liabilities	302	300	300	300	300	300	300	300
Total Long-Term Liabilities	25,166	29,100	27,100	26,200	25,700	25,300	24,800	24,300
Total Liabilities	40,926	47,900	44,950	44,200	43,700	43,400	43,050	42,600
Net Equity	21,241	12,290	17,545	23,218	29,343	36,136	43,884	52,131

Source: Company data, Cowen and Company estimates

Roche 2013-20 Working Capital Analysis (CHF MM)

	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Inventories	5,906	6,450	6,150	6,250	6,250	6,300	6,400	6,450
COGS	11,892	11,631	11,036	11,246	11,235	11,370	11,520	11,621
Inventory Turns	2.0	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Months	6.0	6.7	6.7	6.7	6.7	6.7	6.7	6.7
Accounts Receivable	8,808	8,600	8,750	9,000	9,300	9,650	10,000	10,350
Sales	46,780	46,175	46,865	48,430	49,950	51,880	53,715	55,460
Receivables Days	68.7	68.0	68.0	68.0	68.0	68.0	68.0	68.0
Other Current Assets	2,297	2,400	2,100	2,200	2,250	2,350	2,400	2,500
% of Sales	4.9%	5.2%	4.5%	4.5%	4.5%	4.5%	4.5%	4.5%
Accounts Payable	2,162	2,050	1,950	2,000	2,000	2,000	2,050	2,050
COGS	11,892	11,631	11,036	11,246	11,235	11,370	11,520	11,621
Payables Days	66.4	65.0	65.0	65.0	65.0	65.0	65.0	64.0
Other Current Liabilities	7,425	6,750	6,400	6,500	6,500	6,600	6,700	6,750
% of COGS	62.4%	58.0%	58.0%	58.0%	58.0%	58.0%	58.0%	58.0%
Net Working Capital (Ex. Cash, Debt)	CHF 7,424	CHF 8,650	CHF 8,650	CHF 8,950	CHF 9,300	CHF 9,700	CHF 10,050	CHF 10,500

Source: Company data, Cowen and Company estimates

Roche 2013-20 Cash Flow Analysis (CHF MM)

	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Operating Activities								
Net Income (Operations)	17,904	18,175	18,934	19,839	21,200	22,735	24,150	25,454
Depreciation & Amortization	2,381	2,400	2,450	2,500	2,550	2,600	2,650	2,700
Change in Working Capital	506	(1,226)	0	(300)	(350)	(400)	(350)	(450)
Payments for Defined Benefit Plans	(483)	(500)	(500)	(500)	(500)	(500)	(500)	(500)
Restructuring, Legal, Other Provisions	(1,000)	(500)	(500)	(500)	(500)	(500)	(500)	(500)
Other, net	(195)	0	0	0	0	0	0	0
Income Taxes Paid	(3,341)	(3,981)	(4,014)	(4,248)	(4,586)	(4,965)	(5,315)	(5,641)
Net Cash Provided By Operations	15,772	14,368	16,369	16,791	17,814	18,971	20,135	21,064
Investing Activities								
Capital Expenditures Net	(2,451)	(2,500)	(2,550)	(2,600)	(2,650)	(2,700)	(2,750)	(2,800)
Asset Sales (net)	(338)	0	0	0	0	0	0	0
Interest and Dividend Expense	51	0	0	0	0	0	0	0
Acquisitions	(233)	(7,800)	0	0	0	0	0	0
Net Purchases/Sales Mkt Securities	1,644	0	0	0	0	0	0	0
Other, net	25	0	0	0	0	0	0	0
Net Cash Provided By Investing	(1,302)	(10,300)	(2,550)	(2,600)	(2,650)	(2,700)	(2,750)	(2,800)
Financing Activities								
Long-Term Debt Financings (net)	0	0	0	0	0	0	0	0
Increase (Decrease) In Other LTD	(6,633)	2,500	(2,000)	(1,000)	(1,000)	(1,000)	(1,000)	(1,000)
Increase (Decrease) In STD	555	\$500	(\$500)	0	0	0	0	0
Dividends Paid	(6,362)	(6,728)	(7,065)	(7,418)	(7,789)	(8,178)	(8,587)	(9,016)
Interest paid	(1,299)	(1,300)	(1,250)	(1,200)	(1,150)	(1,100)	(1,050)	(1,000)
Other, net	(930)	(500)	(500)	(500)	(500)	(500)	(500)	(500)
Net Cash Provided By Financing	(14,669)	(5,528)	(11,315)	(10,118)	(10,439)	(10,778)	(11,137)	(11,516)
Cash and Equivalents on January 1	4,530	4,000	2,540	5,045	9,118	13,843	19,336	25,584
Net Change in Cash & Equivalents	(199)	(1,460)	2,505	4,074	4,725	5,493	6,248	6,747
Ending Cash & Equivalents	4,000	2,540	5,045	9,118	13,843	19,336	25,584	32,331

Source: Company data, Cowen and Company estimates

RHHBY DCF Analysis

Assumptions:			Output											
Share Price	\$37		Equity Value (\$MM)	\$288,810										
			Estimated Share Price	\$42										
Discount Rate	6.8%		Net Cash (\$MM)	(\$7,580)										
Shares Outstanding (000)	863		Enterprise Value (\$MM)	\$296,390										

RHHBY DCF

(CHF MM)	2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021P	2022P	2023P	2024P	2025P	Terminal
Total Revenues	48,612	48,473	48,875	50,550	52,160	54,180	56,105	57,940	59,678	61,469	63,313	65,212	67,168	
% Change	+2%	-0%	+1%	+3%	+3%	+4%	+4%	+3%	+3%	+3%	+3%	+3%	+3%	+3%
Cost of Goods	11,892	11,631	11,036	11,246	11,235	11,370	11,520	11,621	11,836	12,294	12,663	13,042	13,424	
Gross Profit	36,720	36,842	37,839	39,304	40,925	42,810	44,585	46,319	47,743	49,175	50,650	52,170	53,735	
Gross Margin - Total	75.5%	76.0%	77.4%	77.8%	78.5%	79.0%	79.5%	79.9%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%
SG&A	10,116	9,852	9,980	10,340	10,525	10,775	11,035	11,365	11,936	12,294	12,663	13,042	13,434	
% of Revs	20.8%	20.3%	20.4%	20.5%	20.2%	19.9%	19.7%	19.6%	20.0%	20.0%	20.0%	20.0%	20.0%	20.0%
R&D	8,700	8,815	8,925	9,125	9,200	9,300	9,400	9,500	9,847	10,142	10,447	10,760	11,083	
% of Revs	17.9%	18.2%	18.3%	18.1%	17.6%	17.2%	16.8%	16.4%	16.5%	16.5%	16.5%	16.5%	16.5%	16.5%
Operating Expenses	18,816	18,667	18,905	19,465	19,725	20,075	20,435	20,865	21,783	22,436	23,109	25,802	24,516	
% of Revenues	38.7%	38.5%	38.7%	38.5%	37.8%	37.1%	36.4%	36.0%	36.5%	36.5%	36.5%	36.5%	36.5%	36.5%
Operating Income	17,904	18,175	18,934	19,839	21,200	22,735	24,150	25,454	25,960	26,739	27,541	28,367	29,218	
% Operating Margin	36.8%	37.5%	38.7%	39.2%	40.6%	42.0%	43.0%	43.9%	43.5%	43.5%	43.5%	43.5%	43.5%	43.5%
Non-operating income	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
EBIT	17,904	18,175	18,934	19,839	21,200	22,735	24,150	25,454	25,960	26,739	27,541	28,367	29,218	
% of Revs	36.8%	37.5%	38.7%	39.2%	40.6%	42.0%	43.0%	43.9%	43.5%	43.5%	43.5%	43.5%	43.5%	43.5%
D&A	2,381	2,400	2,450	2,500	2,550	2,600	2,650	2,700	2,750	2,800	2,850	2,900	2,900	
EBITDA	20,285	20,575	21,384	22,339	23,750	25,335	26,800	28,154	28,710	29,539	30,391	31,267	32,118	
% of Revs	41.7%	42.4%	43.8%	44.2%	45.5%	46.8%	47.8%	48.6%	48.1%	48.1%	48.0%	47.9%	47.8%	
Net Interest Income (Expense)	(1,699)	(1,293)	(1,480)	(1,370)	(1,260)	(1,150)	(1,040)	(930)	(900)	(850)	(800)	(750)	(700)	
Pre-Tax Income	16,205	16,882	17,454	18,469	19,940	21,585	23,110	24,524	25,060	25,889	26,741	27,617	28,518	
Taxes	3,679	3,981	4,014	4,248	4,586	4,965	5,315	5,641	5,971	6,150	6,334	6,524	6,720	
Income Tax Rate	22.7%	23.6%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%
Minority Interest	210	213	235	245	255	265	275	285	295	305	315	325	335	
Net Income	12,316	12,688	13,204	13,976	15,099	16,356	17,520	18,599	18,794	19,434	20,092	20,768	21,463	
% of Revs	25.5%	26.2%	27.0%	27.6%	28.9%	30.2%	31.2%	32.1%	31.5%	31.6%	31.7%	31.8%	32.0%	
% Change	+7%	+3%	+4%	+6%	+8%	+8%	+7%	+6%	+1%	+3%	+3%	+3%	+3%	+3%
NOPAT	14,225	14,194	14,919	15,591	16,614	17,771	18,835	19,814	19,989	20,589	21,207	21,843	22,498	
<i>Adjustments:</i>														
Capex	(2,451)	(2,500)	(2,550)	(2,600)	(2,650)	(2,700)	(2,750)	(2,800)	(2,850)	(2,900)	(2,950)	(3,000)	(3,000)	
Depreciation & Amortization	2,381	2,400	2,450	2,500	2,550	2,600	2,650	2,700	2,750	2,800	2,850	2,900	2,900	
Change In Working Capital	506	(1,226)	0	(300)	(350)	(400)	(350)	(450)	(300)	(300)	(250)	(250)	(200)	
Operating Free Cash Flow	12,762	11,982	13,104	13,576	14,648	15,856	17,070	18,049	18,394	19,034	19,742	20,418	21,163	31,121

Source: Company data, Cowen and Company estimates

Roche Key Upcoming Events

Time Frame	Event Type	Product	Event
2014	Clinical	ACE910 (w/Chugai)	Phase I Hemophilia data at ASH (Dec 6-9)
		Alectinib (w/Chugai)	Phase I/II Japan update (ALK+ NSCLC) at MSTO (Oct 30 - Nov 1)
		Avastin	BEYOND study in NSCLC (China) at MSTO (planned)
		Etrolizumab	Phase studies (6) starting in 2014, one presently enrolling
		Gazyva	GREEN study G + various chemo backbones at ASH
		Kadcyla/Perjeta	MARIANNE (1st line mBC) read-out by YE
		Lampalizumab	Phase III design presentation at EURETINA, Phase III initiation
		PD-L1 immunotherapy	OAK Phase III trial started; data on new tumor type in Q4:14
		PI3 kinase	Solid tumor data readout possible
		RG7090 (mGluR5 Antagonist)	Phase II MARIGOLD data (treatment-resistant depression) at ECNP (Oct 18-21)
	Regulatory	Avastin	E.U. approval for glioblastoma (CHMP negative opinion, re-examinations ongoing)
		Avastin	E.U. approval for cervical cancer
		Avastin	U.S. (priority review) approval for pt-resistant ovarian cancer
		Pirfenidone	PDUFA 11/23/14
		Zelboraf+Cobimetinib (w/Exelixis)	U.S. filing for 1st-line BRAF+ melanoma in Q4:14

Source: Company data

ROCHE R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Arthritis/Inflammation							
Actemra (MRA)			.	.	Jun-13		Humanised anti-IL-6 recombinant Mab; DMARD IR 1st line biologic; early RA (EU, 6/2013); PIII giant cell arteritis; PII systemic sclerosis; with Chugai
Suvenyl			.	.			Enthesopathy; with Chugai
Blood And Clotting Products							
RG6013		.	.		>2017		FIXa/FX bispecific Mab; hemophilia A; with Chugai
Cancer/Oncology/Hematology							
Gazyva			.		2013->2017		Obinutuzumab (RG7159/GA101); CD20 HuMab; approved in U.S., CHMP recommended approval May, 2014 for CLL; PIII front-line and relapsed indolent NHL, diffuse large B-cell lymphoma
Avastin			.	.	.		Anti-VEGF monoclonal antibody; combination therapies; PI/II combo with PD1
Zelboraf		.	.	.	Apr-14		RG7204; B-RAF kinase inhibitor; filed April 2014 for adjuvant metastatic melanoma; PIII in combo with RG7421 for solid tumors; PI combo with PD-L1 for metastatic melanoma adj., BRAF mutation positive; with Plexxikon
RG7853			.		Oct-13		Alectinib; ALK inhibitor; NSCLC; with Chugai; filed in Japan
Perjeta			.		2015->2017		RG1273; PIII for early HER2+ breast cancer, HER2+ gastric cancer; 2nd line HER2+ mBC
RG7421		.	.	.	2014		Cobimetinib + Zelboraf; MEK inhibitor; metastatic melanoma; 495-patient PIII trial showed increase in PFS
Kadcyla (RG3502/T-DM1)			.		2015->2017		PIII for 1st line metastatic BC HER2+, HER2+ gastric cancer; HER2+ adjuvant; PII HER2+ early BC, PIII in combo with Perjeta for HER2+ BC adjuvant and neoadjuvant
RG7446		.	.		>2017		PD-L1 monoclonal antibody; PIII for 2nd line NSCLC; PII for 2nd/3rd line NSCLC, bladder cancer; PII combo therapy with Avastin for RCC; PI combo therapies with Zelboraf, Avastin, Tarceva, and cobimetinib; tumor immunotherapy; solid tumors
RG7601		.	.		2016->2017		Bcl-2 inhibitor; PII/III relapsed or refractory chronic lymphocytic leukemia; PII DLBCL; PI in hematological indications, combo with Gazyva, CLL
Erivedge (Vismodegib)			.		>2017		RG3616; small molecule; hedgehog pathway inhibitor; PII for acute myelogenous leukemia
RG7155		⇒	.		>2017		CSF-1R Mab; PVNS
RG7221		⇒	.		>2017		ANG2-VEGF huMAb; CRC
RG7321		.			>2017		Pictilisib; P13 kinase inhibitor; solid tumors
RG7440		.			>2017		Ipatasertib (AKT inhibitor); solid tumors
RG7593		.			>2017		Pinatuzumab; anti-CD22 monoclonal antibody; hematologic malignancies
RG7596		.			>2017		Polatuzumab; antibody drug conjugate; hematologic malignancies
RG7597		.			>2017		Anti-HER3/EGFR monoclonal antibody; metastatic epithelial tumors
RG7599		⇒	.		>2017		NaPi2b antibody drug conjugate; NSCLC and ovarian cancer
RG7604		⇒	.		>2017		PI3 kinase inhibitor; solid tumors
RG7686		.			>2017		Anti-Glycan Mab; metastatic liver cancer; with Chugai
P13K inh.		.					Solid tumors; with Chugai

ROCHE R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
RG6016		.					LSD1 inhibitor; AML
RG7116		.					HER3 Mab; solid tumors
RG7304		.					Solid tumors; Raf/MEK dual inhibitor
RG7388		.					MDM2; solid and hemalological tumors
RG7450		.					Stap 1 antibody drug conjugate; prostate cancer
RG7458		.					MUC16 antibody drug conjugate; ovarian cancer
RG7600		.					Antibody drug conjugate; pancreatic and ovarian cancer
RG7636		.					ETBR antibody drug conjugate; metastatic melanoma
RG7666		.					P13K inhibitor; progressive or recurrent high-grade glioblastoma
RG7741		.					Chk1 inhibitor; solid tumors and lymphoma
RG7775		.					MDM2 (4) antagonist IV prodrug; AML
RG7813		.					CEA IL2v; solid tumors
RG7841		.					ADC; solid tumors
RG7842		.					ERK inhibitor; solid tumors
RG7845		.					Hematological tumors
RG7882		.					ADC, ovarian cancer
Cardiovascular							
RG1512		.					Inclacumab; P-selectin huMAb; peripheral vascular disease (PVD), ACS; with Genmab; exploring partnering options
Central Nervous System							
Gantenerumab			.		>2017		RG1450; monoclonal antibody; anti-amyloid B peptide antibody; Alzheimer's disease
RG1594			.		2015		Ocrelizumab; humanized anti-CD20 monoclonal antibody; PPMS, RMS
RG1678		.	.		>2017		Bitoperitin; small molecule; inhibitor of glycine transporter 1; PII for OCD; with Chugai
RG1577		.	.		>2017		Monoamine oxidase type B (MOA-B) inhibitor; Alzheimer's disease
RG1578		.	.		>2017		Decoglurant; mGluR2 NAM; depression
RG1662	⇒	.					GABRA5 negative allosteric modulator (NAM); Down syndrome
RG7090		.			>2017		Basimglurant; mGluR5 NAM; treatment resistant depression; fragile X syndrome
RG7314		.			>2017		V1 receptor antagonist; autism
RG7412		.			>2017		Crenezumab; monoclonal antibody; anti-Abeta; Alzheimer's disease
RG7203		.					PDE10A inhibitor; schizophrenia
RG7342		.					mGlu5 PAM; schizophrenia
RG7410		.					TARR1 ago; schizophrenia
RG7800		.					SMN2 splicing modifier; spinal muscular atrophy
RG7935		.					a-synuclein Mab; Parkinson's Disease
Dermatologic							
IL-31R Mab		.					Atopic dermatitis; with Chugai
Diabetes							
RG7697		.					Type 2 diabetes; GIP/GLP-1 dual agonist
Gastrointestinal							
RG7413		⇒	.		>2017		Entolizumab; monoclonal antibody; rhuMAb Beta7; ulcerative colitis
Immunological							
Anti-IL-6 receptor monoclonal antibody			.				Neuromyelitis optica; with Chugai
RG7624		.					IL-17 Mab; autoimmune diseases

ROCHE R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
URAT1 inhibitor		.					Gout; with Chugai
Infectious Disease							
RG7128		.			>2017		Mericitabine; polymerase inhibitor; HCV; with Pharmasset
RG7227		.			>2017		Danoprevir; protease inhibitor; HCV; with InterMune
RG7667		.			>2017		CMV disease
RG7745		.			>2017		Flu A MAB; influenza
RG7790		.					Setrobuvir; hepatitis C
RG7929		.			>2017		LptD antibiotic
RG7795	.						TLR7 agonist; HBV
Ophthalmology							
Lucentis	.				Aug-14		Sustained delivery AMD/RVO/DME; sBLA filed for label expansion for treatment of diabetic retinopathy
Lampalizumab			⇒	.	>2017		RG7417; anti-factor D, geographic atrophy associated with AMD
RG7716	.						Wet AMD
Respiratory							
RG3637		.	.	.	2016->2017		Lebrikizumab; anti-IL 13; severe asthma; PII idiopathic pulmonary fibrosis
RG7449		.			>2017		Quilizumab; anti-M1 prime Mab; asthma
Urology							
RG7641	.						Kidney disease
Total Drugs In Development	0	28	27	13	6		74

Progress since last update in bold; movement marked by arrow

Investor Relations Contact: Karl Mahler 41-61-687 8503

Sanofi (ADR)

Await Clarity On Growth Recovery, Pipeline Progress

Price: \$56.43 (09/30/2014)
Price Target: \$59.00 (Prior \$55.00)

MARKET PERFORM (2)

Steve Scala, R.Ph., CFA

617.946.3923
steve.scala@cowen.com

Kathleen Miner, R.Ph., CFA

617.946.3857
kathy.miner@cowen.com

Jean Perreault

617.946.3967
jean.perreault@cowen.com

Key Data

Symbol	NYSE: SNY
52-Week Range:	\$57.42 - 47.06
Market Cap (MM):	\$149,359.0
Net Debt (MM):	\$6,333.0
Cash/Share:	NA
Dil. Shares Out (MM):	2,646.8
Enterprise Value (MM):	NA
ROIC:	NA
ROE (LTM):	NA
BV/Share:	NA
Dividend:	\$1.91
Yield:	3.38%

FY (Dec)	2013A	2014E	2015E
Earnings Per Share			
Q1	€1.20	€1.17A	€1.28
Prior Q1	€1.22	-	€1.23
Q2	€1.12	€1.17A	€1.22
Prior Q2	€1.11	-	€1.08
Q3	€1.36	€1.43	€1.52
Prior Q3	€1.35	€1.46	€1.54
Q4	€1.37	€1.43	€1.53
Prior Q4	-	€1.45	€1.55
Year	€5.05	€5.20	€5.55
Prior Year	-	€5.25	€5.40

Business EPS excludes amortization and one-time items.

Revenue (MM)

Year	€32,951.0	€33,520.0	€35,040.0
Prior Year	-	€33,200.0	€34,630.0

The Cowen Insight

Good diversified business, but subpar near-term EPS growth, mixed pipeline prospects, and potential competition for Lantus are overhangs.

While EPS growth returned in Q4:13, 2014 prospects are lackluster, with EPS growth of only 3%. Lantus' outlook appears on solid footing for now, but franchise extension strategies are not convincing and new competition is on the way. Pipeline progress continues at Sanofi, but is stronger at other companies. Sanofi's diversification and emerging markets exposure are distinguishing points, but don't offset risks. Sanofi's valuation looks fair but not overly compelling.

Post Modest Growth In 2014, Sustainable Recovery Should Begin In 2015

We forecast a sales and EPS rebound in 2014, with sales estimated to be up 2% and EPS forecast at €5.20 (+3%). Thereafter, EPS growth should range between 2-9% on 1-5% top-line growth, but our conviction in these prospects is not high. 2016 looks to be the most challenging year as Lantus competition enters the market.

New Products Have Moderate Potential

Alirocumab (PCSK9) has met efficacy endpoints in ten Phase III trials to date; U.S. and EU filings are expected by year end. Aubagio (MS) has enjoyed a better-than-expected rollout, and Lemtrada could be important in a subset of MS patients.

Lyxumia (diabetes) is rolling out in the E.U., but the filing has been delayed in the U.S. Lantus/Lyxumia (LixiLan) combination started Phase III in Q1:14 (filing possible by YE 2015), and Toujeo (U300) was filed in the U.S. and E.U. in Q2:14. Cerdelga (Gaucher's disease; U.S. approved August 2014), and Dengue vaccine (filing expected early 2015) are significant opportunities.

Diabetes Franchise Powerful, Although Lantus Competition A Lingering Risk

Sanofi has many efforts to protect its diabetes franchise, including new products, bundling existing products, and emerging market distribution. Lantus's patent expiration in 2014-15 is a risk, but the legal action against LLY's 505(b)2 filing of its biosimilar glargine should extend Lantus exclusivity by up to 18 months in the U.S. (mid-2016). However, Lilly's biosimilar has gained tentative approval in the U.S. and full approval in the EU, with launch expected mid-2015 post 2/15 patent expiry.

Diversification A Strength

Sanofi has built a presence in emerging markets through strategic acquisitions and expansion of pediatric vaccines. Merial Animal Health and Consumer Health are in need of new products to spur growth. Two recent launches hold promise: NexGard (fleas/ticks) and Nasacort (seasonal allergy).

Modest EPS Growth In 2014; Stronger Gains Expected in 2015 and 2017-2020

3% EPS Gain On Tap In 2014

EPS growth returns in 2014, to €5.20 (+3%), driven by a 2% increase in sales (to €33,520MM). Cost of sales as a percentage of sales is pegged at 32.3% versus 33.4% in 2013. We forecast a 1% increase in both R&D (to €4.835B) and SG&A (to €8.685B). Net interest expense is estimated to decline by €158MM, and the tax rate may increase by 0.9pp to 25.1%.

Sanofi 2014 Guidance Versus Cowen Estimates

	2014 Guidance	Our 2014 Forecast
Cost of sales as % of sales	Improvement versus 2013 @ CER	-1.1pp
Other revenues	NA	€294MM
SG&A as % of sales	Stable ratio of sales	25.9%
R&D	Slight increase in absolute terms but less than €5B	€4.835B
Associates line contribution from Regeneron	€45MM	
Tax	25.0%	25.1%
Business EPS	6-8% higher @ CER	+3% to €5.20 including Fx

Bold= revised

Source: Cowen and Company

Sanofi Cost Of Sales Versus Gross Margin (€MM)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CAGR 2014-20	CAGR 2013-20
Net sales	€ 32,951	€ 33,520	€ 35,040	€ 35,465	€ 36,920	€ 38,490	€ 40,185	€ 42,125	4%	4%
Change Y/Y	-6%	2%	5%	1%	4%	4%	4%	5%		
Other revenues	355	294	240	230	220	210	200	190	-7%	-9%
Cost of sales	10,992	10,839	11,115	11,210	11,575	11,935	12,320	12,685		
Cost of sales as % of net sales	33.4%	32.3%	31.7%	31.6%	31.4%	31.0%	30.7%	30.1%		
Gross profit	22,314	22,975	24,165	24,485	25,565	26,765	28,065	29,630	4%	4%
GPM	67.7%	68.5%	69.0%	69.0%	69.2%	69.5%	69.8%	70.3%		

Source: Company data, Cowen and Company

Sanofi 2013-15 Estimated Divisional P&L Buildup (€MM)

	2013			2014E			2015E		
	Sales	Op. Inc.	Est. P.M.	Sales	Op. Inc.	Est. P.M.	Sales	Op. Inc.	Est. P.M.
Pharma	€ 22,621	€ 7,374	28.9%	€ 22,315	€ 7,421	29.1%	€ 22,830	€ 8,495	30.5%
Vaccines	3,716	909	24.5%	3,990	987	24.7%	4,700	1,335	28.4%
Animal Health	1,985	502	25.3%	2,000	499	25.0%	1,985	390	19.6%
Total Sanofi	€ 32,951	€ 9,314	28.3%	€ 33,520	€ 9,482	28.3%	€ 35,040	€ 10,370	29.6%
Share of profits/loss from associates and JVs	(€ 85)			(€ 120)			(€ 190)		
Net income attributable to non controlling interests	€ 162			€ 95			€ 80		
Financial Income	(612)			(565)			(490)		
Interest Expense	109			220			210		
Non-Op Inc./Exp)	(503)			(345)			(280)		
Pretax Income (% of sales)	€ 8,811	26.7%		€ 9,137	27.3%		€ 10,090	28.8%	
Tax Rate	24.2%			25.1%			28.0%		
Net Income (% of sales)	€ 6,677	20.3%		€ 6,848	20.4%		€ 7,265	20.7%	
EPS Basic	€ 5.05			€ 5.20			€ 5.55		
Shares Basic (MM)	1,323			1,316			1,310		

Source: Cowen and Company estimates

7% EPS Growth Expected In 2015, Slowing To 2% In 2016, Then Recovery To +8-9% For 2017-2020

In 2015 EPS growth is expected to ramp +7% to €5.55 on sales growth of 5% (to €35,040MM) with margin expansion (GPM and Operating) slightly offset by a 2.9pp increase in the tax rate to 28.0%.

In 2016, we forecast sales of €35,465MM (+1%) and EPS of €5.65 (+2%) reflecting the impact of competitive pressures on Lantus. and stable operating margins. For 2017-2020 we expect EPS growth of 8-9% on 4-5% top-line growth. We forecast expansion in gross profit margin of 0.2-0.5 percentage point in each year from 2017 to 2020. We forecast annual increases in operating margin on the order of 0.9-1.2pp, a tax rate of 28%, and a stable share count. All told, we forecast EPS at €6.10 (+8%) in 2017, €6.60 (+8%) in 2018, and €7.85 (+9%) in 2020, implying 7% compound annual growth during 2014-2020.

Speculation On EPS Outcomes (€)

	2013	2014E	2015E	2016P	2017P	2018P	2019P	2020P	CAGR 2013-16	CAGR 2013-20	CAGR 2014-20 Notes
Lantus	€ 1.37	€ 1.52	€ 1.61	€ 1.44	€ 1.34	€ 1.25	€ 1.15	€ 1.05	2%	-4%	-6% - Basal insulin; 17% share 7/14, SoloStar Pen 20.5% share; pat. exp. 8/2014 + 6 months pedi but generic competition likely limited
Plavix*	0.44	0.42	0.40	0.37	0.35	0.33	0.31	0.30	-5%	-5%	-6% - U.S. patent expired 5/12 including pedi exclusivity
Lovenox	0.40	0.38	0.34	0.32	0.29	0.27	0.25	0.24	-8%	-7%	-8% - Brand retains 30% share of market, authorized generic 22% (recorded in generics line) or 52% of molecule sales
Apridra	0.07	0.08	0.09	0.10	0.12	0.13	0.14	0.16	15%	13%	12% - Rapid acting insulin; <1% of insulin market
Aprovel*	0.21	0.18	0.17	0.16	0.15	0.15	0.14	0.15	-9%	-5%	-3% - U.K., France, Germany patent expiration 8/12; other countries 3/11
Depakine	0.10	0.09	0.10	0.10	0.11	0.12	0.12	0.13	3%	4%	5% - Valproate; epilepsy and mood stabilization
Amaryl	0.09	0.09	0.08	0.09	0.09	0.09	0.09	0.10	-1%	1%	2% - QD sulphonylurea for diabetes
Multaq	0.06	0.07	0.06	0.06	0.06	0.06	0.05	0.05	-1%	-3%	-4% - Novel anti-arrhythmic for atrial fibrillation
Tritace	0.07	0.07	0.06	0.05	0.04	0.04	0.03	0.03	-11%	-13%	-14% - ACE inhibitor, generics launched
Eloxatin	0.05	0.04	0.04	0.04	0.03	0.03	0.03	0.03	-10%	-10%	-8% - Generics off market July 2010-Aug 2012, but generics now re-entered
Taxotere	0.10	0.07	0.06	0.05	0.04	0.03	0.03	0.02	-20%	-19%	-18% - Compound pat exp. + pedi 11/10; Hospira approved
Ambien Franchise	0.09	0.07	0.05	0.04	0.03	0.02	0.02	0.01	-21%	-24%	-24% - Multiple ANDAs but no approvals; Citizen's Petition outstanding
Actonel	0.02	0.02	0.02	0.01	0.01	0.01	0.01	0.01	-15%	-19%	-19% - Bisphosphonate; patent expires 12/10 in majority EU; P&G has most EU countries
Copaxone	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	NM	NM	NM - 25% royalty from Teva ended April 2010
Other products	1.24	1.11	0.96	0.87	0.81	0.77	0.72	0.68	-11%	-8%	-8%
Pipeline Contribution	0.12	0.23	0.42	0.65	0.96	1.27	1.60	1.97	78%	50%	43% - Toujeo, alirocumab, Eylea, Dengue Vaccine, Aubagio, Lemtrada, LixiLan, Lyxumia, most important
Total Pharma Contribution	4.42	4.43	4.45	4.35	4.44	4.56	4.71	4.91	-1%	2%	2%
OTC	0.30	0.33	0.34	0.36	0.38	0.40	0.42	0.44	6%	5%	5% - Chattem acquisition boosted starting Q1/10; Nasocort OTC rolling out; 50% of sales to emerging markets
Generics	0.15	0.18	0.19	0.20	0.22	0.23	0.24	0.25	10%	7%	5% - Winthrop, Zentiva, Kendle, Medley
Vaccines	0.72	0.78	0.89	1.03	1.18	1.33	1.48	1.63	13%	12%	13% - In line vaccines; includes Dengue but excludes MSD-Pasteur sales
Total Product Contribution	5.60	5.72	5.87	5.94	6.22	6.52	6.85	7.23	2%	4%	4%
Other	-0.55	-0.51	-0.33	-0.29	-0.11	0.08	0.35	0.62	NM	NM	NM - Includes equity income; animal health including Nexgard
EPS	€ 5.05	€ 5.20	€ 5.55	€ 5.65	€ 6.10	€ 6.60	€ 7.20	€ 7.85	4%	7%	7% - Versus industry averages of +4%, +6% and +8%
EPS Change	-18%	3%	7%	2%	8%	8%	9%	9%			

Source: Company data, Cowen and Company estimates

2013-20 Quarterly P&L Buildup (€ MM)

	Net Sales Total*		Gross P.M.	SG&A		R&D		Operating Inc		Non-op. Inc.	As Reported Tax Rate	Share of Profit from Assoc.	Business Net Income			Shares
	€MM	% Chg	% Sls	€MM	% Rev	€MM	% Rev	€MM	% Rev	€MM	%	€MM	€MM	EPS	Chg %	(MM)
Q1	€ 8,059	-5%	69.5%	€ 2,140	26.6%	€ 1,157	14.4%	€ 2,312	28.7%	(€ 140)	26.6%	(€ 18)	€ 1,589	€ 1.20	-34%	1,322
Q2	8,003	-10%	67.7%	2,306	28.8%	1,185	14.8%	2,024	25.3%	(137)	21.2%	(3)	1,479	1.12	-24%	1,326
Q3	8,432	-7%	67.0%	2,012	23.9%	1,182	14.0%	2,484	29.5%	(123)	24.0%	(38)	1,795	1.36	-19%	1,324
Q4	8,457	-1%	66.8%	2,145	25.4%	1,246	14.7%	2,494	29.5%	(103)	24.0%	(26)	1,814	1.37	17%	1,321
2013	€ 32,951	-6%	67.7%	€ 8,603	26.1%	€ 4,770	14.5%	€ 9,314	28.3%	(€ 503)	24.2%	(€ 85)	€ 6,677	€ 5.05	-18%	1,323
Q1	€ 7,842	-3%	69.0%	€ 2,078	26.5%	€ 1,139	14.5%	€ 2,145	27.4%	(€ 76)	25.2%	(€ 13)	€ 1,547	€ 1.17	-2%	1,320
Q2	8,075	1%	68.6%	2,255	27.9%	1,188	14.7%	2,145	26.6%	(94)	25.1%	(26)	1,537	1.17	5%	1,315
Q3E	8,835	5%	68.4%	2,225	25.2%	1,225	13.9%	2,596	29.4%	(90)	25.0%	(40)	1,879	1.43	5%	1,314
Q4E	8,790	4%	68.3%	2,127	24.2%	1,283	14.6%	2,596	29.5%	(85)	25.0%	(41)	1,883	1.43	4%	1,314
2014E	€ 33,520	2%	68.5%	€ 8,685	25.9%	€ 4,835	14.4%	€ 9,482	28.3%	(€ 345)	25.1%	(€ 120)	€ 6,848	€ 5.20	3%	1,316
Q1E	€ 8,185	4%	69.5%	€ 2,130	26.0%	€ 1,170	14.3%	€ 2,405	29.4%	(€ 80)	28.0%	(€ 45)	€ 1,674	€ 1.28	9%	1,320
Q2E	8,440	5%	69.0%	2,320	27.5%	1,220	14.5%	2,295	27.2%	(75)	28.0%	(45)	1,598	1.22	4%	1,315
Q3E	9,245	5%	68.8%	2,290	24.8%	1,255	13.6%	2,835	30.7%	(65)	28.0%	(50)	1,994	1.52	6%	1,314
Q4E	9,170	4%	68.7%	2,175	23.7%	1,310	14.3%	2,835	30.9%	(60)	28.0%	(50)	1,998	1.53	6%	1,314
2015E	€ 35,040	5%	69.0%	€ 8,915	25.4%	€ 4,955	14.1%	€ 10,370	29.6%	(€ 280)	28.0%	(€ 190)	€ 7,265	€ 5.55	7%	1,310
2016P	€ 35,465	1%	69.0%	€ 9,050	25.5%	€ 5,030	14.2%	€ 10,530	29.7%	(€ 250)	28.0%	(€ 240)	€ 7,402	€ 5.65	2%	1,310
2017P	€ 36,920	4%	69.2%	€ 9,260	25.1%	€ 5,150	13.9%	€ 11,305	30.6%	(€ 200)	28.0%	(€ 290)	€ 7,996	€ 6.10	8%	1,310
2018P	€ 38,490	4%	69.5%	€ 9,550	24.8%	€ 5,300	13.8%	€ 12,135	31.5%	(€ 125)	28.0%	(€ 340)	€ 8,647	€ 6.60	8%	1,310
2019P	€ 40,185	4%	69.8%	€ 9,735	24.2%	€ 5,475	13.6%	€ 13,145	32.7%	(€ 50)	28.0%	(€ 390)	€ 9,428	€ 7.20	9%	1,310
2020P	€ 42,125	5%	70.3%	€ 10,035	23.8%	€ 5,700	13.5%	€ 14,255	33.8%	€ 25	28.0%	(€ 440)	€ 10,282	€ 7.85	9%	1,310

*Net sales excludes "Other Revenue". Other Revenue is predominantly royalty income (includes Plavix and Avapro). Reflects Merial beginning in 2010.

Source: Company data, Cowen and Company estimates

Sanofi Quarterly Revenue Buildup (€MM)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Euro/U.S. Dollar (Quarter average)								-0.5%	4.1%		4.8%	4.9%	1.8%	0.0%	
Other blend								100%	101%		102.5%	102%	101%	100%	
Cardiovascular															
Lovenox U.S. (Fx)	49	48	39	51	187	32	29	25	25	110	25	25	20	20	90
Lovenox U.S. (Lc)								25	25		25	25	20	20	
Lovenox E.U.	213	215	208	222	858	229	222	205	205	860	200	195	190	185	770
Lovenox Emerging Countries (Fx)	143	148	130	142	563	135	148	125	135	545	130	140	115	110	495
Lovenox Emerging Countries (Lc)								125	135		125	135	115	110	
Lovenox ROW (Fx)	23	25	24	23	95	20	22	25	20	85	20	20	20	15	75
Lovenox ROW (Lc)								25	20		20	20	20	15	
Lovenox Total	428	436	401	438	1,703	416	421	380	385	1,600	375	380	345	330	1,430
Multaq U.S. (Fx)	49	57	53	57	216	60	52	50	50	210	60	50	50	45	205
Multaq U.S. (Lc)								50	50		55	50	50	45	
Multaq E.U.	10	11	10	12	43	10	12	10	10	40	10	10	10	5	35
Multaq Emerging Countries (Fx)	2	2	2	2	8	2	2	5	5	15	0	5	5	5	15
Multaq Emerging Countries (Lc)								5	5		0	5	5	5	
Multaq ROW (Fx)	1	-1	2	0	2	1	0	5	5	10	0	5	5	5	15
Multaq ROW (Lc)								5	5		0	5	5	5	
Multaq Total	62	69	67	71	269	73	66	70	70	275	70	70	70	60	270
Plavix U.S. (Fx)	0	5	0	0	5	0	1	0	5	5	0	0	0	5	5
Plavix U.S. (Lc)								0	5		0	0	0	5	
Plavix E.U.	65	69	63	60	257	62	54	50	50	215	45	45	40	40	170
Plavix Emerging Countries (Fx)	206	219	169	213	807	204	222	175	210	810	215	235	180	215	845
Plavix Emerging Countries (Lc)								175	210		210	230	180	215	
Plavix ROW (Fx)	179	200	191	218	788	221	148	175	180	725	205	155	155	160	675
Plavix ROW (Lc)								175	180		200	150	155	160	
Plavix Total	450	493	423	491	1,857	487	425	400	445	1,755	465	435	375	420	1,695
Aprovel E.U.	99	94	78	67	338	54	52	50	50	205	50	45	40	35	170
Aprovel Emerging Countries (Fx)	103	108	97	102	410	95	106	100	105	405	105	115	105	110	435
Aprovel Emerging Countries (Lc)								100	105		100	115	105	110	
Aprovel ROW (Fx)	39	36	35	24	134	30	35	30	30	125	25	25	25	25	100
Aprovel ROW (Lc)								30	30		25	25	25	25	
Aprovel Total	241	238	210	193	882	179	193	180	185	735	180	185	170	170	705
Tritace E.U.	34	35	34	33	136	32	33	30	30	125	25	25	25	25	100
Tritace Emerging Countries (Fx)	41	43	38	38	160	34	40	35	35	145	35	35	35	30	135
Tritace Emerging Countries (Lc)								35	35		35	35	35	30	
Tritace ROW (Fx)	3	2	3	3	11	2	2	0	0	5	5	0	0	0	5
Tritace ROW (Lc)								0	0		5	0	0	0	
Tritace Total	78	80	75	74	307	68	75	65	65	275	65	60	60	55	240
Alirocumab													25	50	75
SAR438714															
Cardiovascular Total	1,259	1,316	1,176	1,267	5,018	1,223	1,180	1,095	1,150	4,640	1,155	1,130	1,045	1,085	4,415
Y/Y Change	-15%	-14%	-15%	-3%	-12%	-3%	-10%	-7%	-9%	-8%	-6%	-4%	-5%	-6%	-5%

Source: Cowen and Company

Sanofi Quarterly Revenue Buildup (€MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Diabetes And Metabolism															
Lantus U.S. (Fx)	862	903	985	997	3,747	951	1,035	1,120	1,170	4,275	1,125	1,180	1,245	1,225	4,775
Lantus U.S. (Lc)								1,125	1,125		1,075	1,125	1,225	1,225	
Lantus E.U.	196	203	201	204	804	208	213	210	215	845	195	200	200	205	800
Lantus Emerging Countries (Fx)	212	230	198	234	874	225	243	220	255	945	250	275	240	275	1,040
Lantus Emerging Countries (Lc)								220	255		245	270	240	275	
Lantus ROW (Fx)	68	73	72	77	290	64	66	75	75	280	65	70	80	80	295
Lantus ROW (Lc)								75	75		65	70	80	80	
Lantus Total	1,338	1,409	1,456	1,512	5,715	1,448	1,557	1,625	1,715	6,345	1,635	1,725	1,765	1,785	6,910
Toujeo U.S. (Fx)														25	50
Toujeo U.S. (Lc)														25	50
Toujeo EU														25	50
Toujeo Emerging Countries (Fx)														0	0
Toujeo Emerging Countries (Lc)														0	0
Toujeo ROW (Fx)														0	0
Toujeo ROW (Lc)														0	0
Toujeo Total														50	100
Apidra U.S. (Fx)	26	23	29	34	112	28	27	35	35	125	35	35	40	40	150
Apidra U.S. (Lc)								35	35		35	35	40	40	
Apidra E.U.	19	21	21	23	84	23	24	25	25	95	25	25	25	30	105
Apidra Emerging Countries (Fx)	14	16	16	17	63	17	18	20	20	75	20	20	20	25	85
Apidra Emerging Countries (Lc)								20	20		20	20	20	25	
Apidra ROW (Fx)	7	8	7	7	29	7	8	10	10	35	10	10	10	10	40
Apidra ROW (Lc)								10	10		10	10	10	10	
Apidra Total	66	68	73	81	288	75	77	90	90	330	90	90	95	105	380
Amaryl U.S. (Fx)	0	1	0	1	2	0	1	0	5	5	0	0	0	5	5
Amaryl E.U.	6	6	5	5	22	6	4	5	5	20	5	5	5	5	20
Amaryl Emerging Countries (Fx)	67	71	65	66	269	65	77	70	70	280	70	70	75	75	290
Amaryl Emerging Countries (Lc)								70	70		70	70	75	75	
Amaryl ROW (Fx)	21	21	21	19	82	15	14	15	15	60	10	10	10	10	40
Amaryl ROW (Lc)								15	15		10	10	10	10	
Amaryl Total	94	99	91	91	375	86	96	90	95	365	85	85	90	95	355
Actonel E.U.	6	5	6	5	22	4	5	5	5	20	5	5	5	0	15
Actonel Emerging Countries (Fx)	15	10	11	12	48	11	10	10	10	40	10	10	10	5	35
Actonel Emerging Countries (Lc)								10	10		10	10	10	5	
Actonel ROW (Fx)	7	9	6	8	30	6	5	5	5	20	5	5	5	0	15
Actonel ROW (Lc)								5	5		5	5	5	0	
Actonel Total	28	24	23	25	100	21	20	20	20	80	20	20	20	5	65
Lyxumia			1	3	5	5	6	10	10	30	15	15	20	20	70
Insuman	33	32	34	33	132	32	33	35	35	135	30	30	35	35	130
Elitek/Rasuritek	5	5	5	5	20	5	5	10	10	30	10	10	10	10	40
LixiLan															
Sarilumab															
SAR339658															
SAR156597															
Diabetes/Metabolism Total	1,564	1,638	1,685	1,752	6,639	1,672	1,794	1,880	1,975	7,315	1,885	1,975	2,085	2,155	8,100
	16%	12%	11%	11%	13%	7%	10%	12%	13%	10%	13%	10%	11%	9%	11%

Source: Company data, Cowen and Company estimates.

Sanofi Quarterly Revenue Buildup (€MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Oncology															
Taxotere U.S. (Fx)	11	19	3	9	42	3	2	5	5	15	5	5	5	0	15
Taxotere U.S. (Lc)								5	5		5	5	5	0	
Taxotere E.U.	8	6	5	3	22	4	4	5	5	20	5	5	5	0	15
Taxotere Emerging Countries (Fx)	56	54	46	55	211	39	36	35	35	145	30	30	25	25	110
Taxotere Emerging Countries (Lc)								35	35		30	30	25	25	
Taxotere ROW (Fx)	33	35	30	36	134	23	25	30	30	110	30	30	25	25	110
Taxotere ROW (Lc)								30	30		30	30	25	25	
Taxotere Total	108	114	84	103	409	69	67	75	75	290	70	70	60	50	250
Eloxatin U.S. (Fx)	8	7	1	3	19	1	0	0	0	0	5	0	0	0	5
Eloxatin U.S. (Lc)								0	0		5	0	0	0	
Eloxatin E.U.	2	1	2	1	6	1	1	0	0	0	0	0	0	0	0
Eloxatin Emerging Countries (Fx)	34	31	32	30	127	30	29	30	25	115	30	25	25	25	105
Eloxatin Emerging Countries (Lc)								30	25		30	25	25	25	
Eloxatin ROW (Fx)	15	21	15	18	69	14	17	15	15	60	15	15	15	15	60
Eloxatin ROW (Lc)								15	15		15	15	15	15	
Eloxatin Total	59	60	50	52	221	46	47	45	40	175	50	40	40	40	170
Jevtana	52	54	59	66	231	66	66	70	75	275	75	75	80	80	310
Auvi-Q	6	9	27	9	51	10	16	20	15	60	15	20	20	15	70
Zaltrap (Afilbercept)	11	14	13	15	53	16	15	15	20	65	20	20	25	25	90
SAR3419															
SAR245409/pimasertib															
SAR650984															
Oncology	236	251	233	245	965	207	211	225	225	865	230	225	225	210	890
Y/Y Change	-60%	-58%	-27%	-10%	-46%	-12%	-16%	-3%	-8%	-10%	11%	7%	0%	-7%	890
CNS															
Ambien/CR U.S. (Fx)	19	20	20	20	79	16	18	15	15	65	15	15	10	10	50
Ambien/CR U.S. (Lc)								15	15		15	15	10	10	
Ambien/CR E.U.	11	10	11	10	42	11	10	5	5	30	5	5	5	5	20
Ambien/CR Emerging Countries (Fx)	20	14	16	15	65	16	16	15	15	60	15	15	15	10	55
Ambien/CR Emerging Countries (Lc)								15	15		15	15	15	10	
Ambien/CR ROW (Fx)	51	48	47	45	191	35	29	30	30	125	25	25	25	25	100
Ambien/CR ROW (Lc)								30	30		25	25	25	25	
Ambien/CR Total	101	92	94	90	377	78	73	65	65	280	60	60	55	50	225
Depakine E.U.	33	34	35	36	138	33	34	40	40	145	40	40	40	45	165
Depakine Emerging Countries (Fx)	70	65	63	54	252	56	61	60	60	235	55	55	55	55	220
Depakine Emerging Countries (Lc)								60	60		55	55	55	55	
Depakine ROW (Fx)	3	4	4	4	15	3	4	5	5	15	5	5	5	10	25
Depakine ROW (Lc)								5	5		5	5	5	10	
Depakine Total	106	103	102	94	405	92	99	105	105	395	100	100	100	110	410
Lemtrada						2	2	5	6	30	15	15	20	20	70
Aubagio	20	33	44	69	166	78	97	110	120	405	130	140	150	160	580
SAR391786															
CNS Total	227	228	240	255	950	253	275	290	300	1,110	305	315	325	340	1,285
Y/Y Change	-9%	-1%	4%	12%	1%	11%	21%	21%	18%	17%	21%	15%	12%	13%	16%

Source: Company data, Cowen and Company estimates

Sanofi Quarterly Revenue Buildup (€MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Infection															
Ferroquine/OZ439															
SAR279356															
Infection Total															
Allergy/Asthma															
Allegra U.S. (Fx)	0	0	-2	-1	-3	0	0	0	0	0	0	0	0	0	0
Allegra U.S. (Lc)						0	0	0	0	0	0	0	0	0	0
Allegra E.U.	2	4	2	2	10	3	3	5	0	10	0	5	5	0	10
Allegra Emerging Countries (Fx)	29	31	30	30	120	1	2	0	0	5	0	0	0	0	0
Allegra Emerging Countries (Lc)						0	0	0	0	0	0	0	0	0	0
Allegra ROW (Fx)	138	44	41	56	279	76	34	40	40	190	65	35	40	40	180
Allegra ROW (Lc)						40	40	40	40	205	65	35	40	40	180
Allegra Total	169	79	71	87	406	80	39	45	40	205	65	40	45	40	190
Nasacort U.S. (Fx)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Nasacort U.S. (Lc)						0	0	0	0	0	0	0	0	0	0
Nasacort E.U.	5	5	5	5	20	5	5	0	0	10	5	0	0	0	5
Nasacort Emerging Countries (Fx)	5	0	0	0	5	0	0	0	5	5	5	0	0	0	5
Nasacort Emerging Countries (Lc)						0	0	0	5	5	5	0	0	0	5
Nasacort ROW (Fx)	0	0	0	0	0	1	0	5	5	10	0	5	5	5	15
Nasacort ROW (Lc)						5	5	5	5	10	0	5	5	5	15
Nasacort Total	10	5	5	5	25	6	5	5	10	25	10	5	5	5	25
Dupilumab															
Allergy Total	179	84	76	92	431	86	44	50	50	230	75	45	50	45	215
Urinary Tract															
Renagel/Renvela U.S. (Fx)	121	115	132	163	531	114	88	90	50	340	10	10	10	20	50
Renagel/Renvela U.S. (Lc)						90	50	50	50	10	10	10	10	20	50
Renagel/Renvela E.U.	32	36	32	33	133	32	33	40	40	145	25	25	25	25	100
Renagel/Renvela Emerging Countries (Fx)	13	19	18	17	67	22	11	20	20	75	20	20	20	20	80
Renagel/Renvela Emerging Countries (Lc)						20	20	20	20	20	20	20	20	20	80
Renagel/Renvela ROW (Fx)	5	5	5	4	19	4	5	10	10	30	10	10	10	10	40
Renagel/Renvela ROW (Lc)						10	10	10	10	10	10	10	10	10	40
Renagel/Renvela Total	171	175	187	217	750	172	137	160	120	590	65	65	65	75	270
Xatral U.S. (Fx)	2	0	1	0	3	0	0	0	0	0	5	0	0	0	5
Xatral U.S. (Lc)						0	0	0	0	0	5	0	0	0	5
Xatral E.U.	9	10	10	10	39	10	9	5	5	30	5	5	5	5	20
Xatral Emerging Countries (Fx)	14	15	14	15	58	14	13	10	10	45	15	15	10	10	45
Xatral Emerging Countries (Lc)						10	10	10	10	15	10	10	10	10	45
Xatral ROW (Fx)	1	0	1	-1	1	0	1	0	0	0	0	0	0	0	0
Xatral ROW (Lc)						0	0	0	0	0	0	0	0	0	0
Xatral Total	26	25	26	24	101	24	23	15	15	75	25	15	15	15	70
Urinary Total	197	200	213	241	851	196	160	175	135	665	90	80	80	90	340
Osteoarthritis															
Synvisc U.S. (Fx)	63	82	72	78	295	53	74	70	80	275	65	80	70	80	295
Synvisc U.S. (Lc)						70	75	60	75	70	70	75	70	80	295
Synvisc E.U.	5	7	6	7	25	6	8	10	10	35	10	10	10	10	40
Synvisc Emerging Countries (Fx)	6	8	10	8	32	8	9	10	10	35	10	10	10	10	45
Synvisc Emerging Countries (Lc)						10	10	10	10	10	10	10	10	10	45
Synvisc ROW (Fx)	3	8	2	6	19	3	2	5	5	15	5	5	5	5	25
Synvisc ROW (Lc)						5	5	5	5	5	5	5	5	5	25
Synvisc Total	77	105	90	99	371	70	93	95	105	365	90	105	95	115	405

Source: Company data, Cowen and Company estimates

Sanofi Quarterly Revenue Buildup (€MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Rare Diseases															
Cerezyme U.S. (Fx)	43	45	46	44	178	45	45	50	50	190	50	60	55	55	220
Cerezyme U.S. (Lc)								50	50		50	55	55	55	
Cerezyme E.U.	57	56	52	60	225	59	60	60	60	240	65	65	65	65	260
Cerezyme Emerging Countries (Fx)	60	57	57	67	241	56	59	60	70	245	60	65	65	75	265
Cerezyme Emerging Countries (Lc)								60	70		60	65	65	75	
Cerezyme ROW (Fx)	11	13	10	10	44	8	11	15	15	50	10	15	20	20	65
Cerezyme ROW (Lc)								15	15		10	15	20	20	
Cerezyme Total	171	171	165	181	688	168	175	185	195	725	185	205	205	215	810
Myozyme/Lumizyme U.S. (Fx)	30	30	32	31	123	31	33	35	35	135	35	40	40	40	155
Myozyme/Lumizyme U.S. (Lc)								35	35		35	40	40	40	
Myozyme/Lumizyme E.U.	66	69	68	71	274	63	67	70	75	275	65	75	80	80	300
Myozyme/Lumizyme Emerg. Countries (Fx)	14	20	19	21	74	20	26	25	25	95	25	30	30	30	115
Myozyme/Lumizyme Emerg. Countries (Lc)								25	25		25	30	30	30	
Myozyme/Lumizyme ROW (Fx)	6	7	8	8	29	7	7	10	10	35	10	10	15	15	50
Myozyme/Lumizyme ROW (Lc)								10	10		10	10	15	15	
Myozyme/Lumizyme Total	116	126	127	131	500	121	133	140	145	540	135	155	165	165	620
Fabrazyme U.S. (Fx)	47	50	50	49	196	51	55	55	55	215	65	70	65	65	265
Fabrazyme U.S. (Lc)								55	55		60	65	65	65	
Fabrazyme E.U.	20	21	20	26	87	25	28	25	25	105	30	30	30	30	120
Fabrazyme Emerging Countries (Fx)	16	8	12	15	51	9	27	20	20	75	10	25	25	25	85
Fabrazyme Emerging Countries (Lc)								20	20		10	25	25	25	
Fabrazyme ROW (Fx)	9	12	14	14	49	13	13	20	20	65	20	20	20	20	85
Fabrazyme ROW (Lc)								20	20		20	20	20	20	
Fabrazyme Total	92	91	96	104	383	98	123	120	120	460	125	145	140	145	555
Cerdelga (eliglustat)								20	40	60	50	60	70	80	260
Kynamro	5	5	5	5	20	5	5	10	10	30	15	15	15	15	60
Fresolimumab (GC1008)															
Patisiran															
Other	115	132	136	130	513	135	140	140	145	560	150	150	150	150	600
Rare Diseases Total	499	525	529	551	2,104	527	576	615	655	2,375	660	730	745	770	2,905
Total Strategic Products	4,238	4,347	4,242	4,502	17,329	4,234	4,333	4,425	4,595	17,565	4,490	4,605	4,650	4,810	18,555
Y/Y Change	-6%	-8%	-2%	5%	-3%	0%	0%	4%	2%	1%	6%	6%	5%	5%	6%
Other Products	1,336	1,338	1,266	1,352	5,292	1,157	1,205	1,150	1,240	4,750	1,050	1,075	1,050	1,100	4,275
Y/Y Change	-13%	-16%	-15%	-11%	-14%	-13%	-10%	-9%	-8%	-10%	-9%	-11%	-9%	-11%	-10%
Total Branded Pharmaceuticals	€ 5,574	€ 5,685	€ 5,508	€ 5,854	€ 22,621	€ 5,391	€ 5,538	€ 5,575	€ 5,835	€ 22,315	€ 5,540	€ 5,680	€ 5,700	€ 5,910	€ 22,830
Y/Y Change	-8%	-10%	-5%	1%	-6%	-3%	-3%	1%	0%	-1%	3%	3%	2%	1%	2%
OTC	811	729	742	722	3,004	885	816	800	765	3,265	925	850	850	825	3,450
Y/Y Change	1%	-1%	1%	-1%	0%	9%	12%	8%	6%	9%	5%	4%	6%	8%	6%
Generics	423	300	424	478	1,625	421	466	515	550	1,950	445	495	550	585	2,075
Y/Y Change	-4%	-36%	-11%	4%	-12%	0%	55%	21%	15%	20%	6%	6%	7%	6%	6%

Source: Company data, Cowen and Company estimates

Sanofi Quarterly Revenue Buildup (€MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Vaccines															
Polio/Pertussis/Hib U.S. (Fx)	42	81	50	102	275	76	90	75	135	375	100	125	90	140	455
Polio/Pertussis/Hib U.S. (Lc)								75	130		95	120	90	140	
Polio/Pertussis/Hib E.U.	6	11	8	10	35	6	6	15	15	40	15	15	15	15	60
Polio/P/Hib Emerging Countries (Fx)	146	166	155	177	644	92	149	165	190	595	130	185	170	190	675
Polio/P/Hib Emerging Countries (Lc)								165	190		125	180	170	190	
Polio/Pertussis/Hib ROW (Fx)	76	35	31	52	194	37	39	40	60	175	45	50	50	70	215
Polio/Pertussis/Hib ROW (Lc)								40	60		45	50	50	70	
Polio/Pertussis/Hib Total (Fx)	270	293	244	341	1,148	211	284	295	400	1,190	290	375	325	415	1,405
Y/Y Change	10%	7%	-24%	-1%	-3%	-22%	-3%	21%	17%	4%	37%	32%	10%	4%	18%
Adult Booster Vaccines U.S. (Fx)	58	84	56	70	268	64	59	65	85	275	75	70	70	85	300
Adult Booster Vaccines U.S. (Lc)								65	80		70	65	70	85	
Adult Booster Vaccines E.U.	14	25	13	8	60	8	8	10	10	35	15	10	15	15	55
Adult Booster Emerging Countries (Fx)	8	13	12	15	48	7	12	15	20	55	10	15	15	20	60
Adult Booster Emerging Countries (Lc)								15	20		10	15	15	20	
Adult Booster Vaccines ROW (Fx)	5	2	3	5	15	2	4	5	5	15	5	5	5	10	25
Adult Booster Vaccines ROW (Lc)								5	5		5	5	5	10	
Adult Booster Vaccines Total	85	124	84	98	391	81	83	95	120	380	105	100	105	130	440
Y/Y Change	-2%	-15%	-40%	-20%	-21%	-5%	-33%	13%	22%	-3%	30%	20%	11%	8%	16%
Influenza Vaccines U.S. (Fx)	15	-5	402	121	533	21	0	425	125	570	0	0	460	150	610
Influenza Vaccines U.S. (Lc)								425	120		0	0	450	150	
Influenza Vaccines E.U.	0	1	77	5	83	0	1	90	10	100	0	0	100	15	115
Influenza Emerging Countries (Fx)	93	54	76	68	291	105	55	90	75	325	105	65	100	85	355
Influenza Emerging Countries (Lc)								90	75		100	65	100	85	
Influenza Vaccines ROW (Fx)	11	3	4	4	22	9	3	5	5	20	10	10	10	5	35
Influenza Vaccines ROW (Lc)								5	5		10	10	10	5	
Influenza Vaccines Total	119	53	559	198	929	135	59	610	215	1,020	115	75	670	255	1,115
Y/Y Change	34%	-34%	-8%	85%	5%	13%	11%	9%	9%	10%	-15%	27%	10%	19%	9%
Travel Vaccines U.S. (Fx)	15	25	38	19	97	15	31	40	25	110	20	30	45	30	125
Travel Vaccines U.S. (Lc)								40	25		20	30	45	30	
Travel Vaccines E.U.	5	3	4	6	18	5	8	5	10	30	5	10	10	10	35
Travel Vaccines Emerging Countries (Fx)	42	55	48	70	215	41	53	55	70	220	50	65	60	75	250
Travel Vaccines Emerging Countries (Lc)								55	70		50	65	60	75	
Travel Vaccines ROW (Fx)	12	15	11	14	52	14	11	15	20	60	15	15	15	25	70
Travel Vaccines ROW (Lc)								15	20		15	15	15	25	
Travel Vaccines Total	74	98	101	109	382	75	103	115	125	420	90	120	130	140	480
Y/Y Change	-4%	-2%	22%	5%	5%	1%	5%	14%	15%	10%	20%	17%	13%	12%	14%
Meningitis/Pneumonia Vaccines U.S. (Fx)	42	79	179	52	352	38	93	190	105	425	45	90	200	105	440
Meningitis/Pneumonia Vaccines U.S. (Lc)								190	100		45	85	195	105	
Meningitis/Pneumonia Vaccines E.U.	1	2	1	1	5	0	0	5	5	10	5	5	10	10	30
Meningitis/P Emerging Countries (Fx)	35	41	29	27	132	15	22	30	30	95	25	30	35	35	125
Meningitis/P Emerging Countries (Lc)								30	30		25	30	35	35	
Meningitis/Pneumonia Vaccines ROW (Fx)	2	1	2	2	7	3	0	5	5	15	5	0	5	10	20
Meningitis/Pneumonia Vaccines ROW (Lc)								5	5		5	5	5	10	
Meningitis/Pneumonia Vaccines Total	80	123	211	82	496	56	115	230	145	545	80	125	250	160	615
Y/Y Change	10%	-5%	-8%	-62%	-24%	-30%	-7%	9%	77%	10%	43%	9%	9%	10%	13%
Dengue U.S. (Fx)											5	5	5	5	10
Dengue U.S. (Lc)											5	5	5	5	
Dengue EU											5	5	5	5	10
Dengue Emerging Countries (Fx)											20	40	40	40	60
Dengue Emerging Countries (Lc)											20	40	40	40	60
Dengue ROW (Fx)											20	40	40	40	60
Dengue ROW (Lc)											20	40	40	40	60
Dengue Total											50	90	90	90	140
Y/Y Change															
Other Vaccines U.S. (Fx)	63	65	94	125	347	65	67	105	140	375	80	90	115	145	430
Other Vaccines U.S. (Lc)								105	135		75	85	115	145	
Other Vaccines EU	0	0	2	1	3	2	-1	5	5	10	0	5	5	5	15
Other Vaccines Emerging Countries (Fx)	3	3	1	4	11	1	4	5	10	20	5	5	10	10	30
Other Vaccines Emerging Countries (Lc)								5	10		5	5	10	10	
Other Vaccines ROW (Fx)	3	1	4	1	9	2	4	10	10	25	5	5	10	10	30
Other Vaccines ROW (Lc)								10	10		5	5	10	10	
Other Vaccines Total	69	69	101	131	370	70	74	125	165	435	90	105	140	170	505
Y/Y Change	50%	25%	1%	11%	16%	1%	7%	24%	26%	18%	29%	42%	12%	3%	16%
Vaccines Total	€ 697	€ 760	€ 1,300	€ 959	€ 3,716	€ 628	€ 718	€ 1,470	€ 1,170	€ 3,890	€ 770	€ 800	€ 1,670	€ 1,380	€ 4,700
Y/Y Change	13%	-3%	-12%	-6%	-5%	-10%	-6%	13%	22%	7%	23%	25%	14%	16%	18%

Source: Company data, Cowen and Company estimates

Sanofi Quarterly Revenue Buildup (€MM) (continued)

	Q1:13	Q2:13	Q3:13	Q4:13	2013	Q1:14	Q2:14	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
Animal Health															
Fipronil U.S. (Fx)	101	88	73	27	289	75	89	50	25	240	50	50	25	25	150
Fipronil U.S. (Lc)								50	25		50	50	25	25	
Fipronil EU.	62	49	41	25	177	62	50	40	25	175	50	40	30	20	140
Fipronil Emerging Countries (Fx)	22	25	25	27	99	22	24	20	20	85	15	15	15	15	60
Fipronil Emerging Countries (Lc)								20	20		15	15	15	15	
Fipronil ROW (Fx)	11	6	12	17	46	12	6	10	10	40	10	10	5	5	30
Fipronil ROW (Lc)								10	10		10	10	5	5	
Fipronil Total	196	168	151	96	611	171	169	120	80	540	125	115	75	65	380
Y/Y Change						-13%	1%	-21%	-17%	-12%	-27%	-32%	-38%	-19%	-30%
Vaccines U.S. (Fx)	33	43	36	40	152	34	38	40	40	150	35	45	45	45	170
Vaccines U.S. (Lc)								40	40		35	45	45	45	
Vaccines EU.	43	48	38	53	182	42	46	40	55	185	45	50	45	50	190
Vaccines Emerging Countries (Fx)	84	101	82	107	374	75	91	80	110	355	80	100	85	105	370
Vaccines Emerging Countries (Lc)								80	105		80	100	85	105	
Vaccines ROW (Fx)	4	5	4	6	19	3	5	5	5	20	5	5	5	5	20
Vaccines ROW (Lc)								5	5		5	5	5	5	
Vaccines Total	164	197	160	206	727	154	180	165	210	710	165	200	180	205	750
Y/Y Change						-6%	-9%	3%	2%	-2%	7%	11%	9%	-2%	6%
Avermectines U.S. (Fx)	91	58	48	28	225	67	57	45	25	195	65	45	40	20	170
Avermectines U.S. (Lc)								45	25		60	45	40	20	
Avermectines EU.	16	12	12	18	58	16	12	10	15	55	10	10	10	10	40
Avermectines Emerging Countries (Fx)	12	16	14	17	59	12	13	15	15	55	10	10	15	15	50
Avermectines Emerging Countries (Lc)								15	15		10	10	15	15	
Avermectines ROW (Fx)	23	17	16	15	71	19	16	15	15	65	15	15	15	15	60
Avermectines ROW (Lc)								15	15		15	15	15	15	
Avermectines Total	142	103	90	78	413	114	98	85	70	365	100	80	80	60	320
Y/Y Change						-20%	-5%	-6%	-10%	-12%	-12%	-18%	-6%	-14%	-12%
Nexgard U.S. (Fx)						22	31	30	25	110	35	40	45	45	150
Nexgard U.S. (Lc)								30	25		30	35	40	45	
Nexgard EU						1	3	10	15	30	20	25	30	35	110
Nexgard Emerging Countries (Fx)						0	0	0	0	0	0	0	0	0	0
Nexgard Emerging Countries (Lc)								0	0		0	0	0	0	
Nexgard ROW (Fx)						0	1	0	0	0	0	0	0	0	0
Nexgard ROW (Lc)								0	0		0	0	0	0	
Nexgard Total						23	35	40	40	140	50	60	70	80	260
Y/Y Change											117%	71%	75%	100%	86%
Other U.S. (Fx)	16	25	20	20	81	19	17	20	20	75	20	20	25	25	90
Other U.S. (Lc)								20	20		20	20	25	25	
Other EU	21	20	20	24	85	21	19	25	25	90	25	20	25	25	95
Other Emerging Countries (Fx)	11	12	13	19	55	12	15	15	20	60	15	15	15	20	65
Other Emerging Countries (Lc)								15	20		15	15	15	20	
Other ROW (Fx)	4	4	4	1	13	3	4	5	5	15	5	5	5	10	25
Other ROW (Lc)								5	5		5	5	5	10	
Other Total	52	61	57	64	234	55	55	65	70	245	65	60	70	80	275
Y/Y Change						6%	-10%	14%	9%	5%	18%	9%	8%	14%	12%
Animal Health Total	€ 554	€ 529	€ 458	€ 444	€ 1,985	€ 617	€ 537	€ 475	€ 470	€ 2,000	€ 505	€ 515	€ 475	€ 490	€ 1,985
Y/Y Change	-4%	-8%	-12%	-12%	-9%	-7%	2%	4%	6%	1%	-2%	-4%	0%	4%	-1%
Total Net Sales	€ 8,059	€ 8,003	€ 8,432	€ 8,457	€ 32,951	€ 7,842	€ 8,075	€ 8,835	€ 8,790	€ 33,520	€ 8,185	€ 8,440	€ 9,245	€ 9,170	€ 35,040
Y/Y Change	-5%	-10%	-7%	-1%	-6%	-3%	1%	5%	4%	2%	4%	5%	5%	4%	5%

Source: Company data, Cowen and Company estimates

Sanofi Annual Revenue Buildup (€MM)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CAGR 2014-20	CAGR 2013-20	Comments
Euro/U.S. Dollar (Quarter average)											
Other blend				100%	100%	100%	100%	100%			
Cardiovascular											
Lovenox U.S. (Fx)	187	110	90	70	50	30	20	10	-33%	-34%	- Brand retains 30% share of market, authorized generic 22% (recorded in generics line) or 52% of molecule sales
Lovenox U.S. (Lc)				70	50	30	20	10			
Lovenox E.U.	858	860	770	720	670	620	580	540	-7%	-6%	- Biosimilar/generics required to do studies
Lovenox Emerging Countries (Fx)	563	545	495	450	400	375	350	325	-8%	-8%	
Lovenox Emerging Countries (Lc)				450	400	375	350	325			
Lovenox ROW (Fx)	95	85	75	65	55	45	35	25	-18%	-17%	
Lovenox ROW (Lc)				65	55	45	35	25			- Canada, Australia, New Zealand, Japan
Lovenox Total	1,703	1,600	1,430	1,305	1,175	1,070	985	900	-9%	-9%	
Multaq U.S. (Fx)	216	210	205	180	160	140	120	100	-12%	-10%	- 6.7% share of antiarrhythmic market in 7/14; FDA analysis complete; patent expiration 7/16
Multaq U.S. (Lc)				180	160	140	120	100			
Multaq E.U.	43	40	35	30	25	20	15	10	-21%	-19%	- Launched in 2010 with reimbursement; EU analysis complete; exclusivity expires 2019
Multaq Emerging Countries (Fx)	8	15	15	20	25	30	35	40	18%	26%	
Multaq Emerging Countries (Lc)				20	25	30	35	40			
Multaq ROW (Fx)	2	10	15	20	25	30	35	40	26%	53%	
Multaq ROW (Lc)				20	25	30	35	40			- Assumes launch in additional markets; Canada, Australia, New Zealand, Japan
Multaq Total	269	275	270	250	235	220	205	190	-6%	-5%	- Novel anti-arrhythmic for atrial fibrillation
Plavix U.S. (Fx)	5	5	5	5	5	5	5	5	0%	0%	- U.S. patent expired 5/12 including pedi exclusivity
Plavix U.S. (Lc)				5	5	5	5	5			
Plavix E.U.	257	215	170	130	90	50	25	10	-40%	-37%	- Broad adoption of non AB-rate generics in EU
Plavix Emerging Countries (Fx)	807	810	845	860	885	910	935	960	3%	3%	
Plavix Emerging Countries (Lc)				860	885	910	935	960			- SNY has full economics in China
Plavix ROW (Fx)	788	725	675	550	450	350	250	150	-23%	-21%	
Plavix ROW (Lc)				550	450	350	250	150			- Japanese pat exp in 2013, exclusivity exp in 2014; SNY has full economics in Japan; Canada, Australia, New Zealand, Japan
Plavix Total	1,857	1,755	1,695	1,545	1,430	1,315	1,215	1,125	-7%	-7%	
Aprovel E.U.	338	205	170	125	75	50	25	10	-40%	-40%	- U.K., France, Germany patent expiration 8/12; other countries 3/11
Aprovel Emerging Countries (Fx)	410	405	435	450	470	490	510	530	5%	4%	
Aprovel Emerging Countries (Lc)				450	470	490	510	530			
Aprovel ROW (Fx)	134	125	100	80	60	40	20	10	-34%	-31%	
Aprovel ROW (Lc)				80	60	40	20	10			- Japanese patent expiration 2016; Canada, Australia, New Zealand, Japan
Aprovel Total	882	735	705	655	605	580	555	550	-5%	-7%	
Tritace E.U.	136	125	100	80	60	40	20	10	-34%	-31%	- ACE inhibitor, generics launched
Tritace Emerging Countries (Fx)	160	145	135	125	115	105	95	85	-9%	-9%	
Tritace Emerging Countries (Lc)				125	115	105	95	85			
Tritace ROW (Fx)	11	5	5	5	5	5	5	5	0%	-11%	
Tritace ROW (Lc)				5	5	5	5	5			- Canada, Australia, New Zealand, Japan
Tritace Total	307	275	240	210	180	150	120	100	-16%	-15%	
Alirocumab				75	150	300	450	600	750	NM	NM - Anti-PCSK-9 mAB; hypercholesterolemia; Phase III readouts positive; Q4 filings, priority review voucher to be used
SAR438714					25	50	75	100	NM	NM	NM - ALN-TTRsc; RNA1; familial amyloid cardiomyopathy; Phase II
Cardiovascular Total	5,018	4,640	4,415	4,115	3,950	3,835	3,755	3,715	-4%	-4%	
Y/Y Change	-12%	-8%	-5%	-7%	-4%	-3%	-2%	-1%			

Source: Company data, Cowen and Company estimates

Sanofi Annual Revenue Buildup (€MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CAGR 2014-20	CAGR 2013-20	Comments
Diabetes And Metabolism											
Lantus U.S. (Fx)	3,747	4,275	4,775	4,000	3,500	3,000	2,500	2,000	-12%	-9% - Basal insulin; 17% share 7/14, SoloStar Pen 20.5% share; pat. exp. 8/2014 + 6 months pedi but generic competition likely limited	
Lantus U.S. (Lc)				4,000	3,500	3,000	2,500	2,000			
Lantus E.U.	804	845	800	750	700	650	600	550	-7%	-5% - Regulatory exclusivity 6/10; patent expiration 11/2014	
Lantus Emerging Countries (Fx)	874	945	1,040	1,100	1,200	1,300	1,400	1,500	8%	8%	
Lantus Emerging Countries (Lc)				1,100	1,200	1,300	1,400	1,500			
Lantus ROW (Fx)	290	280	295	310	325	340	355	370	5%	4% - Japan patent expiration 2014; market exclusivity 10/11; Canada, Australia, New Zealand,	
Lantus ROW (Lc)				310	325	340	355	370			
Lantus Total	5,715	6,345	6,910	6,160	5,725	5,290	4,855	4,420	-6%	-4%	
Toujeo U.S. (Fx)		75	150	300	450	600	750	NM	NM - Q2:14 filing; CV study not likely necessary		
Toujeo U.S. (Lc)			150	300	450	600	750				
Toujeo EU		75	150	300	450	600	750	NM	NM - Q2:14 filing		
Toujeo Emerging Countries (Fx)		0	0	0	0	0	0				
Toujeo Emerging Countries (Lc)				0	0	0	0				
Toujeo ROW (Fx)		0	0	0	0	0	0			- Canada, Australia, New Zealand, Japan	
Toujeo ROW (Lc)				0	0	0	0				
Toujeo Total		150	300	600	900	1,200	1,500	NM	NM - U300 concentration of Lantus; type 1 and 2 diabetes		
Apidra U.S. (Fx)	112	125	150	170	190	210	230	250	12%	12% - 0.6% share of rapid acting insulin market in 7/14; launch of Solostar formulation	
Apidra U.S. (Lc)			170	190	210	230	250				
Apidra E.U.	84	95	105	115	125	135	145	155	9%	9%	
Apidra Emerging Countries (Fx)	63	75	85	95	105	115	125	135	10%	12%	
Apidra Emerging Countries (Lc)				95	105	115	125	135			
Apidra ROW (Fx)	29	35	40	45	50	55	60	65	11%	12% - Canada, Australia, New Zealand, Japan	
Apidra ROW (Lc)				45	50	55	60	65			
Apidra Total	288	330	380	425	470	515	560	605	11%	11% - Rapid acting insulin; <1% of insulin market	
Amaryl U.S. (Fx)	2	5	5	5	5	5	5	5	0%	14% - QD sulphonylurea for diabetes	
Amaryl E.U.	22	20	20	20	20	20	20	20	0%	-1%	
Amaryl Emerging Countries (Fx)	269	280	290	300	310	320	330	340	3%	3%	
Amaryl Emerging Countries (Lc)				300	310	320	330	340			
Amaryl ROW (Fx)	82	60	40	30	20	10	5	5	-34%	-33% - Japan leading oral antidiabetic by vol; FDC with metformin launched in 2007; Canada, Australia, New Zealand, Japan	
Amaryl ROW (Lc)				30	20	10	5	5			
Amaryl Total	375	365	355	355	355	355	360	370	0%	0%	
Actonel E.U.	22	20	15	15	10	5	5	5	-21%	-19% - Bisphosphonate; patent expires 12/10 in majority E.U.; P&G has most E.U. countries	
Actonel Emerging Countries (Fx)	48	40	35	30	25	20	15	10	-21%	-20%	
Actonel Emerging Countries (Lc)				30	25	20	15	10			
Actonel ROW (Fx)	30	20	15	15	10	10	5	5	-21%	-23% - Canada, Australia, New Zealand, Japan	
Actonel ROW (Lc)				15	10	10	5	5			
Actonel Total	100	80	65	60	45	35	25	20	-21%	-21% - Licensed from P&G; royalty reflected in cost of sales	
Lyxumia	9	30	70	125	175	225	275	325	49%	NA - Lixisenatide; GLP1 agonist; differentiation vs. other GLP-1s unclear; type 2 diabetes; approved in EU and Japan; 2015 filing in U.S.	
Insuman	132	135	130	125	120	115	110	105	-4%	-3% - Prefilled rapid insulin -mix; in Germany	
Elitek/Rasuritek	20	30	40	45	50	55	60	65	14%	18% - Management of hyperuricemia of malignancy; approved 10/09 U.S. and Japan	
LixiLan				100	200	300	400	500	NM	NM - Lixisenatide/Lantus combination; Flex pen delayed, mechanical pen advancing	
Sarilumab				25	50	100	150	NM	NM - SAR153191; Anti-IL-6R mAb; first RA Phase III met endpoint, AS; AS; uveitis (PiI)		
SAR339658				25	50	75	100	NM	NM - Anti-VLA2 mAb; multiple sclerosis; Phase II		
SAR156597				25	50	25	100	NM	NM - IL4/IL13 Bi-specific mAb; idiopathic pulmonary fibrosis; Phase II		
Diabetes/Metabolism Total	6,639	7,315	8,100	7,695	7,815	7,940	8,095	8,260	2%	3%	
	13%	10%	11%	-5%	2%	2%	2%	2%			

Source: Company data, Cowen and Company estimates

Sanofi Annual Revenue Buildup (€MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CAGR 2014-20	CAGR 2013-20	Comments
Oncology											
Taxotere U.S. (Fx)	42	15	15	10	5	5	5	5	-17%	-26%	- Compound pat exp. + pedi 11/10; Hospira approved
Taxotere U.S. (Lc)				10	5	5	5	5			
Taxotere E.U.	22	20	15	10	5	5	5	5	-21%	-19%	- E.U. patent expiration 11/10 in most countries; off patent in smaller countries
Taxotere Emerging Countries (Fx)	211	145	110	80	60	40	20	10	-36%	-35%	
Taxotere Emerging Countries (Lc)				80	60	40	20	10			
Taxotere ROW (Fx)	134	110	110	100	90	80	70	60	-10%	-11%	- Approval in Japan for PRCA; patent expired 6/12; Canada, Australia, New Zealand,
Taxotere ROW (Lc)				100	90	80	70	60			
Taxotere Total	409	290	250	200	160	130	100	80	-19%	-21%	- SNY guidance of 300-400MM on sustainable basis
Eloxatin U.S. (Fx)	19	0	5	5	5	5	5	5	#NUM!	-17%	- Generics off market July 2010-Aug 2012, but generics now re-entered
Eloxatin U.S. (Lc)				5	5	5	5	5			
Eloxatin E.U.	6	0	0	0	0	0	0	0			- Powder form generics on the market
Eloxatin Emerging Countries (Fx)	127	115	105	95	85	75	65	55	-12%	-11%	
Eloxatin Emerging Countries (Lc)				95	85	75	65	55			
Eloxatin ROW (Fx)	69	60	60	55	50	45	40	35	-9%	-9%	- Continued growth; Canada, Australia, New Zealand, Japan
Eloxatin ROW (Lc)				55	50	45	40	35			
Eloxatin Total	221	175	170	155	140	125	110	95	-10%	-11%	- SNY guidance of 200-300MM on sustainable basis
Jevtana	231	275	310	350	400	450	475	500	10%	12%	- Cabazitaxel; taxotere refractory prostate cancer; marketed in U.S. and EU; Phase II small cell lung cancer; exclusivity exp. 3/21 (U.S.)
Auvi-Q	51	60	70	80	90	100	110	120	NM	NM	- Novel epinephrine auto-injector
Zaltrap (Affilbercept)	53	65	90	115	140	165	190	215	22%	22%	- VEGF-trap; PIII 1st line mpraca, 2nd line NSCLC, 2nd line mCRC FDA approved 8/3/12, EU approved 1/13; partnered with Regeneron
SAR3419					25	50	75	100	NM	NM	- Maytansin-loaded anti-CD19 mAb; B-cell malignancies refractory/relapsed; NHL/ALL;
SAR245409/pimasertib					25	50	75	100	NM	NM	- Oral dual inhibitor of PI3K & mTOR; ovarian cancer; Phase II
SAR650984					25	50	75	100	NM	NM	- Anti-CD38 naked mAb; multiple myeloma; Phase II
Oncology	965	865	890	900	1,005	1,120	1,210	1,310	7%	4%	
Y/Y Change	-46%	-10%	3%	1%	12%	11%	8%	8%			
			890								
CNS											
Ambien/CR U.S. (Fx)	79	65	50	35	20	10	5	5	-35%	-33%	- Multiple ANDAs but no approvals; Citizen's Petition outstanding
Ambien/CR U.S. (Lc)				35	20	10	5	5			
Ambien/CR E.U.	42	30	20	15	10	5	5	5	-26%	-26%	
Ambien/CR Emerging Countries (Fx)	65	60	55	50	45	40	35	30	-11%	-10%	
Ambien/CR Emerging Countries (Lc)				50	45	40	35	30			
Ambien/CR ROW (Fx)	191	125	100	80	60	40	20	10	-34%	-34%	- Majority Japan; regulatory exclusivity exp. 2010; Canada, Australia, New Zealand,
Ambien/CR ROW (Lc)				80	60	40	20	10			
Ambien/CR Total	377	280	225	180	135	95	65	50	-25%	-25%	
Depakine E.U.	138	145	165	180	190	200	210	220	7%	7%	- Valproate; epilepsy and mood stabilization
Depakine Emerging Countries (Fx)	252	235	220	220	220	220	220	220	-1%	-2%	
Depakine Emerging Countries (Lc)				220	220	220	220	220			
Depakine ROW (Fx)	15	15	25	30	35	40	45	50	22%	19%	- Canada, Australia, New Zealand, Japan
Depakine ROW (Lc)				30	35	40	45	50			
Depakine Total	405	395	410	430	445	460	475	490	4%	3%	
Lemtrada	2	30	70	110	150	200	250	300	47%	NM	- Alemtuzumab; anti-CD52 mAb; multiple sclerosis; approved in 30 mkts; Q2:14 sBLA resubmission with 6 month review, Q4 action anticipated
Aubagio	166	405	580	700	550	400	300	200	-11%	3%	- Teriflunomide; oral, MS; monotherapy/adjunct tx & CIS; marketed in U.S., EU positive opinion; exclusivity expires 2017 (U.S.), 2023 (EU)
SAR391786					25	50	75	100	NM	NM	- GDF8 mAb; sarcopenia; Phase II
CNS Total	950	1,110	1,285	1,420	1,305	1,205	1,165	1,140	0%	3%	
Y/Y Change	1%	17%	16%	11%	-8%	-8%	-3%	-2%			

Source: Company data, Cowen and Company estimates

Sanofi Annual Revenue Buildup (€MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CAGR 2014-20	CAGR 2013-20	Comments
Infection											
Ferroquine/OZ439				20	40	60	80	100	NM	NM - Antimalarial combination; Phase II	
SAR279356					25	50	75	100	NM	NM - Anti-PNAG mAb; serious infections; Phase II	
Infection Total				20	65	110	155	200	NM	NM	
Allergy/Asthma											
Allegra U.S. (Fx)	-3	0	0	0	0	0	0	0			- Teva began selling Allegra-D 12 hours 11/09
Allegra U.S. (Lc)				0	0	0	0	0			
Allegra E.U.	10	15	10	10	10	10	10	10	-7%	0%	
Allegra Emerging Countries (Fx)	120	105	125	145	165	185	205	225	14%	9%	
Allegra Emerging Countries (Lc)				145	165	185	205	225			
Allegra ROW (Fx)	279	195	185	175	150	125	100	75	-15%	-17% - Canada, Australia, New Zealand, Japan	
Allegra ROW (Lc)				175	150	125	100	75			
Allegra Total	406	315	320	330	325	320	315	310	0%	-4%	
Nasacort U.S. (Fx)	0	0	0	0	0	0	0	0	NM	NM - Settled with Barr, sell generic 6/11	
Nasacort U.S. (Lc)				0	0	0	0	0			
Nasacort E.U.	20	10	5	5	5	5	5	5	-11%	-18%	
Nasacort Emerging Countries (Fx)	5	5	5	5	5	5	5	5	0%	0%	
Nasacort Emerging Countries (Lc)				5	5	5	5	5			
Nasacort ROW (Fx)	0	10	15	20	25	30	35	40	26%	NM - Canada, Australia, New Zealand, Japan	
Nasacort ROW (Lc)				20	25	30	35	40			
Nasacort Total	25	25	25	30	35	40	45	50	12%	10% - Clipped by OTC form	
Dupilumab					50	150	250	500	NM	NM - SAR231893; anti-IL4 R mAb; asthma, atopic dermatitis, nasal polyposis; Phase II	
Allergy Total	431	340	345	360	410	510	610	860	17%	10%	
Urinary Tract											
Renagel/Renvela U.S. (Fx)	531	345	50	25	15	5	5	5	-51%	-49% - Patent exp 9/12; settlement: first-filer 3/16/14, second filers 9/16/14	
Renagel/Renvela U.S. (Lc)				25	15	5	5	5			
Renagel/Renvela E.U.	133	145	100	50	25	15	15	15	-31%	-27% - Patent expires 2015 in EU	
Renagel/Renvela Emerging Countries (Fx)	67	95	115	135	155	175	195	215	15%	18%	
Renagel/Renvela Emerging Countries (Lc)				135	155	175	195	215			
Renagel/Renvela ROW (Fx)	19	30	40	50	60	70	80	90	20%	25%	
Renagel/Renvela ROW (Lc)				50	60	70	80	90			
Renagel/Renvela Total	750	615	305	260	255	265	295	325	-10%	-11% - Control of serum phosphorus in pts with chronic kidney disease (CKD)	
Xatral U.S. (Fx)	3	0	5	5	5	5	5	5	#NUM!	8% - BPH; several paragraph IV filings; generics assumed 2011; competitor generics available	
Xatral U.S. (Lc)				5	5	5	5	5			
Xatral E.U.	39	30	20	10	5	5	5	5	-26%	-25% - Generics launched in majority of E.U.	
Xatral Emerging Countries (Fx)	58	50	45	40	35	30	25	20	-14%	-14%	
Xatral Emerging Countries (Lc)				40	35	30	25	20			
Xatral ROW (Fx)	1	0	0	0	0	0	0	0	NM	NM - Japanese regulatory discussions underway; Canada, Australia, New Zealand, Japan	
Xatral ROW (Lc)				0	0	0	0	0			
Xatral Total	101	80	70	55	45	40	35	30	-15%	-16%	
Urinary Total	851	695	375	315	300	305	330	355	-11%	-12%	
Osteoarthritis											
Synvisc U.S. (Fx)	295	265	285	305	325	345	365	385	6%	4%	
Synvisc U.S. (Lc)				305	325	345	365	385			
Synvisc E.U.	25	30	40	50	60	70	80	90	20%	20%	
Synvisc Emerging Countries (Fx)	32	40	45	50	55	60	65	70	10%	12%	
Synvisc Emerging Countries (Lc)				50	55	60	65	70			
Synvisc ROW (Fx)	19	25	30	35	40	45	50	55	14%	16%	
Synvisc ROW (Lc)				35	40	45	50	55			
Synvisc Total	371	355	400	440	480	520	560	600	9%	7% - Treatment of pain in osteoarthritis (OA) of the knee; OA of hip in Phase III	

Source: Company data, Cowen and Company estimates

Sanofi Annual Revenue Buildup (€MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CAGR 2014-20	CAGR 2013-20	Comments
Rare Diseases											
Cerezyme U.S. (Fx)	178	190	220	240	270	300	330	360	11%	11% - U.S. supply established; Allston plant to add two bioreactors	
Cerezyme U.S. (Lc)				240	270	300	330	360			
Cerezyme E.U.	225	240	260	280	300	320	340	360	7%	7% - Working to build global supply	
Cerezyme Emerging Countries (Fx)	241	245	265	285	305	325	345	365	7%	6%	
Cerezyme Emerging Countries (Lc)				285	305	325	345	365			
Cerezyme ROW (Fx)	44	50	65	80	95	110	125	140	19%	18%	
Cerezyme ROW (Lc)				80	95	110	125	140			
Cerezyme Total	688	725	810	885	970	1,055	1,140	1,225	9%	9% - Long-term enzyme replacement therapy - type 1 Gaucher disease; supply constrained	
Myozyme/Lumizyme U.S. (Fx)	123	135	155	175	195	215	235	255	11%	11%	
Myozyme/Lumizyme U.S. (Lc)				175	195	215	235	255			
Myozyme/Lumizyme E.U.	274	275	300	320	340	360	380	400	6%	6%	
Myozyme/Lumizyme Emerg. Countries (Fx)	74	95	115	135	155	175	195	215	15%	16%	
Myozyme/Lumizyme Emerg. Countries (Lc)				135	155	175	195	215			
Myozyme/Lumizyme ROW (Fx)	29	35	50	60	70	80	90	100	19%	19%	
Myozyme/Lumizyme ROW (Lc)				60	70	80	90	100			
Myozyme/Lumizyme Total	500	540	620	690	760	830	900	970	10%	10% - Pompe disease, infantile-onset (Myozyme); late-onset (Lumizyme)	
Fabrazyme U.S. (Fx)	196	215	265	285	315	345	375	405	11%	11% - U.S. supply established; Framingham plant approved	
Fabrazyme U.S. (Lc)				285	315	345	375	405			
Fabrazyme E.U.	87	105	120	140	160	180	200	220	13%	14% - Working to build global supply	
Fabrazyme Emerging Countries (Fx)	51	75	85	95	105	115	125	135	10%	15%	
Fabrazyme Emerging Countries (Lc)				95	105	115	125	135			
Fabrazyme ROW (Fx)	49	65	85	95	105	115	125	135	13%	16%	
Fabrazyme ROW (Lc)				95	105	115	125	135			
Fabrazyme Total	383	460	555	615	685	755	825	895	12%	13% - Fabry disease; supply restored	
Cerdelga (eliglustat)		60	260	400	550	650	750	850	56%	NM - Glucosylceramide synthetase inh.; Gaucher disease in adults; EU validated filing in 10/13; FDA approved 8/14	
Kynamro	20	30	60	80	100	120	140	160	32%	NM - Mipomersen; apolipoprotein B-100 antisense; approved for hoFH in U.S., hoFH and severe heFH EU; severe HeFH PIII U.S.; patent exp 12/25 US, 11/23 EU	
Fresolimumab (GC1008)					25	50	75	100	NM	NM - TGF beta antagonist; focal segment glomerulosclerosis; Phase II	
Patisiran					25	50	75	100	NM	NM - SAR438037; mRNA inhibitor; familial amyloid polyneuropathy; Phase III	
Other	513	560	600	650	700	750	800	850	7%	7%	
Rare Diseases Total	2,104	2,375	2,905	3,320	3,815	4,260	4,705	5,150	14%	14% - Genzyme acquired on 4/1/11 for \$20.1B in cash, excluding CVR	
Total Strategic Products	17,329	17,565	18,555	18,385	18,925	19,555	20,305	21,280	3%	3%	
Y/Y Change	-3%	1%	6%	-1%	3%	3%	4%	5%			
Other Products	5,292	4,750	4,275	3,850	3,600	3,400	3,200	3,000	-7%	-8% - Emerging markets temper decline	
Y/Y Change	-14%	-10%	-10%	-10%	-6%	-6%	-6%	-6%			
Total Branded Pharmaceuticals	€ 22,621	€ 22,315	€ 22,830	€ 22,235	€ 22,525	€ 22,955	€ 23,505	€ 24,280	1%	1%	
Y/Y Change	-6%	-1%	2%	-3%	1%	2%	2%	3%			
OTC	3,004	3,265	3,450	3,600	3,750	3,900	4,050	4,200	4%	5% - Chattem acquisition boosted starting Q1:10; Nasocort OTC rolling out; 50% of sales to emerging markets	
Y/Y Change	0%	9%	6%	4%	4%	4%	4%	4%			
Generics	1,625	1,950	2,075	2,175	2,275	2,375	2,475	2,575	5%	7% - Zentiva, Medley, and Kendrick consolidated Q2:09; 2/3 emerging markets, with Brazil the biggest portion	
Y/Y Change	-12%	20%	6%	5%	5%	4%	4%	4%			

Source: Company data, Cowen and Company estimates

Sanofi Annual Revenue Buildup (€MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CAGR 2014-20	CAGR 2013-20	Comments
Vaccines											
Polio/Pertussis/Hib U.S. (Fx)	275	375	455	525	600	675	750	825	14%	17% - Progressive supply recovery beginning Q4:13	
Polio/Pertussis/Hib U.S. (Lc)				525	600	675	750	825			
Polio/Pertussis/Hib E.U.	35	40	60	70	80	90	100	110	18%	18%	
Polio/P/Hib Emerging Countries (Fx)	644	595	675	725	775	800	825	850	6%	4%	
Polio/P/Hib Emerging Countries (Lc)				725	775	800	825	850			
Polio/Pertussis/Hib ROW (Fx)	194	175	215	350	400	450	500	550	21%	16% - Canada, Australia, New Zealand, Japan	
Polio/Pertussis/Hib ROW (Lc)				350	400	450	500	550			
Polio/Pertussis/Hib Total (Fx)	1,148	1,190	1,405	1,670	1,855	2,015	2,175	2,335	12%	11% - Pediatric vaccines for developing economy; \$340MM U.N. contract awarded 2010-12	
Y/Y Change	-3%	4%	18%	19%	11%	9%	8%	7%			
Adult Booster Vaccines U.S. (Fx)	268	275	300	355	385	415	445	475	10%	9%	
Adult Booster Vaccines U.S. (Lc)				355	385	415	445	475			
Adult Booster Vaccine E.U.	60	35	55	90	110	130	150	170	30%	16%	
Adult Booster Emerging Countries (Fx)	48	55	60	65	70	75	80	85	8%	9%	
Adult Booster Emerging Countries (Lc)				65	70	75	80	85			
Adult Booster Vaccines ROW (Fx)	15	15	25	30	35	40	45	50	22%	19% - Canada, Australia, New Zealand, Japan	
Adult Booster Vaccines ROW (Lc)				30	35	40	45	50			
Adult Booster Vaccines Total	391	380	440	540	600	660	720	780	13%	10%	
Y/Y Change	-21%	-3%	16%	23%	11%	10%	9%	8%			
Influenza Vaccines U.S. (Fx)	533	570	610	650	700	750	800	850	7%	7%	
Influenza Vaccines U.S. (Lc)				650	700	750	800	850			
Influenza Vaccines E.U.	83	100	115	130	140	150	165	180	10%	12%	
Influenza Emerging Countries (Fx)	291	325	355	375	400	425	450	475	7%	7%	
Influenza Emerging Countries (Lc)				375	400	425	450	475			
Influenza Vaccines ROW (Fx)	22	20	35	40	45	50	55	60	20%	15% - Canada, Australia, New Zealand, Japan	
Influenza Vaccines ROW (Lc)				40	45	50	55	60			
Influenza Vaccines Total	929	1,020	1,115	1,195	1,285	1,375	1,470	1,565	7%	8% - Increase in flu capacity by 100MM doses	
Y/Y Change	5%	10%	9%	7%	8%	7%	7%	6%			
Travel Vaccines U.S. (Fx)	97	110	125	145	165	185	205	225	13%	13%	
Travel Vaccines U.S. (Lc)				145	165	185	205	225			
Travel Vaccines E.U.	18	30	35	45	55	65	75	85	19%	25%	
Travel Vaccines Emerging Countries (Fx)	215	220	250	270	290	310	330	350	8%	7%	
Travel Vaccines Emerging Countries (Lc)				270	290	310	330	350			
Travel Vaccines ROW (Fx)	52	60	70	75	80	85	90	95	8%	9% - Canada, Australia, New Zealand, Japan	
Travel Vaccines ROW (Lc)				25	30	35	40	45			
Travel Vaccines Total	382	420	480	535	590	645	700	755	10%	10%	
Y/Y Change	5%	10%	14%	11%	10%	9%	9%	8%			
Meningitis/Pneumonia Vaccines U.S. (Fx)	352	425	440	460	490	520	550	580	5%	7% - ACIP recommended usage down to 18 months of age	
Meningitis/Pneumonia Vaccines U.S. (Lc)				460	490	520	550	580			
Meningitis/Pneumonia Vaccines EU	5	10	30	40	50	60	70	80	41%	49%	
Meningitis/P Emerging Countries (Fx)	132	95	125	155	185	215	240	265	19%	10%	
Meningitis/P Emerging Countries (Lc)				155	185	215	240	265			
Meningitis/Pneumonia Vaccines ROW (Fx)	7	15	20	25	30	35	40	45	20%	30% - Canada, Australia, New Zealand, Japan	
Meningitis/Pneumonia Vaccines ROW (Lc)				25	30	35	40	45			
Meningitis/Pneumonia Vaccines Total	496	545	615	680	755	830	900	970	10%	10% - Saturated Men A,C,W,Y U.S. market; pediatric Men A,C,W,Y approval '11	
Y/Y Change	-24%	10%	13%	11%	11%	10%	8%	8%			
Dengue U.S. (Fx)				10	20	30	40	50	60	NM	NM
Dengue U.S. (Lc)				20	30	40	50	60	60	NM	NM
Dengue EU				10	20	30	40	50	60	NM	NM
Dengue Emerging Countries (Fx)				60	100	200	300	400	500	NM	NM - Dengue vaccine Phase III efficacy results solid
Dengue Emerging Countries (Lc)				100	200	300	400	500	500	NM	NM - Canada, Australia, New Zealand, Japan
Dengue ROW (Fx)				60	100	200	300	400	500	NM	NM - Canada, Australia, New Zealand, Japan
Dengue ROW (Lc)				100	200	300	400	500	500	NM	NM - Dengue fever; new facility came on line 2013: 100MM doses
Dengue Total				140	240	460	680	900	1,120	NM	
Y/Y Change				71%	92%	48%	32%	24%			
Other Vaccines U.S. (Fx)	347	375	430	470	520	570	620	670	10%	10% - C. difficile toxoid (P3), Quadracel (filed), Fluzone (filed), VaxiGrip (P3), PRSI (P3)	
Other Vaccines U.S. (Lc)				470	520	570	620	670			
Other Vaccines EU	3	10	15	20	25	30	35	40	26%	45%	
Other Vaccines Emerging Countries (Fx)	11	20	30	40	50	60	70	80	26%	33%	
Other Vaccines Emerging Countries (Lc)				40	50	60	70	80			
Other Vaccines ROW (Fx)	9	25	30	40	50	60	70	80	21%	37% - Canada, Australia, New Zealand, Japan	
Other Vaccines ROW (Lc)				40	50	60	70	80			
Other Vaccines Total	370	435	505	570	645	720	795	870	12%	13%	
Y/Y Change	16%	18%	16%	13%	13%	12%	10%	9%			
Vaccines Total	€ 3,716	€ 3,980	€ 4,700	€ 5,430	€ 6,190	€ 6,925	€ 7,080	€ 8,385	13%	12% - New vaccines fuel growth; market growing 9%, emerging markets growing 15%	
Y/Y Change	-5%	7%	18%	16%	14%	12%	11%	10%			- Guidance of double digit growth in 2014-16

Source: Company data, Cowen and Company estimates

Sanofi Annual Revenue Buildup (€MM) (continued)

	2013	2014E	2015E	2016E	2017P	2018P	2019P	2020P	CAGR 2014-20	CAGR 2013-20	Comments
Animal Health											
Fipronil U.S. (Fx)	289	240	150	100	75	50	25	10	-41%	-38%	
Fipronil U.S. (Lc)				100	75	50	25	10			
Fipronil E.U.	177	175	140	100	80	60	40	20	-30%	-27%	
Fipronil Emerging Countries (Fx)	99	85	60	50	40	30	20	10	-30%	-28%	
Fipronil Emerging Countries (Lc)				50	40	30	20	10			
Fipronil ROW (Fx)	46	40	30	20	15	10	5	5	-29%	-27% - Canada, Australia, New Zealand, Japan	
Fipronil ROW (Lc)				20	15	10	5	5			
Fipronil Total	611	540	380	270	210	150	90	45	-34%	-31% - Anti-parasiticide	
Y/Y Change		-12%	-30%	-29%	-22%	-29%	-40%	-50%			
Vaccines U.S. (Fx)	152	150	170	180	190	200	210	220	7%	5%	
Vaccines U.S. (Lc)				180	190	200	210	220			
Vaccines E.U.	182	185	190	195	200	205	210	215	3%	2%	
Vaccines Emerging Countries (Fx)	374	355	370	390	410	430	450	470	5%	3%	
Vaccines Emerging Countries (Lc)				390	410	430	450	470			
Vaccines ROW (Fx)	19	20	20	20	20	20	20	20	0%	1% - Canada, Australia, New Zealand, Japan	
Vaccines ROW (Lc)				20	20	20	20	20			
Vaccines Total	727	710	750	785	820	855	890	925	5%	4%	
Y/Y Change		-2%	6%	5%	4%	4%	4%	4%			
Avermectines U.S. (Fx)	225	195	170	145	125	105	85	65	-17%	-16%	
Avermectines U.S. (Lc)				145	125	105	85	65			
Avermectines E.U.	58	55	40	30	20	10	5	5	-33%	-30%	
Avermectines Emerging Countries (Fx)	59	55	50	45	40	35	30	25	-12%	-12%	
Avermectines Emerging Countries (Lc)				45	40	35	30	25			
Avermectines ROW (Fx)	71	65	60	55	50	45	40	35	-10%	-10% - Canada, Australia, New Zealand, Japan	
Avermectines ROW (Lc)				55	50	45	40	35			
Avermectines Total	413	365	320	275	235	195	160	130	-16%	-15% - Heartgard	
Y/Y Change		-12%	-12%	-14%	-15%	-17%	-18%	-19%			
Nexgard U.S. (Fx)		110	150	200	300	400	500	600	33%	NM - Rollout underway	
Nexgard U.S. (Lc)			200	300	400	500	600				
Nexgard EU	30	110	200	300	400	500	600	600	65%	NM	
Nexgard Emerging Countries (Fx)	0	0	0	0	0	0	0	0	NM	NM - Launched in France	
Nexgard Emerging Countries (Lc)				0	0	0	0	0			
Nexgard ROW (Fx)	0	0	0	0	0	0	0	0	NM	NM - Canada, Australia, New Zealand, Japan	
Nexgard ROW (Lc)				0	0	0	0	0			
Nexgard Total	140	260	400	600	800	1,000	1,200	1,200	43%	NM - Fleas and ticks; chewable beef favored	
Y/Y Change		86%	54%	50%	33%	25%	20%				
Other U.S. (Fx)	81	75	90	95	100	105	110	115	7%	5%	
Other U.S. (Lc)			95	100	105	110	115				
Other EU	85	90	95	100	105	110	115	120	5%	5%	
Other Emerging Countries (Fx)	55	60	65	70	75	80	85	90	7%	7%	
Other Emerging Countries (Lc)				70	75	80	85	90			
Other ROW (Fx)	13	15	25	30	35	40	45	50	22%	21% - Canada, Australia, New Zealand, Japan	
Other ROW (Lc)				30	35	40	45	50			
Other Total	234	245	275	295	315	335	355	375	7%	7%	
Y/Y Change		5%	12%	7%	7%	6%	6%	6%			
Animal Health Total	€ 1,985	€ 2,000	€ 1,985	€ 2,025	€ 2,180	€ 2,335	€ 2,495	€ 2,675	5%	4% - Growth recovery keyed to new products	
Y/Y Change	-9%	1%	-1%	2%	8%	7%	7%	7%			
Total Net Sales	€ 32,951	€ 33,520	€ 35,040	€ 35,485	€ 36,920	€ 38,490	€ 40,185	€ 42,125	4%	4%	
Y/Y Change	-6%	2%	5%	1%	4%	4%	4%	5%			

Source: Company data, Cowen and Company estimates

Diabetes And Metabolism

Lantus Franchise On Solid Footing Although Competition On The Horizon

Lantus (insulin glargine) is a once-daily, long-acting basal insulin injection used for type 1 diabetes (absolute insulin deficiency) and type 2 diabetes (relative insulin deficiency or insulin resistance). Lantus offers lower hypoglycemia risk and improved metabolic control, given 24-hour basal insulin coverage, with no pronounced peak concentrations. The efficacy benefits provided by Lantus (dosed via a once-daily subcutaneous injection) in combination with mealtime fast-acting insulin injections raised the benchmark for glucose control in type 1 diabetics. Lantus is the leading branded insulin in the U.S. (with an estimated 80% share) and in many major European markets. The SoloStar pen, launched in 2007, is the major growth driver for the Lantus franchise. SoloStar is a prefilled disposable pen that allows patients to administer doses, from 1 up to 80 units, in one injection.

Lantus is marketed in more than 70 countries, including Japan. Sanofi pays Novo an undisclosed royalty on Lantus sales due to cross-licensing of patent rights. Lantus is covered by a compound patent expiring in November 2014, and six-month pediatric exclusivity has been granted in the U.S. (2/15). In December 2013, Lilly filed its insulin glargine biosimilar; in January 2014, Sanofi filed a patent infringement suit against Eli Lilly over four patents related to Lantus triggering a 30-month stay (to mid-2016).. In July 2014, Sanofi filed an additional lawsuit accusing Lilly of infringement on seven patents related to Lantus and the SoloStar pen. The trial is scheduled for September 2015.

In August 2014, the FDA granted tentative approval to Lilly's biosimilar, but final approval cannot be granted until end of the 30-month stay (mid-2016). In September 2014, the Lilly biosimilar was approved in the EU, with launch anticipated mid 2015 post the 2/15 patent expiry. In September 2014, Mylan announced that it was initiating Phase III trials for its Lantus biosimilar

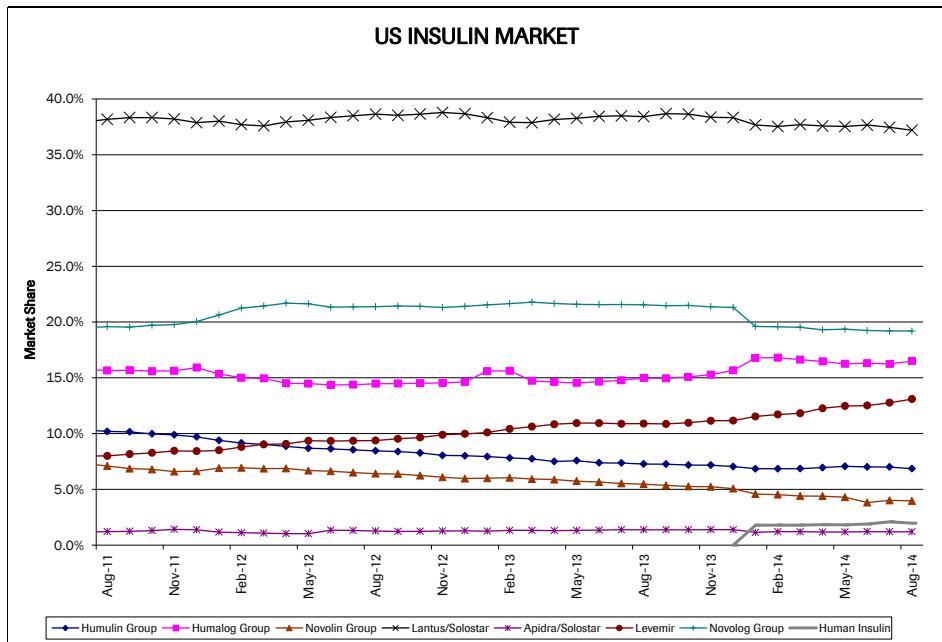
We estimate Lantus sales of €6.345B (+11%) in 2014, €6.91B in 2015, €6.16B in 2016 (reflecting competitive launch from Lilly), €5.29B in 2018, and €4.42B in 2020.

Strong Commitment To Diabetes Franchise

Sanofi has many efforts to protect its insulin franchise including: 1) bundling diabetes care products (Lantus, test strips, a generic antihypertensive agent), into packages for certain emerging markets; 2) competing on price when necessary; 3) developing lixisenatide both alone and in combination with Lantus (with intellectual property protecting the single agent and combination); 4) SoloStar (prefilled disposable insulin pen which represents about 50% of U.S. sales and majority of E.U. sales); and 5) the new Toujeo formulation.

In January 2010, Sanofi formed a new diabetes division and increased its marketing effort in the U.S. for several reasons. First, competition has increased, accompanied by significant commercial investment from the GLP-1 and DPP-IV competitors. Second, it believes the overall market has slowed, partially due to co-pays, but also due to the economic downturn. Third, Sanofi launched the Agamatrix/BG Star blood glucose monitor in the E.U. in 2011; and in Asia and Latin American in 2012. The Agamatrix/BG Star is the first approved glucose meter that connects to the iPhone and iPod. Given that 60-70% of diabetes patients are potentially under-dosed, the device may help boost sales.

U.S. Insulin Market



Source: IMS America

Novo's Degludec Study To Garner Interim Look In 2015

Degludec (Tresiba) is Novo's ultra-long-acting basal insulin analogue that is dosed once daily. Degludec's 40 hour duration of action provides a prolonged steady state, reducing peaking concentrations, and hypothetically reducing the risk of hypoglycemia. Tresiba was approved in December 2012 in Japan (where reimbursement is similar to Lantus) and in January 2013 in the E.U. Tresiba has been launched in 15 countries through June 2014.

In February 2013, Novo announced it has received a complete response letter (CRL) from the FDA for Tresiba and Ryzodeg requesting additional CV safety data from a dedicated cardiovascular outcomes trial. The CRL followed a positive November 7, 2012 AdCom (8-4 vote in favor of approval). However, the FDA Advisory Committee unanimously recommended (12-0) that a cardiovascular outcomes trial be conducted given the increase in MACE events associated with degludec in Phase III studies.

Novo initiated a CV outcomes study in October 2013 (DEVOTE) with a target enrollment of 7,500 type-2 diabetic patients having moderate to high CV risk. The primary endpoint is time until first MACE (CV death, non-fatal MI, non-fatal stroke). Novo has indicated the study is progressing faster than expected (MACE rate higher than expected so required events accumulated faster) and expects to have interim data around the end of the year (late 2014/early 2015) and submit the interim analysis to the FDA in H1:15 (prior expectation for data was late 2015). The trial is expected to complete 3-4 years from initiation versus previous expectation for 3-5 years.

Possible Link To Cancer Not Substantiated

In June 2009, the Diabetes Journal of the EASD (Diabetologia) published four observational analyses that are conflicting and inconclusive. The German study, after many adjustments, demonstrated a hazard ratio (HR) of 1.31 for the diagnosis of cancer for patients on Lantus. The Swedish analysis found that patients on Lantus

alone had an HR of 1.99 for the risk of breast cancer, but the numbers are small and there was no significant trend for other cancers. The Scottish analysis resulted in an HR of 1.66 for the overall cancer rate for patients on Lantus alone but when combined with other insulins the HR was 0.66. The U.K. database did not demonstrate an increased cancer risk.

In order to refute these data, Sanofi began submitting results from analyses of internal and external databases as well as new clinical data to regulatory authorities in H2:09. In December 2011 Sanofi presented a meta-analysis at the World Diabetes Congress in Dubai, adding to the evidence resulting from more than 80,000 patients enrolled in clinical trials and 38 million patient years of treatment exposure to Lantus. This meta-analysis on the relationship between diabetes and cancer risk demonstrates no increased risk in people using Lantus. The meta-analysis was performed on observational studies derived from databases as well as from randomized controlled clinical trials and from a case-control study in numerous countries (such as Sweden, Germany, Scotland, England and Taiwan) assessing the risk for cancer in individuals with diabetes using different insulins. Sanofi is involved in three additional large studies including two retrospective cohort studies and one case-control study conducted by independent investigators. Final results of the first study based on Nordic databases were communicated to regulatory agencies in late 2011.

In July 2009, Sanofi published the results from a one-year trial comparing Lantus to NPH on the progression of retinopathy in type 2 patients. There was no difference between the groups. Sanofi is hoping that this trial might dispel some concern as the stimulation of IGF1 receptors is involved in this retinopathy process and Lantus' binding to the IGF-1R has been implicated in its association with cancer.

Lack Of Cancer Signal In ORIGIN A Positive For Lantus

Neither an analysis of all cancers combined nor an analysis of any organ-specific cancer demonstrated an increase in cancer risk for Lantus in ORIGIN (HR=1.00, p=0.97). Detection of a cancer signal in ORIGIN represented the worst-case scenario for the Lantus franchise. ORIGIN, together with data from several registry studies, strongly refutes assertions that Lantus is associated with an increased risk of cancer.

Lantus Fails To Demonstrate CV Benefit In ORIGIN

ORIGIN was a six-year trial to evaluate the impact of Lantus on CV outcomes in 12,500 patients with pre-diabetes or early type II diabetes with high CV risk. 6,264 patients were initiated on Lantus therapy and titrated to achieve fasting normoglycemia. The co-primary endpoints for ORIGIN were the composite of CV death, non-fatal MI, or non-fatal stroke (co-primary #1); and the composite of CV death, non-fatal MI non-fatal stroke, revascularization, or hospitalization for heart failure (co-primary #2).

Normalizing blood glucose with Lantus did not improve CV outcomes when compared to standard of care (co-primary #1: HR=1.02, p=0.63; co-primary #2: HR=1.04, p=0.27). Our physician consultants believe that normalizing blood glucose with insulin is important to maintaining endothelial health and preventing vascular complications. However, significant heterogeneity across the ORIGIN population may have masked secondary effects from independent risk factors and contributed to the negative outcome of this study.

Toujeo: The Next Lantus

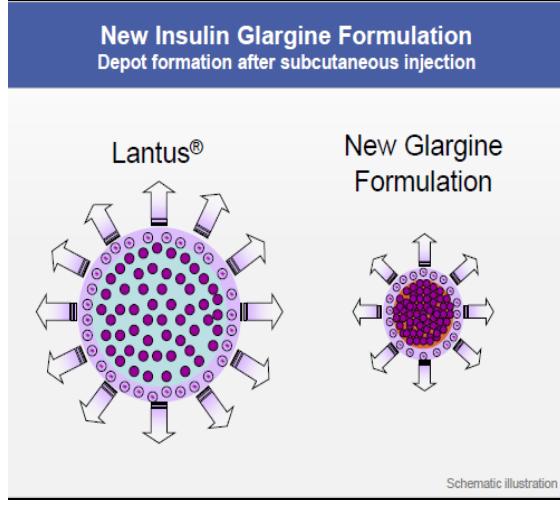
Sanofi's new glargine formulation, Toujeo (U300), is designed to provide a unique PK/PD profile and to allow for a lower injection volume. Sanofi expects Toujeo to

target both high dose insulin users with type II diabetes and users administering more typical doses. A formulation that allows for insulin granules to be packed more densely should allow for greater amounts of insulin to be delivered in smaller volumes. Patents describe the new Lantus formulation as being more concentrated than the current formulation (300mg/mL vs. 100mg/mL). Given the increased glargine concentration in the new Lantus, a greater amount of Lantus precipitates at neutral pH than in the existing formulation and provides a unique PK profile. This is exemplified by more flat glucose infusion rates compared to Lantus, suggesting >24hrs duration of action for U300.

The patent on U300 was filed in 2011 and examination by the USPTO is ongoing. The patent covers a wide range of glargine concentrations. Our legal consultants believe that the dissolution of the new Lantus formulation at neutral pHs is what would be expected by increasing the glargine concentration and does not believe the new Lantus patent application is likely to be granted. A patent was granted in the EU in July 2014 with an expiry in 2031. Toujeo has also been granted patents in Australia, Japan and other smaller markets.

Management indicated that it expects growth for basal insulin to be driven by switches in emerging markets (from pre-mixed insulin to basal) as well as the continued growth in new-to-insulin patients elsewhere. Toujeo was filed in the U.S. and E.U. in April 2014 and in Japan in July 2014. The FDA accepted the filing on July 8, 2014. Sanofi expects regulatory decisions for U.S and E.U. in H1:15. We estimate Toujeo sales of €150MM in 2015, €300MM in 2016, €900MM in 2018, and €1,500MM in 2020.

Lantus Versus U300 Depot Formation



Source: Company data

Pooled Meta-Analysis Demonstrates Reduced Hypoglycemia

Data presented at ADA 2014 (and previously) showed Toujeo (U300 basal insulin) to be as effective at HbA1c control as Lantus (and with slightly less weight gain, but with a lower incidence of hypoglycemia). A pooled meta-analysis of three Phase III EDITION trials in T2DM presented at ADA 2014 showed a decrease in nocturnal hypoglycemia of 31% (as measured by event rate per patient year across the 6 month study period) and a 14% decrease in hypoglycemia at any time. Sanofi believes that patient concerns over hypoglycemia are a key contributor to insulin non-compliance.

However, our physician experts have been more cautious on the U300 product, citing concerns that patient doing errors of the more concentrated product could magnify hypoglycemic reactions.

Data For U300 Insulin Solid But Not Spectacular

EDITION I was an 807 patient Phase III trial comparing U300 to Lantus in patients with T2DM requiring >42U of basal insulin and a mealtime insulin. U300 demonstrated non-inferior lowering of HbA1c compared to Lantus at week-24 (average decrease of 0.81%), but decreased the number of patients experiencing nocturnal hypoglycemia by 21% (46% on Lantus vs. 36.1% on U300). While a statistically significant reduction in nocturnal hypoglycemia is positive, our clinical consultants believe the absolute number of severe hypoglycemic events is low on Lantus and that reductions afforded by novel formulations are of limited clinical utility (5.3% for Lantus vs. 5% on U300 in EDITION I).

In December 2013, Sanofi released complete data for the Phase III EDITION-II trial comparing U300 to Lantus in patients requiring >42U of basal insulin and an oral anti-diabetic drug (n=811). Top line data was presented at the ADA in June 2013. U300 was shown to be non-inferior to Lantus on HbA1c reduction and demonstrated fewer night-time low blood sugar events. The percentage of patients with severe/confirmed nocturnal hypoglycemia from month 3 to 6 was shown to be significantly lower with U300 vs Lantus (21.6% vs 27.9%; 95% CI: 0.61 -0.99, p=0.038). Over the 6 month treatment period, the incidence of any nocturnal hypoglycemia was 30.5% for U300 and 41.6% for Lantus and incidence of any hypoglycemia was 71.5% for U300 and 79.3% for Lantus.

In top-line data for EDITION III (insulin naive, type 2 diabetics; n=878), also released December 2013, U300 demonstrated non-inferiority in HbA1c reduction to Lantus at 6 months. However, while U300 did show a lower percentage of severe/confirmed nocturnal hypoglycemia vs Lantus (15.5% vs 17.4%), the difference was not statistically significant, as had been demonstrated in EDITION I and II trials. The incidence of any hypoglycemia was 49.9% for U300 and 55.3% for Lantus.

In both EDITION IV (type 1 diabetes; n=549) and EDITION JP1 (type 1 diabetics in Japan; n=243), U300 demonstrated non-inferiority to Lantus in HbA1c reduction at 6 months. In EDITION IV, rates of any-time hypoglycemia were similar between Toujeo and Lantus. However, Toujeo demonstrated a statistically significant 31% relative reduction in nocturnal hypoglycemia vs Lantus (7.8% vs 11.2%). Adverse events for U300 and Lantus were reported as similar in all studies.

Novo's Levemir Fails To Make Significant Inroads

Novo Nordisk's Levemir (insulin detemir), was launched in the U.S. in March 2006. Levemir has improved its market share modestly over time (12.5% U.S. NRx share May 2014; +23% Y/Y), although has failed to make significant progress where it competes with Lantus. This is despite weight-gain data presented at the 2006 ADA that may be differentiating. However, in a direct comparison to Levemir, Lantus was shown to have activity levels more than four times greater than Levemir during the period from 12 to 24 hours after administration. The same study showed a marked and highly significant difference in terms of duration of action: Lantus showed 24-hour coverage whereas Levemir had duration of action of only 17.5 hours. Following the Lantus Diebetologia publications, Novo stated that all its insulin analogs have been tested for IGF-1 receptor binding in the early research phase and only insulins with a binding ratio

between the insulin and IGF-1 receptors similar to, or better than, that of human insulin have been accepted for further development. Studies on receptor binding have shown that Levemir in comparison to human insulin has a relative affinity to the IGF-1 receptor, which is equal to or slightly lower than to the insulin receptor. Novo points out that Levemir distinguishes itself from Lantus, which has been shown to have increased affinity for the IGF-1 receptor compared to human insulin. Much of this remains theoretical but is likely to be used by Novo's sales organization in its promotion of Levemir. This could sway prescribers to switch to Levemir, especially for new patients.

Apidra Struggles To Gain A Foothold In Fast-Acting Market

Apidra (insulin glulisine), launched in an OptiClick reusable insulin pen formulation, holds <1% prescription share of the U.S. insulin market. Short-acting or fast-acting insulin analogs are important and useful because, when used properly, they produce less nocturnal hypoglycemia; can be used immediately before meals; assist treatment of children; and enhance quality of life. Fast-acting insulins reduce the glucose spikes that occur after meals, which are linked to the progressive development of diabetic complications (blindness, kidney failure and gangrene requiring limb amputation). In April 2009, Sanofi launched Apidra SoloSTAR, a prefilled disposable pen. Apidra can now be administered using an insulin pump, vial and syringe, the OptiClik device, the SoloSTAR prefilled disposable insulin pen, or intravenously. Lilly's Humalog and Novo's Novolog essentially split the short-acting insulin analog market in the U.S. We forecast Apidra sales of €330MM (+15%) in 2014, €380MM in 2015, €425MM in 2016, €515MM in 2018, and €605MM in 2020.

Lyxumia Approved In The E.U.; Filing Pulled In The U.S.; Refiling Likely Summer 2015

Lyxumia (lixisenatide) is a once-daily GLP-1 analog (by injection pen) that is unlikely to be differentiated from the leading GLP-1 agonists but is strategic to Sanofi as it builds out its diabetes franchise. In February 2013, the European Commission granted marketing authorization for Lyxumia in combination with oral glucose-lowering medications and/or basal insulin when these, together with diet and exercise, do not provide adequate glycemic control. Germany was the first E.U. country to launch, followed by the U.K., Spain, Mexico, and additional countries continue to be rolled out. Lyxumia was also approved in Japan in June 2013. However, in the U.S., the NDA was withdrawn in 2013. The NDA had included early interim results from the ongoing ELIXA CV outcomes study. Sanofi will resubmit Lyxumia after ELIXA completes; data is expected in H1:15 with filing in summer 2015. The decision to withdraw the lixisenatide NDA follows discussions with FDA regarding its proposed process for the review of the interim data. Sanofi believes that potential public disclosure of early interim data could potentially compromise the integrity of the ongoing ELIXA study. Sanofi's decision is not related to safety issues or deficiencies in the NDA.

Data presented at ADA 2014 showed Lyxumia, as an add-on to Lantus, had more pronounced post-prandial (after meal) glucose lowering effect compared to liraglutide. We estimate Lyxumia sales of €30MM in 2014, €70MM in 2015, €125MM in 2016, €225MM in 2018, and €325MM in 2020.

GetGoal Demonstrated Lyxumia's Effectiveness In HbA1c Reduction

Lyxumia entered into a broad Phase III GetGoal program in 2009. There are 10 studies of predominantly 24-week duration using lixisenatide 20 ug once daily. There are two monotherapy studies and numerous combinations in the program. Sanofi will also examine a dose titration regimen and a morning versus evening regimen. In April

2010, Sanofi released positive top-line data from Lyxumia's first Phase III (once daily GLP-1 agonist by injection pen) trial. Detailed data was presented at the 46th Annual Meeting of the European Association for the Study of Diabetes in September 2010. The 12-week, randomized, double-blind study enrolled 361 Type 2 diabetic patients not receiving any therapy to either Lyxumia (two different regimens) or placebo. Relative to placebo, Lyxumia statistically significantly reduced mean HbA1c in both dosing groups ($p < 0.0001$). In addition, patients administered Lyxumia were more likely to achieve a HbA1c < 7% (46.5–52.2% vs. 26.8% respectively; $p < 0.01$). Lyxumia also reduced the mean change from baseline 2-hr postprandial (-4.5 to -5.5, $p < 0.0001$) and reduced mean body weight. Similar to Bydureon, Lyxumia's most common side effect was nausea (20–24%, vs. 4% for placebo). Rates of hypoglycemia were low (1.7%) and similar between drug arms and placebo. There was no evidence of increased treatment-emergent SAEs.

Lyxumia met its primary endpoint of non-inferiority in HbA1c reduction from baseline, compared with exenatide twice-daily in the 24-week Phase III GetGoal-X trial. Lyxumia once daily achieved its primary endpoint of non-inferiority in A1C reduction versus exenatide twice daily (LS mean \pm SE change from baseline: -0.79 ± 0.05 vs. -0.96 ± 0.05). Improvements in mean fasting plasma glucose (LS mean \pm SE change from baseline: -22.0 ± 2.1 vs. -26.1 ± 2.1) and the percentage of patients achieving the study target A1C < 7.0 percent (48.5% vs. 49.8%) were comparable between groups. Mean body weight significantly decreased from baseline in the Lyxumia group compared to the exenatide group (94.5 to 91.7 kg with lixisenatide vs. 96.7 to 92.9 kg with exenatide). Additionally, significantly fewer patients experienced symptomatic hypoglycemia with Lyxumia (2.5% vs. 7.9%, $p < 0.05$), with 6-fold fewer hypoglycemic events (8 vs. 48) versus exenatide. The GetGoal-X trial compared the efficacy and safety of once-daily Lyxumia vs. twice-daily exenatide as add-on therapy for people with type 2 diabetes whose condition is inadequately controlled by metformin. A total of 639 people were randomized to receive either Lyxumia or exenatide. Both groups received a stepwise increase in dose, up to a maximum daily dose of 20 μ g.

Data from the GetGoal-L Asia trial showed in Asian patients with type 2 diabetes insufficiently controlled by basal insulin \pm sulfonylurea, that Lyxumia once daily significantly improved glycemic control (as measured by the number of patients reaching a target A1C < 6.5 percent or < 7.0 percent) versus placebo at week 24 with a pronounced post-prandial glucose and fasting plasma glucose effect, and was well tolerated. In this trial, Lyxumia once daily significantly improved A1C versus placebo (LS mean difference -0.9%) with significantly more Lyxumia patients achieving an A1C \leq 6.5 percent (17.8%) and < 7.0 percent (35.6%) versus placebo (1.3% and 5.2%; $p < 0.0001$). Lyxumia significantly improved two-hour post-prandial glucose, glucose excursion and average 7-point self-measured plasma glucose over placebo (LS mean \pm SE change from baseline: 7.96 ± 0.598 vs. -0.14 ± 0.563 , $p < 0.0001$; -7.09 ± 0.576 vs. 0.14 ± 0.542 , $p < 0.0001$; -1.91 ± 0.272 vs. -0.56 ± 0.271 , $p < 0.0001$, respectively). The most common adverse events and reasons for the discontinuation of Lyxumia in both GetGoal-X and GetGoal-L were gastrointestinal events, which our consultants believe may be a barrier to compliance.

In December 2011, Sanofi announced that the Phase III GetGoal Duo 1 study had met its primary endpoint of improved HbA1c lowering when used in combination with Lantus and metformin compared to patients on Lantus and metformin alone. The study included a 12-week run-in period with Lantus titrated to reach a target fasting plasma glucose of 80–100mg/dL followed by a 24-week randomization where patients received either Lyxumia or placebo while Lantus and metformin were continued. During the run-in period, HbA_{1c} decreased on average from 8.60% to 7.60%. After randomization the addition of Lyxumia led to a further significantly greater HbA_{1c}

decrease compared with placebo ($p<0.0001$) to a mean value of 6.96% after 24 weeks with a significantly higher percentage of patients achieving target HbA_{1c} <7.0% with Lyxumia vs. placebo (56.3% vs. 38.5%, respectively, $p=0.0001$). Lyxumia also significantly improved 2-h post-prandial glucose with a mean difference of -3.16 mmol/L ($p<0.0001$) vs. placebo. The mean difference in change in body weight between the Lyxumia and placebo groups was -0.89 kg ($p=0.0012$).

LixiLan (Lyxumia/Lantus) Combination Started Phase III In Q1:14

Sanofi announced that its fixed-dose lixisenatide/Lantus combination pen started Phase III trials in early 2014. LixiLan-O is evaluating patients not controlled on oral ADs, and the LixiLan-L trial includes patients not at goal on basal insulin. Eventually, Sanofi anticipates that LixiLan will be formulated with Toujeo rather than Lantus. FDA filing could be as early as the end of 2015. We forecast Lyxumia + Lantus combination sales of €100MM in 2016, €300MM in 2018, and €500MM in 2020.

Sanofi Obtains Global Licensing Rights To AfreZZa Inhaled Insulin

In August 2014, Sanofi announced that it entered into an exclusive WW licensing agreement with MannKind for AfreZZa inhaled, rapid-acting insulin. Sanofi will be responsible for global commercial, regulatory, and development activities and MannKind will be responsible for manufacturing the product. MannKind will receive an upfront payment of \$150MM and additional milestone payments of up to \$775MM. Sanofi and MannKind will share profits and losses 65%/35%. AfreZZa was approved in the U.S in June 2014 for use before meals. Sanofi views AfreZZa as broadening its diabetes portfolio and expanding its emphasis on “integrated care”.

Biosimilar Insulin Moving To Phase III

Sanofi's biosimilar short acting insulin (SAR342430) is moving to Phase III studies in both T1DM and T2DM (1,000 patients). SAR342430 is structurally the same as Humalog (LLY's leading short-acting insulin). This product helps round out the Sanofi insulin portfolio.

Medtronic Alliance Part of Diabetes Integration Efforts

In June 2014, Sanofi announced a global strategic alliance with Medtronic to develop drug/device combos. Specific terms of the alliance were not disclosed. Sanofi expects to use its diabetes drugs as part of Medtronic devices (pumps, CGMs) to optimize therapy but will also explore other delivery systems and diabetes management technology.

Cardiovascular

Generic Lovenox Clipping Brand Franchise

Lovenox/Clexane (enoxaparin) was the world's best-selling low-molecular-weight heparin (LMWH). LMWHs have benefited from: (1) replacing unfractionated heparin (UFH) in existing indications, (2) expanding use of anti-coagulation therapy into new indications, and (3) contamination of heparins. The U.S. is the largest opportunity for expansion of the use of LMWH where unfractionated heparin currently accounts for up to 60% of the heparin market. However, uptake across all indications remains disappointing. The penetration of LMWHs in Europe has been rapid, with 60-75%

conversion of the total heparin market. Lovenox is indicated for the prevention of post-surgical deep vein thrombosis (DVT), the prevention of DVT in medical patients, treatment of DVT with or without pulmonary embolism and prevention of morbidity (further strokes or heart attacks) and mortality subsequent to unstable angina with non-Q wave myocardial infarction. In May 2007, Lovenox received FDA approval for the treatment of STEMI patients receiving thrombolysis and being managed medically or with PCI based on the results of EXTRACT-TIMI 25 study. Sanofi believes that medical prophylaxis accounts for 50% of sales and orthopedic sales account for less than 10%. Arixtra (fondaparinux) has failed to be a significant competitor to Lovenox. We estimate Lovenox sales of €1,600MM (-6%) in 2014, €1,430MM in 2015, €1,305MM in 2016, €1,070MM in 2018, and €900MM in 2020.

Brand Holds Strong Share In U.S. Despite Generic

In May 2008, the U.S. Court of Appeals confirmed the Lovenox patents unenforceable and in April 2009, the U.S. Supreme Court refused to hear Sanofi's appeal sealing the fate of the intellectual property. On July 23, 2010, the FDA approved Sandoz/Momenta's ANDA for generic enoxaparin. On August 25, 2010, the United States District Court for the District of Columbia denied Sanofi's request for a preliminary injunction directing the FDA to suspend and withdraw its approval of the ANDA. Sanofi appealed this decision and was denied an appeal. In September 2011, Amphastar received FDA approval for its generic version of Lovenox, but was kept off the market by a U.S. district court's preliminary injunction in a patent infringement suit brought by Momenta. In January 2012, the appellate court decision overturned Sandoz/Momenta's preliminary injunction barring Amphastar/Watson from launching another generic version of Lovenox. As a result two additional Lovenox generics have been launched (Amphastar/Watson and Sanofi's AG).

In Europe, finalization of draft guidelines for LMWH "generics" is expected in Q3:14 and contains the clinical and non-clinical requirements for LMWH generics. The proposed draft requires manufacturers to do a clinical trial. Key points of the draft guidelines include:

- The document confirms that "the heterogeneity of LMWH is high, the structure-effect relationship is presently not fully elucidated and the pharmacodynamic markers anti-FXa and anti-FIIa activity may not fully reflect/predict efficacy. Thus, clinical trials will usually be necessary to address remaining uncertainties resulting from the physicochemical and biological comparison."
- With respect to establishment of similar efficacy, it is stated that a dedicated clinical efficacy study may be waived only if similarity can be convincingly deduced from the comparison of physicochemical characteristics, biological activity/potency and pharmacodynamic fingerprint profiles. The guideline however emphasizes that "it is expected that this is an exceptional scenario since the required amount of reassurance from analytical data and bioassays would be considerable".
- Furthermore and with respect to clinical safety, it is stated that "human safety data on the biosimilar will usually be needed pre-authorization, even if similar efficacy can be concluded from the comparative data on physicochemical characteristics, biological activity/potency and pharmacodynamic fingerprint".

Alirocumab Phase III Positive; Filing Expected By Year End

Sanofi in collaboration with Regeneron is developing Poluent (alirocumab;REGN727/SAR236553), a fully human antibody that targets Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9). PCSK9 is a naturally-occurring molecule involved in regulating cholesterol levels by modulating low-density lipoprotein (LDL) cholesterol receptors.

Sanofi acquired a priority review voucher from BioMarin in July 2014 (for \$67.5MM) which it expects to enable an expedited 6-month review for alirocumab. Sanofi will file on LDL-C lowering alone and anticipates filing in the U.S. and EU by year end 2014, keyed to positive results from the Phase III ODYSSEY trials. We estimate alirocumab sales of €75MM in 2015, €150MM in 2016, €450MM in 2018, and €750MM in 2020.

Ten Of Alirocumab's Phase III ODYSSEY Trials Have Hit Their Primary Endpoints.

In July 2014, Sanofi and Regeneron announced that nine of alirocumab's ODYSSEY trials in people with hypercholesterolemia hit their primary efficacy endpoint of a greater percentage reduction from baseline in low-density lipoprotein cholesterol at 24 weeks compared to placebo or active comparator. In addition, interim data from one trial (LONG TERM) showed alirocumab to decrease cardiovascular event risk. The tenth trial (announced in October 2013) was also positive.

ODYSSEY LONG TERM Produces HR Of 0.46 For Major CV Events.

Alirocumab's ODYSSEY LONG TERM trial is evaluating 2,341 patients who are at high or very high cardiovascular risk. On the primary efficacy endpoint, at 24 weeks alirocumab produced a 61% reduction from baseline in LDL levels compared to a 1% increase in the placebo group ($p<0.0001$). 81% of alirocumab patients achieved their pre-specified LDL goal, compared to 9% of placebo patients. And of particular note, 1.4% of alirocumab patients had a major CV event, compared to 3.0% of placebo patients, resulting in a hazard ratio of 0.46, $p<0.01$. These data are impressive, and suggest that the ODYSSEY OUTCOMES trial will hit its cardiovascular event endpoint (OUTCOMES is employing the same endpoint as analyzed in the LONG TERM *post hoc* analysis) in 2017-18. Nonetheless, it was disclosed that LONG TERM's interim analysis was based on a relatively small number of cardiovascular events (22 in the alirocumab group and 24 in the placebo group) and therefore the exact hazard ratio of alirocumab's benefit is likely to change in subsequent data sets.

Still No Sign Of Neurocognitive Side Effects In ODYSSEY Trials.

Investors have been focused on the neurocognitive side effect profile of the PCSK9's following the disclosure that the FDA is investigating a possible association with neurocognitive adverse events. SNY/REGN have seen no evidence that alirocumab causes neurocognitive adverse events in the ODYSSEY trials, with the rate generally balanced between alirocumab and control groups. In the data reported in September 2014, there was a numeric imbalance in neurocognitive adverse events in the LONG TERM trial that went against alirocumab (1.2% of alirocumab patients compared to 0.5% of placebo); numeric imbalances in neurocognitive adverse events in the other trials generally favored alirocumab. In the pooled FH I and FHII trials, 1.2% of placebo patients had neurocognitive disorders, compared to 0.2% of alirocumab patients. In the COMBO II trial, 1.2% of ezetimibe patients had a neurocognitive disorder, compared to 0.8% of alirocumab patients. Overall alirocumab continues to appear well tolerated, with only minor injection site reactions.

Robust Cholesterol Reductions Produced In COMBO II, FH I and FH II Trials As Well.

The COMBO II trial enrolled 720 patients at high CV risk who had an inadequate LDL reduction at baseline despite stable maximally-tolerated statin therapy. The FH I and FH II trials enrolled a total of 738 HeFH patients, and compared alirocumab to placebo. In COMBO II, at 24 weeks there was a 51% reduction from baseline in LDL in the alirocumab group, compared to a 21% reduction in the ezetimibe group ($p < 0.0001$). In the 24 week primary endpoint of both the FH I and FH II trials, alirocumab produced a 49% reduction from baseline in LDL levels. This compares to an increase of 9% in FH I and 3% in FH II in the placebo groups ($p < 0.0001$). In these three trials, alirocumab was dosed initially at 75mg every two weeks, increasing to 150mg if needed to reach pre-specified LDL levels. The majority of patients were able to achieve target levels at the 75mg dose, and did not need up titration. In particular, in the COMBO II trial, only 18.4% of patients had a dose increase at week 12. In the FH I and FH II trials, 43% and 39% of patients, respectively, needed a dose increase.

No Surprises In First Phase III ODYSSEY Data

In October 2013, Sanofi released top line data from ODYSSEY MONO, a 103-patient trial, with patients randomized to receive either 75 mg alirocumab Q2W or ezetimibe, each as a monotherapy. The primary endpoint was change in LDL-C from baseline at 24 weeks. If patients' LDL-C had not reached 70 mg/dL by week 8, they could be up titrated to 150 mg Q2W at week 12, although in fact the majority of patients achieved the 70 mg/dL goal on the 75 mg dose. Alirocumab produced a 47.2% reduction in LDL-C vs. 15.6% for ezetimibe. Safety appeared good with alirocumab, with fewer patients experiencing TEAEs (69%) than on the ezetimibe arm (78%). Infections were the most common AEs (42% alirocumab vs. 39% ezetimibe), with injection site reactions and muscle-related adverse events relatively uncommon (<2% and <4% in each arm, respectively). Full data was presented in March 2014.

These results appear in line with our physician consultants' prior expectations for the outcome of ODYSSEY MONO. The consultants expected "nearly a 50%" drop in LDL-C from baseline, and a greater than 30% difference vs. the ezetimibe control. The ODYSSEY MONO data would thus appear to have achieved this efficacy hurdle. In the remainder of the alirocumab Phase III readouts, our consultants plan to look for any new safety signals with longer term follow-up (e.g., immunogenicity) and will also focus on tolerability/adherence, given that these are injectable agents.

Phase III ODYSSEY Program Summary

Trial	# Patients	Patient Population	Comparator	Primary Endpoint	Completion Date/Data
ODYSSEY OUTCOMES	18,000	Patients with ACS event 4-16 weeks prior to randomization	Placebo + statins	Composite of coronary heart disease death, non-fatal MI, fatal and non-fatal ischemic stroke, and unstable angina requiring hospitalization	January 2018
ODYSSEY COMBO I	306	Patients with hypercholesterolemia at high CV risk not controlled on statin therapy	Statin +/- other lipid-modifying therapy	Percent change in LDL-C	Top-Line 8/2014: Met primary endpt for LDL-C reduction at 24 weeks,
ODYSSEY COMBO II	720	Patients w/hypercholesterolemia at high CV risk; on statins	Statin + Ezetimibe	Percent change in LDL-C	Top-Line 8/2014: Met primary endpt for LDL-C reduction at 24 weeks: 51% vs 21% for ezetimibe
ODYSSEY OPTIONS I	350	Patients with primary hypercholesterolemia at high CV risk or with heFH who are not adequately controlled on statins	Second-line lipid-lowering agents + statin	Not disclosed	Top-Line 8/2014: Met primary endpt for LDL-C reduction at 24 weeks
ODYSSEY OPTIONS II	300	Patients with primary hypercholesterolemia at high CV risk or with heFH who are not adequately controlled on statins	Second-line lipid-lowering agents + statin	Not disclosed	Top-Line 8/2014: Met primary endpt for LDL-C reduction at 24 weeks
ODYSSEY CHOICE I	803	Patients with primary hypercholesterolemia	placebo + statin	Percent change in LDL-C	May 2015
ODYSSEY LONG TERM	2,341	Patients w/hypercholesterolemia at high CV risk; on statins	placebo + statin	Long-term safety (adverse events, vital signs, and ECG)	Top-Line 8/2014: Met primary endpt for LCL-C reduction at 24 weeks: 61%; at interim, lower rate of major CV events vs placebo ($p < 0.05$)
ODYSSEY FH I	471	Patients with familial hypercholesterolemia not controlled with current lipid-modifying therapy	placebo + statin	Percent change in LDL-C	Top-Line 8/2014: Met primary endpt for LDL-C reduction at 24 weeks
ODYSSEY FH II	249	Patients with familial hypercholesterolemia and LDL-C >160mg/dL on current lipid-modifying therapy	placebo + statin	Percent change in LDL-C	Top-Line 8/2014: Met primary endpt for LDL-C reduction at 24 weeks
ODYSSEY HIGH FH	105	Patients with familial hypercholesterolemia not control with current lipid-modifying therapy	placebo + statin	Percent change in LDL-C	Top-Line 8/2014: Met primary endpt for LDL-C reduction at 24 weeks
ODYSSEY OLE	1,200	Open label extension of FH1, FHII, and HIGH FH in heFH patients	Placebo + statin	Assessment of safety parameters	July 2016
ODYSSEY MONO	100	Patients with hypercholesterolemia	Ezetimibe (no statin)	Percent change in LDL-C	November 2013; met endpoint
ODYSSEY ALTERNATIVE	314	Patients with hypercholesterolemia and moderate, high, or very high CV risk who are intolerant to statins	Ezetimibe (no statin)	Percent change in LDL-C at 24 weeks	Top-Line 8/2014: Met primary endpt for LDL-C reduction at 24 weeks
ODYSSEY CHOICE II	200	Patients with hypercholesterolemia, not treated with statins	placebo+ statin	Percent change in LDL-C	June 2016

Source: Cowen and Company.

Multaq Safety Issues, Labeling Changes, And Failure In Permanent AFib Cap Potential

Multaq (dronedarone) is a novel anti-arrhythmic drug that is less potent than amiodarone, but potentially safer. Multaq had a tortuous regulatory history, but was eventually approved in the U.S. in July 2009, based on the successful ATHENA outcomes trial. In November 2009, the European Union approved Multaq for atrial fibrillation. ATHENA is the first outcomes trial of an anti-arrhythmic drug in atrial fibrillation (AF) to demonstrate an overall benefit versus placebo. The ATHENA data are complex in that a reduction in hospitalization for AF and not death from any cause drove the primary composite primary endpoint. In addition, the results of the DIONOSYS trial demonstrated that Multaq was inferior to amiodarone in controlling AF but was safer. In July 2011, Sanofi announced that it had terminated the Phase IIIb trial, PALLAS, which was designed to assess Multaq in 10,000 patients with permanent atrial fibrillation (AF) to reduce major adverse cardiovascular events. The trial was terminated after the DSMB observed a significant increase in cardiovascular events in the Multaq arm compared to current standard of care. The trial rationale was based on post-hoc findings from the landmark ATHENA trial, in which a trend towards reduction of CV hospitalization and death was seen in patients classified as "permanent." Despite termination of PALLAS, the risk-benefit of Multaq remains unchanged for its currently approved indication in non-permanent AF. Outside Europe and North America, Multaq is commercially available in Israel, Peru, Mexico, Korea and Hong Kong. A September 2011 EMA review of Multaq determined that the drug should only be prescribed for maintaining heart rhythm in patients with paroxysmal or persistent atrial fibrillation after alternative treatment options have been considered. This compares to previous labeling for use in adult clinically stable patients with non-permanent Afib to prevent recurrence or to lower ventricular rate. In December 2011, FDA restricted the use of Multaq to patients with non-permanent AF and added a 3-month ECG monitoring requirement to the label. Sanofi launched Multaq in the U.S. at €7/day. We estimate Multaq sales of €275MM (+2%) in 2014, €270MM in 2015, €250MM in 2016, €220MM in 2018, and €190MM in 2020.

Plavix Facing Generic Erosion

Plavix has generic competition in all major E.U. markets and in the United States. Japan remains a strong growth driver for Plavix but the patent expired in 2013 with exclusivity expiring in 2014. We forecast Plavix revenues recorded by Sanofi of €1,755MM (-5%) in 2014, €1,695MM in 2015, €1,545MM in 2016, €1,315MM in 2018, and €1,125MM in 2020. Revenue from the Plavix alliance is recorded in several lines in Sanofi's P&L including the other revenues line (discovery royalty) and income from associates (50% of Bristol's territory sales). The minority interest line predominantly reflects Sanofi's payment to Bristol for Plavix in its territories.

Aprovel Now Off Patent In Most Major Markets

Aprovel/Avapro/Karvea, an ARB, was part of the joint venture with Bristol-Myers, which was responsible primarily for the U.S. commercialization. Aprovel has been approved for the treatment of diabetic nephropathy based on the results of the PRIME study, which showed that Aprovel reduces morbidity and mortality for patients with Type 2 diabetes and hypertension with early or late alteration of renal function. The results of the 4,500 patient I-PRESERVE study presented at AHA 2008 demonstrated that Aprovel failed to make a difference in mortality or cardiovascular events in patients with heart failure and preserved LVEF. I-PRESERVE randomized 4,128 patients aged >60 years with NYHA class 2-4 heart failure and an LVEF >45% to receive Aprovel or placebo and followed them for a mean of about four years. I-PRESERVE is

the third outcomes study — the others being CHARM and PEP-CHF — where a RAAS active agent failed to make a difference in mortality or CV events when blood pressure is controlled. These results are likely to limit use of ARBs in what is estimated to be 15-20MM patients worldwide suffering from heart failure with preserved systolic function (HF-PSF). ACTIVE-I evaluated the effect of Avapro in reducing vascular events in more than 9,000 patients with AF and at least one risk factor for vascular events. The first co-primary endpoint was the first occurrence of stroke, myocardial infarction (MI), or vascular death. The second co-primary endpoint included all the events of the first co-primary endpoint plus hospitalization for heart failure. Avapro did not reduce the risk of the first co-primary endpoint outcome (5.4% per year per each group). The occurrence of the second co-primary endpoint was slightly lower with Avapro (7.3% vs. 7.7%) but not statistically significant. Aprovel is marketed in more than 80 countries. In Japan, where the product is licensed/sub-licensed to Dainippon and other partners, specific 50 mg and 100 mg dosages were developed and launched in June 2008. The Aprovel patent expired in the U.K., France and Germany in 8/12 and other E.U. countries in 3/11. The patent in Japan expires in 2016. We forecast Aprovel revenues to Sanofi of €735MM (-17%) in 2014, €705MM in 2015, €655MM in 2016, €580MM in 2018, and €550MM in 2020.

Oncology

Jevtana Rollout Has Been Strong In Prostate Cancer

Jevtana (cabazitaxel) is ataxane derivative with a low affinity for P-glycoprotein. In March 2010, Sanofi released results of the pivotal TROPIC study in second-line hormone refractory prostate cancer. Cabazitaxel plus prednisone/prednisolone resulted in a 30% improvement in death [HR=0.70 (95% CI: 0.59–0.83); P<0.0001] with a clinically meaningful improvement in the median overall survival of 15.1 months versus 12.7 months in the mitoxantrone plus prednisone/prednisolone arm. Cabazitaxel was administered as one-hourly i.v. infusion every three weeks at 20 mg/m² up to 25 mg/m². In June 2010, FDA approved Jevtana for the treatment of patients with CRPC previously treated with a docetaxel-containing regimen. Jevtana was approved in the E.U. in March 2011. In July 2014, Jevtana was approved for prostate cancer in Japan. Our consultants believe that Jevtana's efficacy data are compelling and, despite a modest increase in the AE-related death rate, they expect substantial adoption in patients who are well enough to receive further lines of therapy after Taxotere.

The WAC for Jevtana is €8,000 per injection – a total of €48,000 per typical length of therapy based on the median number of cycles (6) of Jevtana in the TROPIC trial. We estimate Jevtana sales of €275MM (+19%) in 2014, €310MM in 2015, €350MM in 2016, €450MM in 2018 and €500MM in 2020.

TROPIC Data Impressive Overall

TROPIC is an international multi-center Phase III that randomized 755 metastatic hormone-refractory prostate cancer patients whose disease had progressed despite previous Taxotere-based chemotherapy. The primary endpoint was overall survival. Secondary endpoints included progression-free survival, tumor response rate, tumor progression, prostate-specific antigen (PSA) response, (PSA) progression, pain response, pain progression. Patients were randomly assigned to receive cabazitaxel plus prednisone/prednisolone or mitoxantrone plus prednisone/ prednisolone (378 and 377 patients, respectively). Patients were to receive either regimen for up to a maximum of 10 cycles.

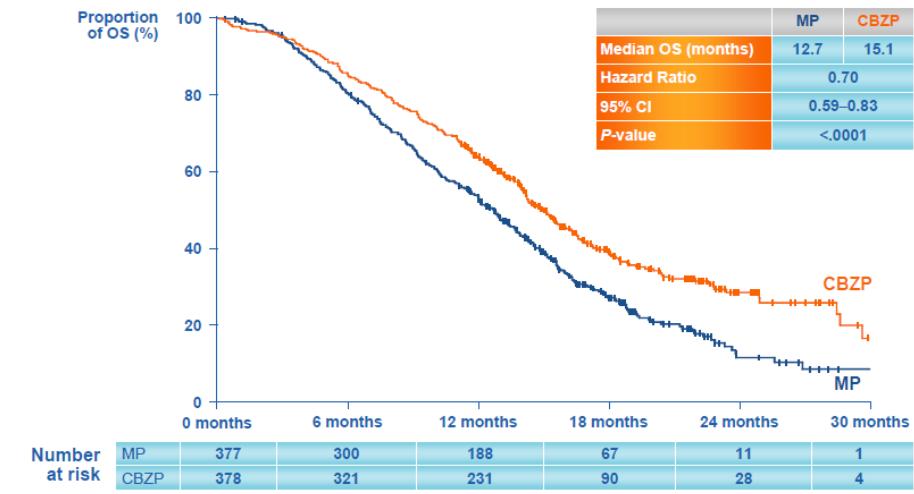
Efficacy Impressive...

Results showed that the combination of cabazitaxel and prednisone/prednisolone significantly reduced the risk of death by 30% [HR=0.70 (95% CI: 0.59-0.83); P<0.0001] with a clinically meaningful improvement in the median overall survival of 15.1 months in the cabazitaxel combination arm vs. 12.7 months in the mitoxantrone combination arm. Patients who received the combination treatment with cabazitaxel also experienced a significant increase in median progression-free survival [2.8 months vs. 1.4 months [HR=0.74 (95% CI: 0.64 - 0.86); P<0.0001].

...But Higher Death Rate Requires Further Details

The most frequent grade 3/4 hematological adverse events with cabazitaxel included neutropenia (81.7%), febrile neutropenia (7.5%) and infections (10.2%); the most frequent grade 3/4 non-hematological adverse events included nausea (1.9%), vomiting (1.9%) and diarrhea (6.2%). Most frequent treatment-emergent adverse events leading to discontinuation with the cabazitaxel arm were neutropenia (2.4%), hematuria (1.3%), diarrhea (1.1%) and fatigue (1.1%). Grade 3/4 peripheral neuropathy occurred in 0.5% patients in the cabazitaxel arm vs. 0.3% in the mitoxantrone arm. Deaths due to adverse events were 4.9% in the cabazitaxel arm (predominantly due to neutropenia and its complications) vs. 1.9% in the mitoxantrone arm.

Median OS 2.4 Months Longer In Jevtana Arm



Source: Company data

Phase II Taxane-Resistant Metastatic Breast Cancer Data Encouraging

In the Phase II taxane-resistant metastatic breast cancer study, 71 patients were enrolled. The ORR was 14% (two complete, eight partial responses). Eighteen patients (25%) had stable disease of >3.0 months duration. At a median follow-up of 20.0 months, the median time to progression was 2.7 months, and the median overall survival 12.3 months. The most common grade 3/4 adverse events were neutropenia (73%) and leucopenia (55%), with a low febrile neutropenia rate (3%) and infrequent grade 3/4, treatment-related, non-hematological adverse events (<5% patients for any adverse events). Two deaths were reported, one related to study drug and one to unknown cause.

Taxotere Generics Launched In E.U. And U.S.

Taxotere (docetaxel), a taxane, is approved in the U.S. and E.U. for adjuvant and first-line treatment of locally advanced or metastatic breast cancer; first- and second-line treatment of non-small cell lung cancer (NSCLC); hormone-refractory prostate cancer (HRPC); advanced gastric carcinoma; and locally advanced squamous cell carcinoma of the head and neck. In the U.S., growth in breast cancer has been offset by competition in NSCLC from Lilly's Alimta. In Japan, Taxotere has been approved for gastric, ovarian, head and neck cancers, and in 2008 for hormone refractory prostate cancer. New indications in China include HRPC (2010), advanced gastric (2012), and head and neck (2014). Many other tumor types are being pursued in emerging markets. Taxotere is available in more than 100 countries as an injectable solution. Sanofi introduced worldwide a one-vial form of Taxotere in 2009.

Hospira's generic taxotere was approved in the U.S. and Canada in March 2011. Generics launched in the E.U. in 2010, and Japanese generics entered the market in June 2012. We estimate Taxotere sales of €290MM (-29%) in 2014, €250MM in 2015, €200MM in 2016, €130MM in 2018, and €80MM in 2020.

Eloxatin Exclusivity Lapsed Again

Eloxatin (oxaliplatin) is a platinum-based chemotherapy drug in the same family as cisplatin and carboplatin. It is typically administered in combination with fluorouracil and leucovorin (FOLFOX) for the treatment of first- and second-line colorectal cancer. In Europe and in the U.S., Eloxatin was granted the adjuvant setting indication for stage III (Duke's C) colon cancer after complete resection of primary tumor, respectively, in September 2004 and November 2004. In February 2005, FDA approved a liquid formulation of Eloxatin that provided greater convenience over the original powder formulation. Sanofi stopped commercializing the powder formulation in the U.S., completely replacing it with the liquid formulation.

In April 2010, Sanofi settled with all seven generic manufacturers that launched Eloxatin generics. Under the terms of the settlement, the generic companies ceased selling their generic oxaliplatin products on June 30, 2010, and resumed selling generic oxaliplatin products on August 9, 2012, under a license to re-enter the market. We forecast Eloxatin sales of €175MM (-21%) in 2014, €170MM in 2015, €155MM in 2016, €125MM in 2018 and €95MM in 2020.

Zaltrap Approved In 2nd-Line mCRC

Zaltrap (VEGF trap/aflibercept), developed by Regeneron, is a fusion protein consisting of portions of the extracellular domains of the human vascular endothelial growth factor (VEGF) receptor VEGFR1 (Flt-1) and VEGFR2 (KDR) fused to the Fc portion of human IgG1. Zaltrap scavenges both VEGF and placental growth factor (PIGF). Given that the circulating VEGF has a half-life of 30 minutes, the fact that Regeneron's VEGF trap has a 17-day half-life enables the drug to remain in circulation to bind and neutralize the factor as it is released. In April 2012, the FDA granted priority review for Zaltrap in combination with irinotecan-flouropyrimidine-based chemotherapy in patients with mCRC previously treated with oxaliplatin-containing regimens. FDA approved Zaltrap for previously treated mCRC on August 3, 2012. Zaltrap was approved in second-line mCRC in the E.U. in February 2013. We estimate Zaltrap sales of €65MM (+23%) in 2014, €90MM in 2015, €115MM in 2016, €165MM in 2018, and €215MM in 2020.

While the half-life of Genentech's Avastin is equivalent to the VEGF trap, pre-clinical models suggest that VEGF trap binds to VEGF at a 100x greater affinity than Avastin. Phase I data presented at ASCO 2008 suggest that the drug can be dosed once weekly or every two weeks. The clinical dose appears to be between 2-6mg/kg week. Several Phase II studies in melanoma, gynecological, and glioblastoma were presented at ASCO 2009. The initial data are early but demonstrated promising efficacy and a reasonable side-effect profile. However, in one study there was a significant rebound in free PIGF levels after the initial reduction. The relevance is unknown.

In 2007, Regeneron advanced Zaltrap into four placebo-controlled Phase III trials. VELOUR, VITAL, VENICE, and VANILLA. VELOUR, a study in 2nd line metastatic CRC, evaluated FOLFIRI ± Zaltrap in 1,200 patients. VITAL was a 2nd line metastatic NSCLC trial of Taxotere ± Zaltrap in 900 patients. VENICE was a 1st line metastatic hormone-resistant prostate cancer of Taxotere/prednisone ± Zaltrap in 1,225 patients. The fourth study, VANILLA in 1st line metastatic pancreatic cancer, was discontinued in September 2009, as Zaltrap was unable to demonstrate a benefit over Gemzar.

In March 2011, Sanofi announced that Zaltrap failed to meet the primary endpoint in the VITAL trial, evaluating its use for the second-line treatment of non small cell lung cancer (NSCLC) in 913 patients. The addition of Zaltrap to docetaxel did not meet the primary endpoint of improvement in overall survival compared with docetaxel plus placebo. Sanofi will conduct a detailed analysis of the efficacy and safety results of VITAL and present full results at an upcoming medical meeting.

In April 2012, Sanofi announced that Zaltrap had failed to meet its primary OS endpoint when added to a regimen of docetaxel and prednisone for the first-line treatment of metastatic androgen-independent prostate cancer in VENICE.

Zaltrap's Price Halved To Improve Share

In October 2012, Memorial Sloan-Kettering Cancer Center made the decision not to use Zaltrap, given that its price was determined to be \$11,063/month on average; twice that of Avastin for similar efficacy. In November 2012, Sanofi lowered the monthly cost of Zaltrap by half by offering an additional discount.

VELOUR Positive In Second-Line mCRC; Approved In U.S. And E.U.

At EMSO 2011 Sanofi presented the results of the VELOUR trial. Patients with metastatic colorectal cancer previously treated with oxaliplatin were randomized to receive Zaltrap or placebo in combination with the FOLFIRI regimen (irinotecan-5-fluorouracil-leucovorin). The addition of Zaltrap to the FOLFIRI regimen significantly improved both overall survival (HR=0.817; p=0.0032) and progression-free survival (HR=0.758; p=0.00007). A similar effect was seen with Zaltrap therapy whether or not patients had received prior bevacizumab therapy. Our consultants agree that VELOUR was well-designed and executed. While the efficacy data, in the consultants' view, is "not overwhelming," it is in line with Avastin's second-line efficacy (in Avastin-naïve patients) from the ECOG 3200 trial. The consultants consider the magnitude of benefit to be modest, but clinically relevant. The consultants take comfort from the subgroup analysis demonstrating no significant difference in OS in patients who had, or had not, received prior Avastin in this trial, and do not find the numerically worse OS in the Avastin-experienced subgroup worrisome. They believe another subgroup analysis, demonstrating a stronger OS benefit in patients with metastases limited to the liver, is difficult to interpret: it may reflect a biological difference in underlying disease, but may also just be a chance finding due to slicing the data too finely.

Zaltrap's safety looks modestly worse than Avastin in terms of both frequency of adverse events and rate of discontinuation. However, our consultants expressed only modest concern over Zaltrap's increase in AEs such as asthenia and chemo side effects. They speculated that this could be due to differences in underlying patient characteristics, or might reflect slight differences in Zaltrap's biological activity vs. Avastin. Regarding the higher discontinuation rate vs. Avastin's trials, patients have many more alternative treatments now than were available when Avastin's pivotal trials were conducted in the early 2000s, likely leading to a lower bar for moving on to other agents in Zaltrap trials than in Avastin's. Overall, the safety profile would not dissuade our consultants from using Zaltrap.

Zaltrap Being Investigated In Additional Tumor Types

In June 2009, a Phase II trial in 55 patients with symptomatic malignant ascites related to ovarian cancer, demonstrated a statistical improvement in the meantime to first repeat paracentesis in the Zaltrap arm (55 versus 23 days). However, the companies announced that they would not submit these data for approval. A registration trial in refractory ovarian cancer as single agent was terminated, as the results, although demonstrating biological activity, are unlikely to meet regulatory requirements. Cancer Therapy Evaluation Program (CTEP) is also sponsoring up to ten exploratory efficacy/safety studies evaluating VEGF trap in a variety of cancer types.

Anti-Inflammatory/CNS

Aubagio Enjoying Solid Rollout

Aubagio (teriflunomide), a pyrimidine synthesis inhibitor with immunomodulatory properties, is a compound similar to Sanofi's leflunomide (Arava – a DMARD indicated for rheumatoid arthritis). In September 2012, FDA approved the 7mg and 14mg doses of Aubagio for the treatment of relapsing multiple sclerosis (RRMS). The label contains a boxed warning on the risk of liver problems (including death) and a risk of birth defects. Baseline liver function tests (LFT) are required prior to starting on Aubagio; monthly LFT monitoring is recommended during the first half-year of treatment. The boxed warning notes teratogenicity associated with animal studies. Aubagio is labeled as a Category X, which means that women must have a negative pregnancy test prior to starting Aubagio and use birth control throughout treatment. Aubagio is the only oral drug to reduce the risk of sustained accumulated disability (EDSS) in two Phase III trials. Our physician consultants view Aubagio as a safe and efficacious oral option for the treatment of the early stages of MS. Sanofi launched Aubagio in the U.S. in October of 2012 at a price of \$45,000 per year. This represents a 6.5% discount to Copaxone (TEVA), an 8% discount to Avonex (BIIB), and a 28% discount to Gilenya (NVS). Aubagio received E.U. approval in August 2013. We estimate Aubagio sales of €405MM (+144%) in 2014, €580MM in 2015, €700MM in 2016, €400MM in 2018 and €200MM in 2020 as exclusivity expires in the U.S. in 2017.

Label Suggests Monitoring Liver Function, Blood Cell Counts, And Blood Pressure

Aubagio was given a boxed warning for hepatotoxicity because of severe liver injury (including fatal hepatotoxicity) with a structurally related drug, leflunomide. The FDA anticipates that a similar risk may exist for Aubagio given that the approved doses of Aubagio and leflunomide result in similar serum concentrations. The label recommends obtaining bilirubin and transaminase levels within 6-months of starting Aubagio and monitoring ALT levels monthly for at least the first six months of treatment. In Phase III trials, ALT elevations greater than 3x normal occurred in 3% of

patients on 7mg of Aubagio, 5% of patients on 14mg of Aubagio, and in 4% of patients on placebo.

The label also recommends obtaining a complete blood count within 6-months of starting Aubagio. Future CBC monitoring should be based on signs and symptoms of infection. The label suggests placing a TB test for latent infection prior to initiating therapy. WBC count decreased by an average of 10% on Aubagio in placebo-controlled studies. BP monitoring is recommended prior to initiating therapy with periodic monitoring recommended thereafter.

TESMO Shows Aubagio To Be Safe And Effective

The 1,070-patient Phase III TESMO trial (initiated in September 2004, data presented 2010) compared once daily teriflunomide (7mg and 14mg) to placebo with a primary endpoint of relapse rate reduction and a secondary endpoint of disability (EDSS) analysis. Investigators performed MRI scans at baseline and weeks 24, 48, 72, and 108. Teriflunomide met its primary endpoint of reduction in annual relapse rate compared to placebo (HR=0.69, p=0.0005) for both the 7mg and 15mg doses; however, only the high dose met the secondary endpoint of time to disease progression. Magnetic resonance imaging data from TEMSO suggest teriflunomide may have the potential to become a first-line oral therapy for multiple sclerosis with relapses. Teriflunomide reduced disability progression and MRI disease activity with an additional 1 in 10 patients progression free and an additional 1 in 4 patients free of gadolinium-enhanced T1 lesions compared with placebo. Relative to placebo, the 7-mg and 14-mg doses cut the annualized relapse rate by 31% and 30%, respectively, in treatment-naive patients and by 36% and 40%, respectively, in the treatment-experienced subgroup. The slightly bigger improvements in annualized relapse rates in the treatment-experienced patients relative to those not receiving such drugs in the previous two years were not statistically significant.

Confirmation Of Efficacy In TOWER Increases Confidence In Aubagio

TOWER was a Phase III placebo-controlled trial comparing the safety and efficacy of teriflunomide to placebo in patients with the primary endpoint of annualized relapse rate. The 14mg dose of Aubagio decreased annualized relapse rate by 36.3% (p<0.0001) and reduced the risk of 12-week sustained accumulation of disability (EDSS) by 31.5% compared to placebo (p=0.0422).

In December 2011, Sanofi released top-line results from teriflunomide's Phase III TENRE study comparing teriflunomide to Rebif. No statistical superiority was observed between the Rebif and teriflunomide arms on risk of treatment failure, the primary composite endpoint of the study. Risk of treatment failure was defined as the occurrence of a confirmed relapse or permanent treatment discontinuation for any cause, whichever came first. In the study, 48.6% of patients receiving 7mg of oral teriflunomide (n=109) and 37.8 percent of patients receiving 14 mg of oral teriflunomide (n=111) reached the primary endpoint, versus 42.3% of patients receiving interferon beta 1-a (n=104).

The teriflunomide 14 mg daily dose (0.259) and Rebif (0.216) were not distinguishable on the endpoint of estimated annual relapse rate. The rate was higher in the 7mg arm (0.410). The percentage of patients experiencing any treatment emergent adverse events was similar across all arms of the study. The rate of permanent treatment discontinuation due to a treatment emergent adverse event was higher in the Rebif arm (21.8% vs. 8.2% in the 7mg teriflunomide arm and 10.9% in the 14 mg teriflunomide arm).

Lemtrada Approved In E.U., Resubmitted In U.S.

In December 2013, Sanofi received a CRL on Lemtrada (alemtuzumab), a monoclonal antibody targeting CD52 and leading to depletion of circulating T and B cells involved in MS inflammation. The FDA denied the application for use in relapsing MS citing inadequately designed and poorly controlled trials. These are the same concerns expressed at the November 13th FDA Adcom meeting which resulted in mixed recommendations. The FDA stated that at least one additional active comparator trial but of different design (double-blinded) would be needed for approval. Using Rebif as a comparator did not seem to be a concern Genzyme re-submitted its sBLA at the end of May 2014 with supplemental analysis and information to specifically address FDA concerns. An FDA decision is expected in Q4:14 Lemtrada is approved in the E.U., Canada, Australia, and Brazil. We forecast Lemtrada sales of €30MM in 2014, €70MM in 2015, €110MM in 2016, €200MM in 2018, and €300MM in 2020.

Safety The Primary Concern

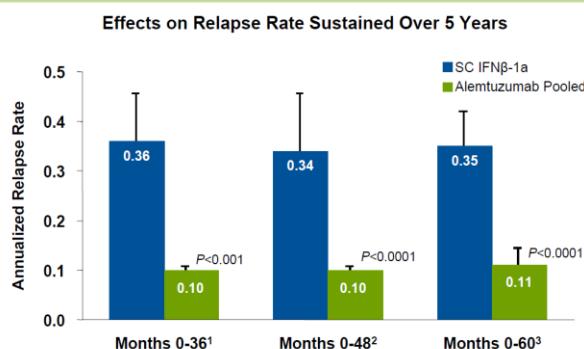
Our consultants think that Lemtrada is effective, but that its safety issues are significant, and that it must demonstrate a clean safety profile in order to be competitive. Physicians have varying degrees of concern over Lemtrada's thyroid adverse events (like Graves' disease and hyperthyroidism), but are quite put off by the side-effects ITP and Goodpasture's disease. Although physicians acknowledge that in most cases ITP is reversible, they note that ITP is nonetheless very inconvenient for the patient and quite disabling. Additionally while the number of reported patients with a complication of Goodpasture's disease is only two, this rare side-effect could lead to permanent renal and pulmonary damage or even death.

Phase III Trials Demonstrate Efficacy

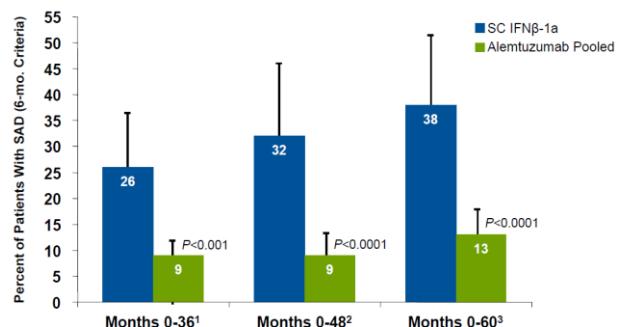
Three-year data were presented at the ECTRIMS meeting in September 2008. Lemtrada produced a 73% reduction in the risk for relapse vs. patients treated with Rebif, $p < 0.00396$ and a 70% reduction in progression of clinically significant disability, $p < 0.01646$. These results were especially impressive given that 80% of patients did not receive their 24-month interval therapy because at that time dosing was being held back by Genzyme due to safety concerns. Importantly, no new cases of ITP or thyroid diseases had been reported. Subsequently, four-year data were presented in September 2009 at the ECTRIMS meeting and were overall consistent with the three-year update (Lemtrada produced a 72% reduction in the risk for relapse vs. patients treated with Rebif, and a 73% reduction in progression of clinically significant disability). Five-year data at ECTRIMS 2010 showed a continued persistence of Lemtrada's effects on relapse rate and disability progression.

Alemtuzumab's Efficacy In MS Persists Over Five Years

Effects on Relapse Rate Sustained Over 5 Years



Reduction in Disability Progression Sustained Over 5 Years



Source: Genzyme

Phase III CARE-MS I Disappoints, CARE-MS II An Improvement; Extension Studies Encouraging

In September 2014, Sanofi released interim results demonstrating that treatment with Lemtrada remained effective in 74% and 66% of patients for 2-3 years beyond the initial studies CARE-MS I and II. Also, 70% of patients did not receive a 3rd course of treatment through the second year of the extension. No new risks were reported in the extension study. Two deaths (previously reported) occurred in the extension study, one from sepsis and other accidental (non drug related). Over four years, approximately 2% of patients treated in the pivotal trials developed ITP, and all responded to treatment.

In September 2007, Genzyme started two large Phase III trials (CARE-MS I and II with 581 and 700 patients, respectively), comparing Lemtrada to Rebif in treatment-naïve and treatment-refractory patients with relapse remitting MS. Both trials included a vigilant risk management program in which patient and physician education and monthly blood count checks are being used to screen for early signs of adverse events, especially low platelets. In July 2011 Sanofi announced the results of CARE-MS I. Two annual cycles of Lemtrada treatment resulted in a 55% reduction in relapse rate compared to Rebif over the two years of the study ($p<0.0001$), satisfying the first primary endpoint. Statistical significance was not achieved for the second primary endpoint, time to six month sustained accumulation of disability, as compared to Rebif. At the two year time point, 8 percent of Lemtrada treated patients had a sustained increase in their Expanded Disability Status Scale (EDSS) score (or worsening) as compared to 11 percent of those who received Rebif (Hazard Ratio=0.70, $p=0.22$). The patients will have the option to be evaluated over the next 3 years as part of a separate protocol.

CARE-MS II Met Both Co-Primary Endpoints

Relapse rate and sustained accumulation (worsening) of disability (SAD) were significantly reduced in MS patients receiving alemtuzumab as compared with Rebif. Results for both of these co-primary endpoints were highly statistically significant. A 49% reduction in relapse rate was observed in patients treated with alemtuzumab 12 mg compared to interferon beta-1a over two years of study ($p<0.0001$). Importantly, there was also a 42 percent reduction in the risk of sustained accumulation (worsening) of disability as measured by the Expanded Disability Status Scale (EDSS) ($p=0.0084$). A statistically significant improvement was observed for alemtuzumab

over Rebif in the percentage of patients with new or enlarging T2-hyperintense lesions ($p<0.0001$) and with gadolinium-enhancing lesions ($p<0.0001$). The change in T2-hyperintense lesion volume from baseline to year two, a secondary endpoint, was not significantly different ($p=0.14$). Patients treated with alemtuzumab experienced less change in brain parenchymal fraction, a measure of brain atrophy or loss of neurons and the connections between them ($p=0.012$).

The annualized relapse rates in the one-year extension phases of CARE-MS I and CARE-MS II were 0.24 and 0.25, respectively. At 3 years, 88% and 81% of patients who received Lemtrada did not experience six-month confirmed sustained accumulation of disability. More than 80% of patients did not receive a third dose of treatment within a year of entering the extension study.

Lemtrada's Phase III Program In MS

	CARE-MS I	CARE-MS II
Patients	581	840
Study Duration	2 years	2 years
Patient Population	Treatment-naive RRMS Onset within 5 yrs EDSS ≤ 3.0	Treatment-experienced RRMS Onset within 10 yrs EDSS ≤ 5.0
Treatment Arms	Alemtuzumab 12 mg IFNB -1a 44 mcg 3x/week	Alemtuzumab 12 mg Alemtuzumab 24 mg IFNB -1a 44 mcg 3x/week
Randomization	2 : 1	2 : 2 : 1
Co-primary Outcomes	Relapse Rate Disability Progression	Relapse Rate Disability Progression
Blinding	Rater-blinded	Rater-blinded

Source: Genzyme

Anti-NGF-mAb Has Much To Prove

Regeneron and Sanofi are developing REGN-475 (SAR-164877), an injectable formulation of fully human nerve growth factor (NGF) monoclonal antibody for the potential treatment of osteoarthritis of the knee and pain in other indications. In May 2010, interim Phase I/II data supported REGN-475 effectiveness in OA but a separate Phase II did not support its efficacy in sciatica. While the class appears effective, and may have opioid sparing benefits, safety concerns are significant. Pfizer's Tanezumab is associated with several peripheral nerve side effects and a worsening of OA. FDA placed all agents in this class on clinical hold. In March 2012 FDA's Arthritis Drugs Advisory Committee voted 21-0 that anti-NGFs should continue to be developed to treat osteoarthritis pain. The panel felt studies should continue if concomitant NSAID use is excluded and additional safeguards are put in place. These could include measuring biomarkers of joint destruction and increasing the use of MRI monitoring. The panel also voted 20-1 that anti-NGFs should be studied in indications for which there are no products with demonstrated analgesic efficacy, such as interstitial cystitis or chronic pancreatitis.

Benefit Demonstrated In OA But Not Sciatica

In an interim efficacy analysis of a randomized, double-blind, four-arm, placebo-controlled Phase II trial, in 217 patients with osteoarthritis of the knee, REGN475 demonstrated significant improvements at the two highest doses tested as compared

to placebo in average walking pain scores over 8 weeks following a single intravenous infusion ($p<0.01$). Pain was measured by the Numeric Rating Scale (NRS), as well as the Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain and function subscales. The primary endpoint of this study is safety, and REGN475 was generally well tolerated. Serious treatment emergent adverse events were rare and balanced between placebo and drug arms with three events (5.5%) in the placebo group and four events (2.5%) in the combined REGN475 groups. The most frequent adverse events reported among patients receiving REGN475 included sensory abnormalities, arthralgias, hyper/hypo-reflexia, peripheral edema, and injection site reactions. The types and frequencies of adverse events reported were similar to those previously reported from other investigational studies involving an anti-NGF antibody.

Dupilumab's Phase IIb Positive, Phase III To Begin Q4:14

Dupilumab (REGN668/SAR231893) is a subcutaneously administered inhibitor targeting the alpha subunit of the IL-4 receptor. This is expected to inhibit signaling through the IL-4 and IL-13 cytokine pathways, as the IL-4r alpha subunit is downstream of both. These cytokines are thought to drive induction and maintenance of a specific type of immune response mediated by Th2 helper T cells, which are thought to be important in atopic dermatitis and eosinophilic asthma.

Our physician consultants have been optimistic for the development of dupilumab in atopic dermatitis. There is an unmet need for a safe and effective treatment for moderate to severe patients. They estimate that there may be 25K U.S. patients in this segment who are not well-managed by available therapies. Dupilumab could represent a breakthrough for these patients if the Phase III data replicate the Phase II experience. Assuming an average price of \$30K per patient per year, the U.S. moderate to severe atopic dermatitis market could represent a \$750MM opportunity for dupilumab.

Phase III trials in atopic dermatitis are slated to begin in Q4:14. Phase IIb results in asthma are expected in Q1:15. In September 2014, positive top-line results were announced for a Phase II proof-of-concept trial of dupilumab in nasal polyps, meeting primary and secondary endpoints. We estimate dupilumab sales of €50MM in 2017, €150MM in 2018, and €500MM in 2020.

Phase II Top-Line Data In Atopic Dermatitis Encouraging

In July 2014, Sanofi/Regeneron released top-line results from dupilumab's Phase IIb in atopic dermatitis. The Phase IIb was a double-blind, placebo-controlled, 16-week dose ranging study that randomized 380 patients with moderate-to-severe atopic dermatitis to receive one of five doses of dupilumab (300 mg weekly, 300 mg every other week, 300 mg monthly, 200 mg every other week, or 100 mg monthly) or placebo. Patients had moderate-to-severe atopic dermatitis and could not be adequately controlled with topical medication or for whom topical medication was not advisable. Patients had approximately 50% of their skin affected by atopic dermatitis at baseline. Within the past year 35% of patients received an oral corticosteroid and approximately 20% had received a systemic non-steroid immunosuppressant.

All doses of dupilumab met the primary endpoint of a greater improvement in Eczema Area and Severity Index (EASI) scores from baseline to week 16 compared to placebo. The improvements ranged from 74% for patients in the 300mg weekly group, to 45% in patients who received 100mg monthly, compared to 18 percent for patients in the placebo group ($p<0.0001$ for all doses). Other efficacy measures were also improved compared to placebo: 12% to 33% of dupilumab-treated patients achieved clearing or

near-clearing of skin lesions as measured by an investigator's global assessment (IGA) score of 0 or 1, compared to 2% with placebo ($p=0.02$ to $p<0.0001$). Dupilumab treated patients experienced a 16.5% to 47% mean reduction in itching as measured by the pruritus numerical-rating scale (NRS) score, compared to an increase of 5% in the placebo group ($p=0.0005$ to $p<0.0001$). As expected, these data are very similar to the results of dupilumab's 12 week monotherapy Phase IIa. In that trial a 300mg weekly dose produced an average decrease in EASI score of 74 percentage points (vs 15 percentage points for placebo), with 40% of patients achieving clearing or near clearing of skin, compared to 7% of placebo patients. Dupilumab continued to appear safe and well-tolerated. The most common treatment emergent adverse events appear to be injection site reactions, which were more frequent in the dupilumab group (5% - 9.5%) compared to placebo (3%), and headaches (12%-15% vs 8%). The most common adverse event was nasopharyngitis, though that was balanced across treatment groups (18.5% - 23%) and placebo (21%). Dupilumab's safety profile also appears similar to that produced in Phase IIa.

Ambien CR Now Generic

Ambien CR is a modified release formulation of Ambien. Ambien CR (12.5mg dose) was launched in the U.S. in September 2005 and gained solid market share, but did not supplant immediate-release Ambien as rapidly as Sanofi had hoped. Sanofi priced Ambien CR at a discount to Ambien in order to encourage patient conversion ahead of the launch of Ambien generics. Ambien CR has both sleep onset and sleep maintenance indications, enabling it to compete head-to-head with Dainippon/Sepracor's Lunesta. Our consultants do not believe Ambien CR is as effective as Lunesta for sleep maintenance, and the clinical data for Ambien CR are not as strong as those for Lunesta. However, the Ambien CR rollout was bolstered by brand name recognition, an aggressive DTC campaign, and an easier Ambien-to-Ambien CR conversion compared to the Ambien-to-Lunesta switch. These advantages spurred Ambien CR uptake in the primary care market, where 60-70% of insomnia treatment prescriptions are written. We estimate Ambien and Ambien CR sales of €280MM (-26%) in 2014, €225MM in 2015, €180MM in 2016, €95MM in 2018, and €50MM in 2020.

Allergy

Allegra Rx-OTC Switch And Generics Clip Sales

Allegra (fexofenadine hydrochloride) is a long-lasting (12- and 24-hour) non-sedating prescription antihistamine for the treatment of seasonal allergic rhinitis (hay fever) and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (hives). Allegra's largest market is in Japan. Allegra faces generic competition in its major markets outside Japan. In January 2011 FDA approved the Allegra Rx-OTC switch. Sanofi is leveraging its Chattem acquisition to commercialize Allegra OTC, an opportunity that could be several hundred million dollars. We estimate Allegra Franchise sales of €205MM (-50%) in 2014, €190MM in 2015, €175MM in 2016, €135MM in 2018, and €85MM in 2020.

Rare Disease Portfolio

Rare Diseases Provide Attractive Niche Opportunities

The rare disease market has several advantages: (1) Faster development times. The rarity and severity of the diseases and absence of effective treatment results in the

acceleration of clinical development timelines. (2) 7-10 years of market exclusivity, which can only be broken under limited circumstances. (3) High operating margins. Because treatment is usually restricted to a relatively few physicians/centers, small sales forces can detail the drugs. We estimate rare disease franchise sales of €2.375B (+13%) in 2014, €2.905B in 2015, €3.32B in 2016, €4.26B in 2018, and €5.15B in 2020.

Lysosomal Storage Disorders Are A Sizable Opportunity

Lysosomal storage disorders are rare genetic diseases characterized by intracellular accumulation of glycolipids that eventually lead to a compromise in organ function. Mutations in the genes encoding the enzymes can result in inactive enzymes, inadequate enzyme production, or inaccurate trafficking of the enzymes to the lysosome. The biological underpinning is a defect in the degradation of specific macromolecules within an intracellular lysosomal compartment, thereby resulting in a gradual accumulation of substrates. Because the compounds may accumulate in various organs, the subsequent clinical manifestations vary. Skeletal abnormalities, defects in both the immune and neural systems, and death at an early age are common. At least 40 lysosomal disorders have been identified. Prevalence rates for each disease range between 1,000 and 10,000 people worldwide.

The success of Cerezyme highlights the potential for recombinant enzyme replacement as a viable therapeutic strategy. However, the inability of large proteins to cross the blood-brain barrier limits the utility of systemically administered enzyme to correct underlying neurological manifestations. More progress will have to be made in developing delivery systems before such manifestation of LSD diseases can be effectively treated.

Fabrazyme The Leader In Fabry Disease Enzyme Replacement Therapy

Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency in the enzyme, alpha galactosidase. The resulting accumulation of globotriaosylceramide (variously abbreviated "Gb3" or "GL-3") in multiple tissues of the body (kidneys, heart, CNS) is responsible for the progressive organ dysfunction associated with the disease. Patients with Fabry usually progress to suffer from severe pain of the extremities, impaired kidney function often progressing to full kidney failure, early heart disease, stroke and disabling gastrointestinal symptoms. Patients with Fabry disease are typically diagnosed in their late twenties by nephrologists (poor kidney function), geneticists (family pedigree analysis) or dermatologists (angiokeratomas). Prior to enzyme replacement therapy there were no effective therapies for Fabry's and average life expectancy was 40-50 years.

Given the lack of other treatment options for Fabry disease, the market opportunity for enzyme replacement therapies appears limited only by the number of treatable patients. However, due to the disease's late onset and more mild nature (Fabry patients on average live longer than patients with other lysosomal storage disorders), accurate data on disease prevalence are hard to find. Genzyme estimates that 2,500-3,500 patients suffer from Fabry disease in the U.S., and that a similar number are affected in other countries. However, new disease-causing mutations continue to be identified suggesting the Fabry patient population may be larger than previously estimated. We estimate Fabrazyme sales of €460MM (+20%) in 2014, €555MM in 2015, €615MM in 2016, €755MM in 2018, and €895MM in 2020.

Fabrazyme And Replagal Are Enzyme Replacement Therapies For Fabry, But Replagel OUS Only

In August 2001, the E.U. approved replacement therapies for Fabry disease from TKT/Shire (Replagal, agalsidase alfa) and Genzyme (Fabrazyme, agalsidase beta). Each was granted co-orphan drug status and market exclusivity for 10 years. In April 2003, the FDA approved Fabrazyme for the treatment of Fabry disease – and provided it with Orphan Drug Exclusivity – while declining to approve Replagal based on lack of a head-to-head trial vs. Fabrazyme. Shire refilled its BLA in 2009 and in 2011, but finally withdrew its filing in March 2012 to focus Replagel efforts on non-U.S. markets.

Comparison of Enzyme Replacement Therapies For Fabry Disease

	NIH (Replagal)	MSSG (Fabrazyme)
# Patients in pivotal trial (Treated/placebo)	26 (14/12)	56 (27/29)
Enzyme source/dose	Human/0.2 mg/kg q2wks	Chinese hamster ovary (CHO)/1.0 mg/kg q2wks
Trial	Phase II	Phase III
Centers	Single center (U.S.)	Multi-center (U.S./Europe)
Infusion rate/pre-medication	40 minutes/no pre-medication	4-6 hrs/1000mg paracetamol, 25-50mg hydroxyzine
Primary endpoint	Effect on neuropathic pain	Gb ₃ deposit clearance of renal interstitial capillary endothelium
Secondary endpoint	Glomerular filtration rate (GFR), renal histology, Gb ₃ in plasma, kidney, 24-hr urine sediment	GFR, Gb ₃ clearance from heart & skin, pain, QOL, Gb ₃ in plasma, kidney, heart, 24-hr urine sediment
Study duration	24 wk randomized, 24 wk open label	20 wk randomized, 24-wk open label
Gb ₃ clearance:		
Plasma	54% decrease	Undetectable
Kidney	20% decrease	23% decrease
Urine sediment	29% decrease	34% decrease
Histology	20% increased fraction of normal glomeruli (p=0.01), 33% decrease mesangial widening (p=0.01)	69% had no or trace microvasculature deposits (p<0.001), skin (p<0.001), heart (p<0.001)
Improvement in pain	Trend toward decline in pain scores compared with placebo, 36% patients discontinued analgesics compared with none in placebo	Both treated and placebo improved in pain scores
Renal function	Treatment arm showed stable GFR (p=0.02) and inulin clearance (p=0.19) compared with deterioration in placebo	Stable serum creatinine, no change in GFR without follow-up, no evidence for protective effect
Cardiac function	Decrease QRS-complex duration (p=0.047)	No change
QOL	Pain improvement (p=0.05)	Improved significantly
Body weight	Increased body weight (p=0.02)	No change
Infusion reactions	57% rigors	48% rigors, 24% fevers
IgG antibodies	21% by ELISA at 6 mos	88% by ELISA at 12 mos

Source: Cowen and Company

Supply Issues From 2009 To 2012 Resolved

In June 2009, Genzyme announced that it had found a virus (Vesivirus 2117) that impairs cell growth in one of the six bioreactors in its Allston production facility. Genzyme believes the virus was likely brought into the plant in some of the raw materials used in production. Genzyme temporarily halted production of bulk material at the facility in order to sanitize it and remove the virus.

As the Allston facility was Genzyme's main production facility for Fabrazyme, the problems there led to a shortage in H2:09, 2010 and 2011. After several months during which no Fabrazyme was shipped, Genzyme began shipments again in late December 2009. In January 2011, Genzyme said it was supplying Fabrazyme at approximately 80% of demand. In January 2012 Genzyme announced both FDA and EMA approvals of the company's new manufacturing facility in Framingham, MA for the production of Fabrazyme. On March 1, 2012, the company announced that it had begun shipping Fabrazyme produced at the Framingham plant. As a result, all patients in the U.S. were able to receive full dosing as of March 2012. The global complete return to normal supply levels began in Q2:12, with the most severely affected patients moved to full dose. Fabrazyme is now in position to continue to regain market share. In October 2013, Genzyme announced the investment of \$80MM in the Framingham site to expand the manufacturing capacity for Fabrazyme, anticipating the growth in global demand over the coming years. Genzyme currently supplies Fabrazyme to approximately 2,500 patients and has capacity for more.

Cerezyme Leading Treatment For Gaucher Disease

Gaucher disease is an autosomal recessive disease that results from the deficiency of the enzyme glucocerebrosidase (GCR). GCR is involved in the breakdown of glucocerebroside, a lipid abundant in cell membranes. As red blood cells die and disintegrate, they are taken up by macrophages for breakdown. In the absence of adequate levels of GCR, lipid accumulates inside the macrophages and aggregates in the liver, spleen, and bone marrow. As a result, many systems are disrupted: the liver and spleen are enlarged (hepatosplenomegaly), anemia develops, and bone deteriorates. Gaucher disease has traditionally been divided into three clinical types depending on the involvement of the nervous system. The most prevalent is Gaucher disease type 1, which involves only visceral (non-nervous system) organs. Even Type 1 Gaucher can be debilitating, since if untreated most patients will become disabled as skeletal damage accumulates. Gaucher disease types 2 and 3 are called "neuronopathic" because in both cases the central nervous system deteriorates, typically leading to mental retardation. Enzyme replacement therapy has successfully treated patients with type 1 disease, but not types 2 or 3 as the enzyme does not cross the blood brain barrier. Patients with type 2 Gaucher typically do not survive to their second birthday, while those with type 3 disease live only into their twenties to forties.

Gaucher disease occurs in about 1 out of 75,000 births, suggesting that there are about 6,000 people with the disease in developed nations worldwide.

Clinical Features Of Gaucher Disease

Clinical Features	Type 1	Type 2	Type 3
Onset	Childhood/adulthood	Infancy	Childhood/adolescence
Hepatosplenomegaly	Mild to severe	Moderate	Mild to severe
Skeletal disease	Mild to severe	Minimal	Mild to severe
Neurodegeneration	Absent	Severe	Mild to severe
Survival	<5 to >80 years	2 years	<5 to 50 years
Frequency	1/40K – 1/300K	<1/100K	<1/100K

Source: Cowen and Company, adopted from G.A. Grabowski, Curr Opin Pediatr 17:519-524.

Enzyme Therapy Is An Effective Treatment For Gaucher

Enzyme replacement therapy has been a very effective treatment for Gaucher disease. Enzyme is administered by infusion every two to four weeks and the glucocerebrosidase is taken up by the macrophages, thereby reversing the inherited deficiency. Once inside the macrophage, the enzyme degrades the accumulated glucocerebroside. As glucocerebroside is cleared from the body, over time the clinical manifestations of the disease diminish. Liver and spleen shrink and become normal. Hemoglobin levels rise, and anemia resolves. If a patient starts treatment early enough, skeletal weakening and the resulting disability are avoided. However, if a patient's disease has been untreated for some time, much of the skeletal damage and scarring cannot be reversed, and therefore most specialists emphasize the importance of early diagnosis and treatment. Although some type 1 patients used to die of their disease before their tenth birthday prior to the advent of enzyme replacement therapy, many today live a normal lifespan with a near normal quality of life.

Increased Per-Patient Dosing, Trickle Of New Patients Drive Single Digit Market Growth

Going forward, the two principal drivers of sales growth in Gaucher disease are increasing patient dosing and further market penetration through ongoing efforts to identify patients. Because enzyme replacement therapy's dosage is related to body weight, as Gaucher patients age (and gradually gain weight) the corresponding dosage requirements gradually increase. Additionally, our consultants note that new patients with Gaucher continue to be identified, and they expect more to be found in the coming years as awareness of the disease continues to increase, and new enzyme preparations are launched. While there is not a torrent of patients coming to therapy, our consultants note that one or two new patients are identified each month. We estimate that the combination of these factors will drive a single-digit market CAGR.

Small Trials Key To Ceredase/Cerezyme Therapy

The first product approved for the treatment of Gaucher disease was Genzyme's Ceredase, a preparation of glucocerebrosidase purified from human placenta, which was approved in 1991. Ceredase was approved with data from a single, open-label, 12-patient trial. Study results showed that the hemoglobin concentration in all 12 patients, and platelet counts in seven (58%), increased. In addition, serum acid phosphatase and plasma glucocerebroside levels decreased in 10 and nine patients, respectively. Splenic volume decreased in all patients and hepatic volume in 5 (42%). Initial evidence of skeletal improvement was seen in three patients (25%).

Cerezyme, Genzyme's second product for Gaucher, is a recombinant human enzyme produced in Chinese hamster ovary (CHO) cells that differs by one amino acid from Ceredase. Cerezyme was approved based a single, open-label study in which 30 patients were randomized to receive Ceredase or Cerezyme. The study demonstrated that there was no significant difference in improvement in hemoglobin levels, platelet counts, serum acid phosphatase, and hepatic or splenic volumes between the two groups. The Ceredase group had a 40% incidence of IgG antibodies versus 20% in the Cerezyme group. Even though Cerezyme did not show a statistically significant difference over Ceredase, the fact that the enzyme elicited fewer IgG antibodies and was far easier to produce was sufficient to warrant approval.

Responses To 12-24 Months Of Cerezyme Therapy

Clinical Features	Response to 12-24 Months Of Enzyme Therapy
Hepatomegaly	16-20% decrease in hepatic volume
Enlarged Spleen	40-50% decrease in volume of the spleen
Anemia	1.5gm% hemoglobin increase, with about 40% of patients returning to normal
Thrombocytopenia	Normalize platelet counts if mild, double counts if severe

Source: Cowen and Company, adopted from G.A. Grabowski, *Curr Opin Pediatr* 17:519-524.

Cerezyme's IP Claims Only CHO-Produced Product

Until May of 2001, Cerezyme had orphan drug status, and was therefore protected from competition from any other glucocerebrosidase. Now that orphan drug status has expired, Cerezyme's exclusivity is protected only by its patents. However, since the natural enzyme itself has long been in the public domain, Genzyme does not have a composition-of-matter patent covering glucocerebrosidase. Instead, Cerezyme is protected by two U.S. Patents that claim the production of glucocerebrosidase in Chinese Hamster Ovary (CHO) cells: 5,549,892 (expired August 27, 2013); and 6,451,600 (expires September 17, 2019); and corresponding international counterparts. Therefore, any formulation of glucocerebrosidase that is not produced in CHO cells would not infringe Genzyme's patents.

Manufacturing Issues Resolved

In June 2009, Genzyme announced that it had found a virus (Vesivirus 2117) that impairs cell growth in one of the six bioreactors in its Allston production facility. Genzyme believes the virus was likely brought into the plant in some of the raw materials used in production. Genzyme temporarily halted production of bulk material at the facility in order to sanitize it and remove the virus. Genzyme restarted production at the facility during Q3:09, and by Q2:10 production was back to normal levels.

However, despite new product being available, Genzyme supplied Cerezyme at 50% of demand for much of H1:10 as it attempted to build a small buffer of inventory. With no other source of Cerezyme, this led to a severe supply shortage lasting through September 2010. Genzyme resumed full supply of the U.S. Cerezyme market in October 2010, and resumed to full supply of global demand in December 2010.

Another manufacturing shortage limited the supply of Cerezyme during 2011 and early 2012. This shortage began to improve with the FDA and EMA approvals of the Framingham manufacturing plant in January 2012. When Fabrazyme production was transferred to Framingham, additional production capacity of Cerezyme became available at Sanofi's Allston plant. Sanofi restored unconstrained supply for all patients globally by the end of 2012. Genzyme is currently supplying product for 5,000 patients and has capacity for more. We estimate Cerezyme sales of €725MM (+5%) in 2014, €810MM in 2015, €885MM in 2016, €1,055MM in 2018, and €1,225MM in 2020.

Oral Cerdelga Approved;Expands Treatment Options For Gaucher

Cerdelga (eliglustat tartrate) is a novel ceramide analog that is an inhibitor of glucosylceramide synthase. Eliglustat works through a different mechanism than the enzyme replacement therapies. While an infusion of Cerezyme helps to break down

the glucocerebroside after it accumulates, eliglustat tartrate is designed to stop the glucocerebroside from being produced in the first place.

Sanofi filed for approval in the U.S. and E.U. in Q4:13, received expedited review from the FDA, and was approved in the U.S. in August 2014. The regulatory submissions were supported by two pivotal Phase III studies and four years of safety and efficacy data from the Phase II study. Our consultants predict eliglustat could become a standard of care agent in Gaucher given that eliglustat demonstrated non-inferiority to Cerezyme in its Phase III switching study, ENCORE. They would expect eliglustat to be widely used in developing countries (less access to infusion centers, easier to deliver), and used widely in adults in developed countries. Eliglustat's patent expires in 2023 with the possibility for extension. Eliglustat has not been studied in children and pregnant women (25-30% of Gaucher population) so will not be targeting that patient population. Cerdela was submitted for approval in Japan in June 2014.

We estimate Cerdela sales of €60MM in 2014, €260MM in 2015, €400MM in 2016, €650MM in 2018, and €850MM in 2020.

Phase III Data Confirm Large Potential For Eliglustat

In October 2012, Genzyme reported that eliglustat had met its primary endpoint of reduction in spleen volume at 9 months versus placebo in its Phase III ENGAGE trial. Gaucher disease patients treated with eliglustat demonstrated a 30% absolute reduction in spleen volume ($p < 0.0001$), improved hemoglobin and platelet levels, and reduced liver volume. No serious adverse events were reported and no clinically meaningful differences between treatment groups were observed. Our physician consultants were very impressed with eliglustat's Phase II efficacy data and view ENGAGE as a confirmatory trial. While eliglustat's efficacy in ENGAGE appears slightly below what has been observed with competitive agents, efficacy in Gaucher can be dramatically influenced by differences in patient populations and our physicians await details on patient characteristics before drawing additional conclusions.

Top-line data from the second Phase III trial, ENCORE, was announced in February 2013 at the 9th Annual Lysosomal Disease Network WORLD Symposium. The multi-national, randomized, controlled, open-label ENCORE Study was originally designed to enroll 96 patients who are currently on Cerezyme (for at least three years and reached their therapeutic goal) and compare eliglustat's efficacy and safety to that of Cerezyme over one year. However, Genzyme increased the enrollment to 160 to allow more access to eliglustat. The enrolled patients were randomized 2:1 to receive either eliglustat tartrate or Cerezyme for one year.

The primary efficacy endpoint of stability was a composite endpoint of pre-specified change criteria for each of the following parameters: spleen volume, hemoglobin levels, platelet counts, and liver volume. To meet the endpoint for stability, a patient had to remain stable in all four parameters. Eliglustat tartrate met the pre-specified criteria for non-inferiority to Cerezyme, with the majority of patients in both groups remaining stable one year after randomization (84% of eliglustat tartrate patients and 94% of Cerezyme patients).

In an additional, pre-specified, efficacy analysis of the percent change in spleen volume from baseline, a mean change of -6% was observed in the eliglustat tartrate arm compared with -3% in the Cerezyme arm. This analysis also met the criteria for non-inferiority.

With regard to secondary endpoints, after one year, nearly all patients receiving eliglustat tartrate met the stability criteria for the following individual components of the composite endpoint: spleen volume (94% patients), hemoglobin levels (95% patients), platelet levels (93% patients), and liver volume (96% patients). The majority of patients had normal bone mineral density scores at study entry for total femur and lumbar spine. These scores were maintained over the 12-month study period.

In the ENCORE trial, two percent (n=2) of eliglustat tartrate patients and two percent (n=1) of Cerezyme patients discontinued treatment because of an adverse event. Over the course of one year, four adverse events were observed in the eliglustat tartrate treatment group with ≥10% incidence compared with Cerezyme: fatigue (14%), headache (13%), nausea (12%), and upper abdominal pain (10%). The majority of adverse events were mild or moderate in severity for both groups. There were no serious adverse events in the study that were considered to be related to therapy by the treating physician.

The third Phase III EDGE trial began in early 2010. It is not a registration study but is evaluating QD vs. BID eliglustat in 234 patients over 52 weeks. The trial is designed to assess whether maintenance with once-daily dosing is feasible. With over 350 patients enrolled and sites in more than 30 countries participating, the three trials combined represent the largest clinical program so far in Gaucher disease.

Myozyme/Lumizyme Leaders In Pompe Disease

Pompe disease is an inherited glycogen storage disease due to a deficiency of α-glucosidase. The disease primarily affects skeletal and cardiac muscle and manifests as cardiomyopathy (cardiac muscle wasting), progressive skeletal muscles atrophy, and respiratory distress. The infantile form (most severe form characterized by less than 1% of normal enzyme activity) exhibits a rapidly deteriorating course that is commonly fatal within the first 12 months of life. Infants present with respiratory and feeding difficulties, hypotonia (muscle weakness), and hypertrophic (enlarged heart) cardiomyopathy. The juvenile form presents during childhood and teen years with a skeletal weakness and signifies a slowly deteriorating course with a life span of 20-30 years. Patients typically die of respiratory failure in the juvenile form, as the cardiac muscle is typically spared. The adult form may go undetected well into adulthood, usually manifesting itself in the third or fourth decade of life as respiratory insufficiency. Skeletal and muscle weakness are the main symptoms, with respiratory failure the overriding cause of death. Life span is variable in that population. Enzyme levels for the juvenile and adult forms range between 10-25% of normal levels. As the juvenile and adult onset forms are difficult to differentiate from other muscular dystrophies, there can often be a several year lag between the onset of symptoms and a definitive diagnosis of Pompe disease.

Pompe Disease Demographics

	Infantile	Juvenile	Adult
Incidence		1/ 20,000 - 1/ 100,000	
Prevalence		5,000 - 10,000	
Severity	Severe	Intermediate	Mild
Age at diagnosis	0-12 mos	2-15 yrs	>15 yrs
Age at death	9-15 mos	2-30 yrs	>15 yrs
Progression rate	Rapid	Gradual	Slow
Cardiomyopathy	Yes	No	No
Hypotonia	Yes	Yes	Yes
Respiratory insufficincy	Yes	Yes	Yes

Source: Cowen and Company

The reported incidence of Pompe disease is estimated to be between one in 20,000 to one in 100,000 live births translating into a global prevalence of 2,000-10,000 patients. Our consultants believe the true incidence is approximately 1:40,000 births, suggesting a worldwide population of about 5,000 patients. Our consultants estimated that about 20% of people identified with Pompe disease had the infantile or early onset form, and that 80% juvenile or adult onset forms.

Our consultants think that Pompe disease is currently under-recognized, as until Myozyme's approval, there were no effective treatments. Additionally, our consultants believe that the majority of patients are adults with mild disease whose condition can go undetected or be misdiagnosed for years. However, our consultants are optimistic that Myozyme/Lumizyme's launch, combined with the implementation of easier-to-use blood spot diagnostic tests, could help bring a correct diagnosis to a larger portion of patients. Therefore over time the number of identified Pompe patients could more closely match the prevalence suggested by the literature.

Myozyme/Lumizyme The First Treatment For Pompe Disease

In April 2006, Myozyme, recombinant, human α -glucosidase (rhGAA) enzyme, was approved in the U.S. and E.U. with a broad label for the treatment of patients with Pompe disease. Despite capacity constraints that limited uptake in 2008 and 2009, Myozyme's early launch was strong. We estimate Myozyme/Lumizyme sales of €540MM (+8%) in 2014, €620MM in 2015, €690MM in 2016, €830MM in 2018, and €970MM in 2020.

Consultants Impressed By Myozyme's Pivotal Data

Myozyme's pivotal study in infants, AGLU01602, enrolled 18 patients with infantile-onset Pompe's disease who began receiving Myozyme by six months of age. In the trial's primary endpoint, 83% of patients treated with Myozyme were both alive and free of invasive ventilator support at 18 months of age, compared to 2% of historical controls. All patients in the trial showed a reversal of cardiomyopathy, and 72% had gains in motor development. Our consultants think that these data are very clinically meaningful, particularly the fact that all patients who would otherwise have been expected to die were still alive after 18 months.

While the physicians are impressed by the data, they note that Myozyme is clearly not a cure. They believe the response can be variable from patient to patient, with some having an excellent response and others a minimal one. Moreover, while patients' cardiomyopathy reversed, the physicians believe that no children dependent on a respirator were able to be removed and allowed to breathe on their own.

Myozyme's Adult Onset Trial LOTS Is Successful

In December 2007, Genzyme announced that Myozyme's trial in patients with late-onset Pompe's disease succeeded. In this 90-patient trial, patients received either Myozyme at 20mg/kg or placebo every other week for 18 months. The average age of patients was 44 years. The study had two primary efficacy endpoints (1) Six minute walk test, and (2) Forced Vital Capacity, and both were reached. Patients treated with Myozyme increased their distance walked in six minutes by an average of approximately 30 meters compared to placebo ($p=0.0283$). Percent predicted forced vital capacity in Myozyme-treated patients increased by 1% at 18 months, while it declined by 3% in the placebo group ($p=0.0026$).

This was the first data showing efficacy in older patients. Given that adults make up 80% of patients with Pompe, and therefore use in that population is vital, the positive results were a welcome addition to the Myozyme database. However, our consultants were already using Myozyme in their adult patients and note that the data did not change treatment dramatically. The decision to use Myozyme in adults is made on a case-by-case basis, depending on the severity of disease and the benefits of getting therapy versus the therapeutic risk and cost with payors playing some role in the decision. Our consultants noted that the correct diagnosis of late onset patients is perhaps the biggest limiting factor to getting them on therapy. Many are classified as "muscular dystrophy not otherwise specified" and are seen by other specialists (e.g., pulmonologists).

Batch Scaling Forces Lumizyme Nomenclature

In April 2008, Genzyme announced that the FDA had decided that Myozyme produced at the 2000L scale should be classified as a different product from that produced at the 160L scale. Therefore an entirely new BLA needed to be submitted for the 2000L material, and Genzyme chose the name Lumizyme for the 2000L produced material. The BLA was based on data from the LOTS (late onset) study and in October 2008 the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted strongly in favor of approving Lumizyme for the treatment of the non-infantile form of Pompe disease. Much of the panel's discussion centered on the clinical relevance of the LOTS endpoints of six-minute walk distance, and forced vital capacity (measures of lung function), as well as on trials adaptive design and statistical methods. Overall the panel seemed somewhat underwhelmed by the magnitude of the improvements, and frustrated by the fact that the endpoints and statistics were changed during the study. However, the panel seemed to recognize that the current capacity constraint leaves much of the U.S. market without access to drug. In the end, the urgency to meet the patients' need for drug outweighed any concerns over the trials' methods, and the vote in favor of approval was clear.

Lumizyme Approved In U.S. In 2010

Despite the positive AdCom recommendation in 2008, manufacturing issues at Genzyme's Allston facility prevented approval of Lumizyme in the U.S for nearly two years. On March 2, 2009, Lumizyme's filing received a Complete Response letter that noted, among other things, that Genzyme needed to resolve issues in a manufacturing warning letter before Lumizyme could be approved. This warning letter addressed deficiencies found in September and October 2008 inspections of Genzyme's Allston facility related to monitoring, maintenance, and controls. Unfortunately, while Genzyme was working to resolve the warning letter deficiencies, viral contamination was found in one of Allston's bioreactors, which prompted a full shutdown of the Allston plant and led to severe shortages of Cerezyme and Fabrazyme. Because of these shortages, Genzyme decided it must reserve all of Allston's manufacturing

capacity for Cerezyme and Fabrazyme, and therefore would no longer produce Lumizyme/Myozyme at the 2000L scale. 4000L Myozyme/Lumizyme is produced at a different facility. Therefore, the Lumizyme supply constraints in the U.S. would exist until the 4000L approval.

Subsequently, in November 2009, Genzyme announced that Lumizyme had received another Complete Response letter, where the unresolved issue would seem to be 49 manufacturing problems at the Allston facility. The majority of the issues cited refer to fill and finish operations. Following the November 2009 letter, Genzyme changed its strategy, and sought approval of 4000L-produced Lumizyme from Genzyme's facility in Belgium, so that the FDA's issues with the Allston facility will not prevent its approval.

In December 2009, Genzyme submitted Lumizyme 4000L's BLA. The submission was filed to the Lumizyme 2000L BLA, referencing all information in that BLA. The filing also included comparability data, both biochemical and preclinical, in addition to the routine safety updates that are typically included in such filings. Lumizyme's BLA was approved in May 2010.

Alnylam Collaboration Strengthens Genzyme Pipeline

In January 2014, Genzyme announced an expanded partnership with Alnylam, a biotech company focusing on RNA interference (RNAi). With this new agreement Genzyme will obtain expanded rights to patisiran, which is in Phase III for transthyretin (TTR)-familial amyloid polyneuropathy, a rare disease that damages the nervous system. Genzyme's rights to market patisiran in Japan/Asia Pacific have been expanded to include all areas except North America and Western Europe (which Alnylam retains). Genzyme will also obtain rights to 3 products in Alnylam's pipeline: ALN-TTRsc (Phase II for familial amyloid cardiomyopathy) for markets outside North America and western Europe, and two other products of Genzyme's choosing, post completion of early clinical trials and can choose full global right or co-commercialization. Genzyme also obtains the option (up to 2020) to develop and commercialize (outside of North America and Western Europe) all products in development for rare genetic diseases. In return, Genzyme will make a \$700MM equity investment in Alnylam (12% share).

In addition to Patisiran (Phase III) and ALN-TTRsc (Phase II), Genzyme has a number of other rare disease compounds in the early stage pipeline: Acid sphingomyelinase (Phase II) for Niemann-Pick disease type B; Genz-682452 (to start Phase II), an oral agent for Fabry; AAV-hAAADC gene therapy (Phase I) for Parkinson's; AAV-sFLT gene therapy for macular degeneration; and Neo-GAA (Phase I), 2nd gen enzyme for Pompe.

Osteoarthritis/Metabolic

Synvisc-One Will Grow Franchise, But Not Extend It Out Of Its Niche

Synvisc is a top-selling viscosupplement for the treatment of pain due to osteoarthritis of the knee. In January 2005, Genzyme bought back the sales and marketing rights to Synvisc in the U.S. and portions of Europe from Wyeth. This extended Genzyme's prior Synvisc franchise in the U.K., France, Canada, and Australia, which was also expanded through an approval in Japan.

In order to gain share from competing viscosupplements, Genzyme developed a more convenient formulation of Synvisc called Synvisc-One. Synvisc-One contains the same material and total treatment volume as Synvisc. However, Synvisc-One is a single 6 mL intra-articular injection while Synvisc is administered via a series of three injections.

Genzyme filed for approval of Synvisc based on one randomized, double-blind placebo controlled 26-week trial that was conducted in Europe and enrolled 253 patients. In December 2008, the FDA's Orthopedic and Rehabilitation Devices Advisory Committee voted unanimously, 5 to 0, for approval without conditions concluding that Synvisc-One is safe and effective for the treatment of osteoarthritic knee pain. More specifically, the panel noted that the primary endpoint of Synvisc-One's study (WOMAC A Subscore of 0.15 out of 5 in the 5-point Likert Scale) is clinically meaningful and statistically significant and that the statistical analysis for the secondary endpoints was adequate. In February 2009, the FDA approved Synvisc One for the treatment of pain associated with osteoarthritis of the knee.

We expect Synvisc-One will help Genzyme recapture some share of the viscosupplement market from competitors, but we nonetheless do not expect it to make the franchise a major growth driver for Genzyme. Our consultants generally consider viscosupplementation a niche opportunity in the osteoarthritis market, and use the products in a small percentage of patients. We forecast Synvisc franchise sales of €365MM (-2%) in 2014, €405MM in 2015, €440MM in 2016, €520MM in 2018, and €600MM in 2020.

Renvela Poised For Decline

Renvela (sevelamer carbonate) is a second-generation, phosphate-binder version of Renagel. Our consultants consider Renvela a modest improvement over Renagel. There is some limited concern in the nephrology community that Renagel, which is an acid-based compound (hydrochloride), can worsen an ESRD patient's acidosis, even though dialysis is effective in correcting this metabolic abnormality. Renvela has a base equivalence (carbonate), thus eliminating any concerns about acidosis. There is no evidence to suggest that Renvela, other than having a basic equivalence, is superior to Renagel in terms of lowering serum phosphorus or improving other clinical outcomes (decreasing lipids, vascular calcifications, CRP, and inflammation). Renvela (tablet formulation) was approved by the FDA for the control of serum phosphorous in chronic kidney disease patients on dialysis in October 2007 and was launched in March 2008. Renvela (tablet and powder formulations) was approved by the EMEA with a broader label for the control of serum phosphorous in chronic kidney disease patients both on dialysis and those with serum phosphorus of $\geq 1.78\text{mmol/L}$. Renvela is also approved in India and Brazil.

Renagel/Renvela should benefit from the demographic trends that are increasing the number of patients on dialysis, and trends in medical management that increasingly view the management of phosphorous as important. Our consultants say that Renagel's/Renvela's lipid-lowering ability, prevention of cardiac calcification, reduction of CRP, improvement of bone mineral density, and long-term safety record are attractive attributes that differentiate it from the competition. We estimate Sanofi sales of Renagel/Renvela of €590MM (-21%) in 2014, €270MM in 2015, €215MM in 2016, €200MM in 2018, and €240MM in 2020, clipped by the September 2014 loss of exclusivity in the U.S. and the 2015 patent expiration in the E.U. Sanofi settled with the first-to-file generic who was able to launch limited supply (7-10% of sevelamer 2013 U.S. sales) as of April 2014. The second filer was able to launch on September 16, 2014.

Even though phosphate binders have been on the U.S. market for a number of years, our consultants believe that the management of phosphorous levels is still a major unmet need. According to our consultants, nephrologists are not able to adequately control serum phosphorus levels in many end-stage renal disease (ESRD) patients

who are on dialysis. Using K/DOQI guidelines for phosphorous management, nephrologists are only able to achieve serum levels below 5.5 mg/dL in 45-50% of patients worldwide. Even fewer patients, 35-40% worldwide, are able to achieve levels closer to normalization, below 5.0 mg/dL. (2.5 mg/dL-4.5 mg/dL).

Vaccines

Leading Vaccine Business Adapting For The Global Market

Sanofi Pasteur is a fully integrated vaccine division of Sanofi that has the broadest range of vaccines in the industry. Sanofi Pasteur's vaccine portfolio includes pediatric vaccine combinations, influenza vaccines, meningitis and pneumococcal vaccines, booster vaccines, travel and endemic vaccines, and several others. The pediatric combinations and influenza vaccines are the largest by sales and volume. Total vaccine sales are forecast to be €3.99B (+7%) in 2014, €4.7B in 2015, €5.43B in 2016, €6.925B in 2018, and €8.395B in 2020.

Pediatric Combination And Polio Vaccines A Leading Franchise

Pediatric combination and polio vaccines vary in composition due to diverse immunization schedules throughout the world. This group of products, which protect against up to five diseases in a single injection, is anchored by acellular pertussis components. Products include Daptacel, a trivalent vaccine against pertussis, diphtheria, and tetanus; Act-HIB, for the prevention of *Haemophilus influenzae* type b infections; Pentacel, which is a vaccine protecting against five diseases (pertussis, diphtheria, tetanus, polio and *Haemophilus influenzae* type b); and Pediacel, another acellular pertussis-based pentavalent vaccine formulation that has been submitted in Europe. Sanofi Pasteur is one of the world's leading developers and manufacturers of polio vaccines, both in oral (OPV) and enhanced injectable (eIPV) formulation. Sanofi Pasteur has several pediatric combination vaccinations in development, including Hexaxim, a DTP-HepB-Polio-Hib vaccine for emerging markets.

In April 2013, the EMA approved Sanofi's Hexyon/Hexacima 6-in-1 pediatric vaccine for primary and booster vaccination of infants from 6-weeks of age. The 6-in-1 vaccine is designed to protect infants against diphtheria, tetanus, pertussis, Hepatitis B, poliomyelitis, and invasive infections caused by *Hemophilus influenzae* type b.

Pentacel manufacturing issues have hampered recent U.S. trends, but supply has begun to return to normal with supply increasing each quarter. We estimate sales for this category of €1,190MM (+4%) in 2014, €1,405MM in 2015, €1,670MM in 2016, €2,015MM in 2018, and €2,335MM in 2020.

Sanofi Leads The Flu Market; Quadrivalent Vaccine The Newest Addition To Fluzone Family

Sanofi Pasteur produces approximately 45% of the influenza vaccines distributed worldwide, and supplied over 70% of the flu vaccine to the southern hemisphere. In November 2007, Sanofi Pasteur signed an agreement with the Chinese authorities for a project to build an influenza vaccine facility in Shenzhen (Guangdong Province). The facility was completed in 2010 and commercial productions for the Chinese market began in 2012. Initial capacity is for 25MM doses, but can be scaled up if needed.

In February 2009, the European Commission granted marketing authorization for INTANZA/IDflu, the first intradermal (ID) microinjection seasonal influenza vaccine. The advantages of the formulation include convenience and ease of administration. Intanza/IDflu vaccine is approved for the prevention of seasonal influenza in both the adult (aged 18 and over) and elderly (aged 60 and over) populations. Sanofi launched Intanza for the 2010/11 season. The U.S. intradermal vaccine was approved in May 2011 for adults age 18-64 years.

The Fluzone High Dose IM vaccine was approved in December 2009 and Sanofi launched it in Q4:10. It is the first influenza vaccine designed specifically to generate a more robust immune response in people 65 years of age and older, addressing the issue of immunosenescence, an important unmet clinical need. Sanofi is realizing a significant price premium for High Dose IM as the product differentiates from its competitor products. In August 2014, results from a study in 32,000 patients 65 years and older was published which showed Fluzone to be 24.2% more effective than standard-dose vaccine in this age group in preventing flu. Researchers also determined that most rates for pneumonia, cardio-respiratory condition, hospitalizations, non-routine office visits and medication use were lower for the Fluzone High-Dose group. This study was the basis for Sanofi's late 2013 request for a label modification reflecting the improved effectiveness in the 65+ age group. A decision is expected in late 2014.

In June 2013, FDA approved the sBLA for Sanofi's four-strain flu vaccine, Fluzone Quadrivalent, which has a 50% price premium. The 2013-14 flu season was the first in which quadrivalent vaccines were available in the U.S. We estimate flu sales of €1.02B (+10%) in 2014, €1.115B in 2015, €1.195B in 2016, €1.375B in 2018, and €1.565B in 2020.

Meningococcal Vaccine Expected To Grow Despite Competition; Pneumococcal Vaccine Under Development

Sanofi dominated the meningococcus meningitis vaccine market with Menactra. Menactra was the first quadrivalent (A,C,Y,W-135) conjugated vaccine to be approved; Sanofi's quadrivalent polysaccharide vaccine, Menomune, was previously available. As a conjugate vaccine, Menactra provides longer immunity than the polysaccharide vaccine. The CDC/ACIP recommends routine vaccination with Menactra for all 11 to 18 year olds. In 2007, FDA approved Menactra to include children 2 to 10 years old, increasing the original age span of 11 to 55 years. The ACIP has not recommended routine vaccination of the 2-10 age group. New competition from Novartis, and the fact that the catch-up cohort has been saturated leaving the birth cohort as the market opportunity, suggests that Menactra is unlikely to grow in the U.S. in the foreseeable future. A second-generation conjugated meningitis A,C,Y,W-135 vaccine, which minimizes fever and injection site reactions, has moved into Phase II

Sanofi Pasteur is developing a protein-based pneumococcal vaccine. This approach may result in a vaccine with superior serotype coverage as compared to current polysaccharide- or conjugate-based vaccines. According to Sanofi, data from early clinical trials and supportive epidemiological studies are encouraging. Antigens for the multivalent vaccine formulation have been selected for further development and clinical evaluation. In March, Sanofi partnered with SK Chemical of South Korea to develop and commercialize a pneumococcal conjugate vaccine.

We estimate meningitis/pneumonia vaccine sales of €545MM (+10%) in 2014, €615MM in 2015, €680MM in 2016, €830MM in 2018, and €970MM in 2020.

Travel/Endemic Vaccines Provide Stable Sales

Sanofi Pasteur's Travel/Endemic vaccines provide the widest range of traveler vaccines. The portfolio includes hepatitis A, typhoid, rabies, yellow fever, cholera, measles, mumps, rubella (MMR), and antivenoms. These vaccines are used in endemic settings in the developing world and by military and travelers to endemic areas. We estimate Travel/Endemic vaccine sales of €420MM (+10%) in 2014, €480MM in 2015, €535MM in 2016, €645MM in 2018, and €755MM in 2020.

C. diff Vaccine In Phase III

Clostridium difficile (C. diff) is a potentially life-threatening infection that causes intestinal disease (primarily diarrhea). It is more common in older adults, patients on antibiotics, and seniors in nursing homes (where it can lead to outbreaks). It is estimated that *C. difficile* infects 700,000 patients annually in the U.S., with the incidence potentially higher due to inadequate diagnosis. The infection rate has been on the rise due to demographics and increased use of antibiotics that select out more aggressive *C. difficile* strains. Sanofi's c. diff vaccine program is part of their 2008 acquisition of Acambis. The vaccine has progressed through Phase I and Phase II trials and in August 2013, Phase III (Cdifflense) trials began. This study is a randomized, placebo-controlled trial that will enroll up to 15,000 adults (50 years and older) at 200 sites in 17 countries. The trial is expected to last roughly 4.5 years. The primary endpoint is prevention of primary symptomatic CDiff.

In May 2014, Sanofi announced that Phase II studies met their primary endpoints: the vaccine demonstrated an immune response against toxins A and B and showed reactions that were mild and of short duration. Based on this study, high-dose plus adjuvant vaccine given on days 0, 7, and 30 have been selected for the Phase III trial.

Dengue Vaccine Appears Safe; Phase III Trials Meet Endpoints

Mosquito-borne Dengue infects an estimated 50-100MM people each year and is a leading cause of illness and death in the tropics and subtropics. Approximately 40% of the world's population lives in at-risk areas. The World Health Organization estimates there are 500,000 cases of Dengue hemorrhagic fever and 22,000 deaths (mostly children) each year.

In April 2014, Sanofi announced that the first of two pivotal Phase III studies met its clinical endpoint with a 56.5% reduction in dengue cases ($n=10,000$) in Asian children. Top-line results of the large second Phase III trial ($n=20,875$) in Latin America were released in September 2014 and met the primary endpoint with an overall efficacy of 60.8%

Sanofi expects to file early 2015 with first launch in late 2015/early 2016 likely in Latin American countries including Brazil, Mexico, and Columbia. We estimate Dengue vaccine sales of €140MM in 2015, €240MM in 2016, €680MM in 2018, and €1,120MM in 2020.

Positive Phase III Data From Asian Study

In the Phase III Dengue vaccine study conducted in Asia, the efficacy of the vaccine during the 25-month observation period was consistent across countries but varied by serotype (between 34.7% and 72.4%) and by age. Results also showed an 88.5% reduction of dengue hemorrhagic fever, the severe form of dengue. This trial was

conducted in approximately 10,000 children (2-14 years old); each received 3 doses at 0, 6, and 12 months. Safety data was consistent with prior studies.

Top line data from the Latin American study showed similar efficacy data. The safety analysis showed similar SE trends for vaccine and control groups. Full data will be presented in November 2014 at the American Society of Tropical Medicine and Hygiene meeting.

Summary of Dengue Vaccine Efficacy – Phase III Data

Vaccine Group (n=6,848)	Asian Study			Latin America Study
	Cases (n)	Incidence Density (95% CI)	Vaccine Efficacy (95% CI)	Vaccine Efficacy (95% CI)
All cases	117	1.8 (1.5-2.1)	56.5% (43.8-66.4)	60.8%
Serotype 1	51	0.8 (0.6-1.0)	50.0% (24.6 to 66.8)	50.3%
Serotype 2	38	0.6 (0.4 to 0.8)	35.0% (-9.2 to 61.0)	42.3%
Serotype 3	10	0.2 (0.1 to 0.3)	78.4% (52.9 to 90.8)	74.0%
Serotype 4	17	0.3 (0.2 to 0.4)	75.3% (54.5 to 87.0)	77.7%

Source: www.thelancet.com, July 11, 2014

Dengue Vaccine Shows Promise In Three Of Four Serotypes In Phase II Trials

In September 2012, Sanofi announced that its dengue vaccine (CYD-TDV) failed to meet the primary endpoint of reduction in incidence of virologically confirmed dengue of any serotype in a 4,002 patient Phase IIb PoC study in Thailand. The failure was driven by an apparent lack of efficacy against DENV2. CYD-TDV demonstrated 82-90% efficacy against DENV3/4 and 61% efficacy against DENV1. It is possible that a new variant of DENV2 not covered by the vaccine could exist as the Asian 1 genotype of DENV2 has several lineages with mutations that could elude vaccination with CYD-TDV.

After 3 injections, 95-100% of patients were identified as seropositive for antibodies against DENV1-4. More than 50% of unvaccinated patients were seropositive for dengue neutralizing antibodies, but at much lower titers than what was observed in vaccinated patients. Neutralizing antibody titers, as measured by plaque-reduction neutralization test (PRNT), are provided below:

Antibody Titers 28 Days Post Third Injection

	Dengue Vaccine			Placebo		
	Number of samples	Mean titer (95% CI)	Seropositive (n, %)	Number of samples	Mean titer (95% CI)	Seropositive (n, %)
Serotype 1	95	146 (99, 217)	90 (95%)	49	23.9 (14.0, 40.9)	27 (55%)
Serotype 2	95	310 (224, 431)	94 (99%)	49	52.2 (26.8, 101.7)	29 (59%)
Serotype 3	95	405 (307, 534)	95 (100%)	49	48.9 (25.5, 93.9)	29 (59%)
Serotype 4	95	155 (123, 196)	93 (98%)	49	19.4 (11.6, 32.2)	21 (43%)

Source: Company data

While the study did not meet its primary endpoint of reduction in virologically confirmed dengue of any serotype, the failure was driven by the lack of efficacy in only a single serotype (DENV2) with greater than 70% mean efficacy across all other serotypes (DEV1,3,4). A summary of the overall efficacy data is presented on the next page:

Summary Of Dengue Vaccine Efficacy By Serotype

	% Efficacy (95% CI)	Heterogeneity p-value
All cases	34.9% (6.7, 54.3)	0.0027
Serotype 1 episodes	61.2% (17.4, 82.1)	--
Serotype 2 episodes	3.5% (-59.8, 40.5)	0.0007
Serotype 3 episodes	81.9 (38.8, 95.8)	--
Serotype 4 episodes	90.0 (10.6, 99.8)	--

Source: Company data

It is not outside the realm of possibility that Phase II results may have fallen victim to an antigenic mismatch between the vaccine (wild-type E protein, Asian/American genotype) and the strain of DENV2 endemic to Thailand (mutations at E83, E226, and E228 have been observed in E protein of Asian 1 genotype of DENV). While antibody titers against DENV2 were higher than those observed for DENV1/4, it is also possible that DENV2 titers were not high enough to protect against the particular strain of DENV2 that is prevalent in the Ratchaburi region of Thailand. Data from the ongoing 30,000 patient Phase III studies will provide a clearer picture of the efficacy of CYD-TDV against DENV2 strains across ten countries in Latin America and Asia. Sanofi is confident that when Phase III data is fully analyzed, it will support coverage of all four vectors of Dengue, including DENV2. However, even without coverage of DENV2, the vaccine would still be relevant in many parts of the world where DENV2 is not problematic.

Despite the apparent lack of efficacy against DENV2, the risk of hospitalization was reduced by 45.5% across all patients who received at least one dose of CYD-TDV.

Dengue Vaccine Appears Safe; Antibody-Dependent Enhancement Of DENV Replication A Non-Issue

The rate of serious adverse events (SAEs) was well balanced between treatment groups (12% in CYD-TDV vs. 13% in placebo). No vaccine-related SAEs were reported in the dengue group. A major concern associated with the development of dengue vaccines has been antibody-mediated progression to dengue hemorrhagic fever (DHF) and/or dengue hemorrhagic shock. Pre-existing DENV antibodies that cross-react, but do not neutralize DENV, have been associated with Fc-receptor mediated viral uptake and increased viral replication through a process known as antibody-dependent enhancement of DENV replication (ADE). Despite the lack of efficacy against DENV2, antibodies against DENV2 were not associated with ADE (3 patients progressed to DHF in CYD-TDV group vs. 2 in placebo group).

Animal Health

Merial Growth Recovery Keyed To New Products Such As NexGard

Merial is the third largest animal health care company and employs approximately 5,800 employees worldwide. Merial's most successful product is Frontline, with sales estimated to be more than €1B/year. In 2008, the patent protecting fipronil, the active ingredient of Frontline, expired in several countries, including Japan, Australia, and Brazil. Fipronil's U.S. patent expired in 2010, and generics are now available. Given this, together with competition from Rx-only products in veterinary channels, and high promotional spend from fipronil branded generics, there is an increased need for new products to fuel Merial growth.

In February 2014, Merial launched Nexgard (afoxolaner) in the U.S. Nexgard is the first oral product (chewable, beef-flavored) for canine flea/tick control and could provide a significant boost to sales. Nexgard was just approved in the E.U. and should launch soon. Merial's major markets are Australia, Brazil, Canada, France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States. We estimate Animal Health sales of €2,000MM (+1%) in 2014, €1,985MM in 2015, €2,025MM in 2016, €2,335MM in 2018, and €2,675MM in 2020.

Generics

Acquisitions Have Bolstered Generics Business

Winthrop, Sanofi's base generic business, is responsible for selling generic versions of Sanofi's mature molecules and over 300 generic molecules originating from other laboratories. In 2009, Sanofi acquired the remaining 64.1% of Zentiva that it did not own. Zentiva is a branded generic company with a foothold in Eastern Europe, including Russia and Turkey, and has a portfolio of more than 400 products. Zentiva sales in 2008 were €736MM. In 2009, Sanofi acquired Medley (for €340MM), the largest generic manufacturer in Brazil and Kendrick, a Mexican generic company. These three acquisitions significantly boosted the generic business' top line. We estimate Sanofi generic sales of €1,950MM (+20%) in 2014, €2,075MM in 2015, €2,175MM in 2016, €2,375MM in 2018, and €2,575MM in 2020.

Consumer

OTC Business Expanding With Bolt-On Acquisitions

Sanofi has a significant OTC business that is estimated to be the fifth largest globally. However, up until December 2009, it was almost exclusively focused ex-U.S. In December 2009, Sanofi acquired Chattem which provided a U.S. consumer health platform to help drive Rx-to-OTC switches (eg. Allegra-D). In January 2010, Sanofi entered into a JV with a Chinese company, Minsheng. Providing another boost, Sanofi re-launched Rolaids in Q3:13 and launched Nasacort Allergy 24 in February 2014. In May 2014, Sanofi and Lilly entered an agreement to pursue regulatory approval of Cialis OTC with Sanofi acquiring exclusive rights to apply for and commercialize OTC Cialis in the U.S., E.U., Canada and Australia. We estimate OTC sales of €3.265B (+9%) in 2014, €3.45B in 2015, €3.6B in 2016, €3.9B in 2018, and €4.2B in 2020.

Sanofi Key Upcoming Events

Time Frame	Event Type	Product	Event
2014	Clinical	Dengue vaccine Dupilumab Insulin lispro Rotavirus vaccine	Full Phase III data (Latin America) at ASTMH Nov.2-6 Initiate Phase III in atopic dermatitis in H2:14 Initiate Phase III Initiate Phase III in Q4:14
	Regulatory	Alirocumab Cerdelga (eliglustat) Fluzone QIV ID Lemtrada PR5i pedi vaccine	File EU and U.S in Q4:14 EU approval Q4:14 (Gauchers Disease) U.S. approval Q4:14 U.S. approval Q4:14 U.S. filing Q3:14
	Corporate	Investor Seminar - New Medicines	November 20th, Cambridge, MA

Source: Company data

Sanofi Balance Sheet 2013-20 (€MM)

	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Assets								
PPE	10,182	10,050	10,500	10,650	11,100	11,550	12,050	12,650
Goodwill	37,134	36,500	36,000	35,500	35,000	34,500	34,000	33,500
Intangible assets	15,395	15,000	15,000	15,000	15,000	15,000	15,000	15,000
Investments in associates	448	500	500	500	500	500	500	500
Financial assets non-current	4,826	5,000	5,000	5,000	5,000	5,000	5,000	5,000
Deferred tax assets	4,154	4,200	4,200	4,200	4,200	4,200	4,200	4,200
Non-current assets	72,139	71,250	71,200	70,850	70,800	70,750	70,750	70,850
Assets held for sale	14	0	0	0	0	0	0	0
Inventories	6,352	6,220	6,380	6,450	6,660	6,865	7,055	7,265
Accounts receivables	6,831	6,980	7,295	7,385	7,685	8,015	8,365	8,655
Other current assets	2,287	2,345	2,455	2,485	2,585	2,695	2,815	2,950
Financial assets- current	185	200	200	200	200	200	200	200
Cash and equivalents	8,257	9,101	12,090	15,016	18,315	21,890	26,002	30,622
Current assets	23,926	24,846	28,420	31,536	35,445	39,665	44,437	49,692
Total assets	96,065	96,096	99,620	102,386	106,245	110,415	115,187	120,542
Liabilities								
Long-term debts	10,414	10,000	9,500	9,000	8,500	8,000	7,500	7,000
Provisions and other non-current liabilities	9,619	10,000	10,000	10,000	10,000	10,000	10,000	10,000
Deferred taxes	5,060	5,000	5,000	5,000	5,000	5,000	5,000	5,000
Non-current liabilities	25,093	25,000	24,500	24,000	23,500	23,000	22,500	22,000
Liabilities related to assets held for sale	1	0	0	0	0	0	0	0
Accounts payable	3,003	2,970	3,045	3,070	3,170	3,270	3,375	3,475
Other current liabilities	6,778	6,765	7,000	6,950	7,290	7,520	7,760	7,990
Short-term debt	4,176	4,000	4,000	4,000	4,000	4,000	4,000	4,000
Current liabilities	13,958	13,735	14,045	14,020	14,460	14,790	15,135	15,465
Total liabilities	39,051	38,735	38,545	38,020	37,960	37,790	37,635	37,465
Net Equity	57,014	57,361	61,075	64,366	68,285	72,625	77,552	83,077

Source: Company data, Cowen and Company estimates

Sanofi Working Capital Analysis 2013-20 (€MM)

	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Inventories	6,352	6,220	6,380	6,450	6,660	6,865	7,055	7,265
Cost of sales	10,992	10,839	11,115	11,210	11,575	11,935	12,320	12,685
Inventory Turns	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
Days in inventories	211	210	210	210	210	210	209	209
Accounts Receivable	6,831	6,980	7,295	7,385	7,685	8,015	8,365	8,655
Sales	32,951	33,520	35,040	35,465	36,920	38,490	40,185	42,125
Receivables Days	76	76	76	76	76	76	76	75
Accounts Payable	3,003	2,970	3,045	3,070	3,170	3,270	3,375	3,475
Cost of sales	10,992	10,839	11,115	11,210	11,575	11,935	12,320	12,685
Payables Days	100	100	100	100	100	100	100	100
Other Current Assets	2,472	2,345	2,455	2,485	2,585	2,695	2,815	2,950
% of Sales	8%	7%	7%	7%	7%	7%	7%	7%
Other Current Liabilities	6,778	6,765	7,000	6,950	7,290	7,520	7,760	7,990
% of COGS	62%	62%	63%	62%	63%	63%	63%	63%
Net Working Capital (Ex. Cash, Debt)	5,874	5,810	6,085	6,300	6,470	6,785	7,100	7,405

Source: Company data, Cowen and Company estimates

Sanofi Cash Flow Analysis 2013-20 (€MM)

	2013A	2014E	2015E	2016E	2017P	2018P	2019P	2020P
Operating Activities								
Net Income (operations)	6,677	6,848	7,265	7,402	7,996	8,647	9,428	10,282
Deprec., Depl. & Amortiz.	5,569	4,500	4,600	4,600	4,650	4,700	4,750	4,800
Def. Income Taxes & ITC	(1,010)	(1,200)	(1,200)	(1,200)	(1,200)	(1,200)	(1,200)	(1,300)
Other	(4,779)	0	0	0	0	0	0	0
Changes in working capital	497	64	(275)	(215)	(170)	(315)	(315)	(305)
Net Cash Flow - Operations	6,954	10,212	10,390	10,587	11,276	11,832	12,663	13,477
Investing Activities								
Capital Expenditures	(1,398)	(1,650)	(1,700)	(1,750)	(1,800)	(1,850)	(1,900)	(1,950)
Net Assets from Acq.	(235)	(1,200)	0	0	0	0	0	0
Disposal of Fixed Assets	409	0	0	0	0	0	0	0
Increase in Investments	(18)	(500)	0	0	0	0	0	0
Decrease in Investments	(31)	0	0	0	0	0	0	0
Net Cash Flow - Investing	(1,273)	(3,350)	(1,700)	(1,750)	(1,800)	(1,850)	(1,900)	(1,950)
Financing Activities								
Inc./Dec. Short Term Borrowing	302	0	0	0	0	0	0	0
Long Term Borrowing	3,119	0	0	0	0	0	0	0
Reduction in Long Term Debt	(2,822)	(1,000)	(500)	(500)	(500)	(500)	(500)	(500)
Proceeds from Stock Issue	1,004	0	0	0	0	0	0	0
Purchase/Redemption of Stock	(1,641)	(1,000)	(1,000)	(1,000)	(1,000)	(1,000)	(1,000)	(1,000)
Cash Dividends	(3,650)	(4,018)	(4,201)	(4,411)	(4,631)	(4,863)	(5,106)	(5,361)
Other Source/Use - Financing	(38)	0	0	0	0	0	0	0
Net Cash Flow - Financing	(3,726)	(6,018)	(5,701)	(5,911)	(6,131)	(6,363)	(6,606)	(6,861)
Effect of Exchange on Cash	(79)	0	0	0	0	0	0	0
Net change in cash and equivalents	1,876	844	2,989	2,926	3,344	3,619	4,157	4,665
Cash and equivalents, beginning of period	6,381	8,257	9,101	12,090	15,016	18,315	21,890	26,002
Cash and equivalents, end of period	8,257	9,101	12,090	15,016	18,360	21,935	26,047	30,667

Source: Company data, Cowen and Company estimates

SNY DCF Analysis

9/26/14 Assumptions:		
Share Price	\$56	<i>Output</i>
		Equity Value \$206,594
		Estimated Share Price \$58
Discount Rate	6.4%	Net Cash (\$6,148)
Shares Outstanding (000)	1,314	Enterprise Value \$212,742

SNY DCF													
2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021P	2022P	2023P	2024P	2025P	Terminal
Total Revenues € 33,306	€ 33,814	€ 35,280	€ 35,695	€ 37,140	€ 38,700	€ 40,385	€ 42,315	€ 44,431	€ 46,652	€ 48,985	€ 51,434	€ 54,006	
% Change -7%	+2%	+4%	+1%	+4%	+4%	+4%	+4%	+5%	+5%	+5%	+5%	+5%	+5%
Cost of Goods \$10,992	\$10,839	\$11,115	\$11,210	\$11,575	\$11,935	\$12,320	\$12,685	\$13,329	\$13,762	\$14,451	\$14,916	\$15,392	
Gross Profit \$22,314	\$22,975	\$24,165	\$24,485	\$25,565	\$26,765	\$28,065	\$29,630	\$31,102	\$32,890	\$34,534	\$36,518	\$38,614	
Gross Margin - Total 67.0%	67.9%	68.5%	68.6%	68.8%	69.2%	69.5%	70.0%	70.0%	70.5%	70.5%	71.0%	71.5%	
SG&A \$8,603	\$8,685	\$8,915	\$9,050	\$9,260	\$9,550	\$9,735	\$10,035	\$10,441	\$10,963	\$11,511	\$12,087	\$12,691	
% of Revs 25.8%	25.7%	25.3%	25.4%	24.9%	24.7%	24.1%	23.7%	23.5%	23.5%	23.5%	23.5%	23.5%	
R&D \$4,770	\$4,835	\$4,955	\$5,030	\$5,150	\$5,300	\$5,475	\$5,700	\$5,998	\$6,298	\$6,613	\$6,944	\$7,291	
% of Revs 14.3%	14.3%	14.0%	14.1%	13.9%	13.7%	13.6%	13.5%	13.5%	13.5%	13.5%	13.5%	13.5%	
Operating Expenses \$13,373	\$13,520	\$13,870	\$14,080	\$14,410	\$14,850	\$15,210	\$15,735	\$16,439	\$17,261	\$18,124	\$19,031	\$19,982	
% of Revenues 40.2%	40.0%	39.3%	39.4%	38.8%	38.4%	37.7%	37.2%	37.0%	37.0%	37.0%	37.0%	37.0%	
Operating Income \$8,941	\$9,455	\$10,295	\$10,405	\$11,155	\$11,915	\$12,855	\$13,895	\$14,662	\$15,629	\$16,410	\$17,488	\$18,632	
% Operating Margin 26.8%	28.0%	29.2%	29.1%	30.0%	30.8%	31.8%	32.8%	33.0%	33.5%	33.5%	34.0%	34.5%	
Non-operating income 77	95	80	70	60	50	40	30	20	20	20	20	20	
EBIT \$9,018	\$9,550	\$10,375	\$10,475	\$11,215	\$11,965	\$12,895	\$13,925	\$14,682	\$15,649	\$16,430	\$17,508	\$18,652	
% of Revs 27.1%	28.2%	29.4%	29.3%	30.2%	30.9%	31.9%	32.9%	33.0%	33.5%	33.5%	34.0%	34.5%	
D&A \$5,569	\$4,500	\$4,600	\$4,600	\$4,650	\$4,700	\$4,750	\$4,800	\$4,850	\$4,900	\$4,950	\$5,000	\$5,050	
EBITDA \$14,587	\$14,050	\$14,975	\$15,075	\$15,865	\$16,665	\$17,645	\$18,725	\$19,532	\$20,549	\$21,380	\$22,508	\$23,702	
% of Revs 43.8%	41.6%	42.4%	42.2%	42.7%	43.1%	43.7%	44.3%	44.0%	44.0%	43.6%	43.8%	43.9%	
Net Interest Income (Expense) \$(503)	(\$345)	(\$280)	(\$250)	(\$200)	(\$125)	(\$50)	\$25	\$50	\$75	\$100	\$125	\$150	
Pre-Tax Income \$8,515	\$9,205	\$10,095	\$10,225	\$11,015	\$11,840	\$12,845	\$13,950	\$14,732	\$15,724	\$16,530	\$17,633	\$18,802	
Taxes \$2,134	\$2,289	\$2,825	\$2,878	\$3,109	\$3,363	\$3,667	\$3,998	\$4,228	\$4,513	\$4,744	\$5,061	\$5,396	
Income Tax Rate 23.7%	24.0%	27.2%	27.5%	27.7%	28.1%	28.4%	28.7%	28.7%	28.7%	28.7%	28.7%	28.7%	
Net Income \$6,381	\$6,916	\$7,270	\$7,347	\$7,906	\$8,477	\$9,178	\$9,952	\$10,504	\$11,211	\$11,786	\$12,572	\$13,406	
% of Revs 19.2%	20.5%	20.6%	20.6%	21.3%	21.9%	22.7%	23.5%	23.6%	24.0%	24.1%	24.4%	24.8%	
% Change -14%	+8%	+5%	+1%	+8%	+7%	+8%	+6%	+7%	+5%	+7%	+7%	+7%	
NOPAT \$6,884	\$7,261	\$7,550	\$7,597	\$8,106	\$8,602	\$9,228	\$9,927	\$10,454	\$11,136	\$11,686	\$12,447	\$13,256	
<u>Adjustments:</u>													
Capex \$(1,398)	(\$1,650)	(\$1,700)	(\$1,750)	(\$1,800)	(\$1,850)	(\$1,900)	(\$1,950)	(\$1,975)	(\$1,975)	(\$2,000)	(\$2,000)		
Depreciation & Amortization \$5,569	\$4,500	\$4,600	\$4,600	\$4,650	\$4,700	\$4,750	\$4,800	\$4,850	\$4,900	\$4,950	\$5,000	\$5,050	
Change In Working Capital \$497	\$64	(\$275)	(\$215)	(\$170)	(\$315)	(\$315)	(\$305)	(\$200)	(\$200)	(\$100)	(\$50)	(\$50)	
Operating Free Cash Flow \$11,049	\$9,680	\$9,895	\$9,982	\$10,588	\$11,012	\$11,713	\$12,497	\$13,204	\$13,938	\$14,681	\$15,622	\$16,406	\$26,341

Source: Cowen and Company

SANOFI R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
Arthritis/Inflammation							
Synvisc-One				.			OA hip pain
Sarilumab			.	.			Anti-IL-6R mAb; PIII for rheumatoid arthritis, positive PIII results presented at EULAR 2014; PII for uveitis
Cancer/Oncology/Hematology							
Jevtana				.			Metastatic prostate cancer
Fresolimumab			.				TGF beta antagonist; focal segmental glomerulosclerosis; from Genzyme
SAR245409/MSC1936369B combo		.	.				Combination chemotherapeutic; ovarian cancer, solid tumors
SAR3419		.					Maytansin-loaded anti-CD19 MAB; B-cell malignancies; refractory/relapsed (NHL, ALL)
SAR650984	⇒	.					Anti-CD38 naked mAb; hematological malignancies
SAR125844	.						C-Met kinase inhibitor; solid tumors
SAR245408	.						XL147; oral P13K inhibitor; solid tumors
SAR260301	.						P13K Beta selective inhibitor; PTEN-deficient tumors
SAR307746	.						REGN910; anti-Ang2 mAb; solid tumors
SAR405838	.						HDM2/p53 antagonist; solid tumors
SAR405838/MSC1936369B	.						Combination for solid tumors
SAR405838/MSC1936369B	.						Combo therapy; solid tumors
SAR566658	.						Maytansin-loaded anti-DS6 antibody-drug conjugate; DS6 positive solid tumors
Cardiovascular							
Alirocumab			.		Q4:14		Anti-PCSK9 mAb; hypercholesterolemia; positive results from 4 Phase III Odyssey trials presented at ESC 2014
Kynamro			.				Mipomersen; apolipoprotein B-100 antisense; PIII for severe HeFH in U.S.; from Genzyme
SAR438714	.						ALN-TTRSc; RNAi; familial amyloid cardiomyopathy
Central Nervous System							
Lemtrada			.		Q2:14		Alemtuzumab; anti-CD52 mAb; multiple sclerosis; FDA recommended approval in November, 2013; complete response 12/13; resubmitted Q2:14; positive interim results from the second year of the extension study ; from Genzyme
SAR339658		.					VLA 2 antagonist; multiple sclerosis`
SAR391786	.						GDF-8 Mab; sarcopenia
SAR228810	.						Anti-prototibrillarAB mAb; Alzheimer's disease
Diabetes							
Toujeo			.		Jul-14		New insulin glargine formulation; types 1 and 2 diabetes; all studies in PIII EDITION clinical trial program met primary endpoint; filed in U.S. and EU
LixiLan			.		YE2015		GLP-1 agonist + insulin glargine; Fix-Flex/type 2 diabetes
Lyxumia			.	Mid-2015			Lixisenatide; GLP-1 receptor agonist; Type 2 diabetes; Zealand pharma license; U.S. refilling; approved EU
SAR342434	.						Insulin Lispro; diabetes
SAR425899	.						GLP-1/GCGR agonist; diabetes
Gene Therapy							
Cerdelga (eliglustat tartrate)					2013		Glucosylceramide synthetase inhibitor; Gaucher disease; approved in U.S. August 2014; filed in EU, from Genzyme
SAR438037		.					Patisiran; mRNA inhibitor; familial amyloid polyneuropathy
GZ402663		.					sFLT-01; Age-related macular degeneration (AMD); from Genzyme

SANOFI R&D PIPELINE

Therapeutic Class/Product	PC	I	II	III	NDA	MKT	Comments
GZ402665		.					rhASM; Niemann-Pick type B; from Genzyme
GZ402666		.					Neo GAA; Pompe Disease
GZ402671		.					GCS inhibitor; Fabry disease; FDA granted Orphan Drug designation August, 2014
StarGen		.					Stargardt disease
UshStat		.					Usher syndrome 1B
Immunological							
SAR113244		.					Anti-CXCRS mAb; SLE
SAR252067		.					Anti-LIGHT Mab; Crohn's Disease
Infectious Disease							
Ferroquine/OZ439 combo		.					Malaria
SAR279356		.					F598; anti-PNAG mAb; serious infections
Pseudomonas aeruginosa		.					Antibody fragment; prevention of ventilator-associated pneumonia
Respiratory							
Dupilumab		.					SAR231893; anti-IL4 mAb; asthma; atopic dermatitis; nasal polyposis
SAR156597		.					IL4/IL 13 bi-specific mAb; idiopathic pulmonary fibrosis
Vaccines							
Fluzone QIV ID				.			Quadrivalent inactivated influenza vaccine; intradermal formulation
Quadracel				.			Diphtheria, tetanus, pertussis and polio vaccine; 4-6 years of age
ACAM-Cdiff			.				Prevention of C. difficile-associated diarrhea
Dengue			.		Early 2015		Mild to severe Dengue fever; met primary PIII goal
PR5i			.				Pediatric hexavalent vaccine; DTP-HepB-Polio-Hib
VaxiGrip QIV IM			.				Quadrivalent inactivated influenza vaccines
Meninge A,C,Y,W infant		.					2nd generation conjugated; Neisseria meningitis groups A,C, W & Y prophylaxis; children > 2 months
Rabies VRVg		.					Purified vero rabies vaccine
Rotavirus		.					Live attenuated tetravalent; rotavirus oral vaccine
Tuberculosis Vaccine	⇒	.					Recombinant subunit vaccine
Herpes Simplex Virus Type 2	.						HSV-2 vaccine
Streptococcus pneumonia	.						Meningitis & pneumonia
Total Drugs In Development	0	22	15	12	5		54

Progress since last update in bold; movement marked by arrow

Investor Relations Contact: George Grofik 908-981-5560

Sebastien Martel 33-1-5377-4545

This page left blank intentionally.

Points Of Contact

Analyst Profiles



Steve Scala, R.Ph., CFA

Boston

617.946.3923

steve.scala@cowen.com



Kathleen Miner, R.Ph., CFA

Boston

617.946.3857

kathy.miner@cowen.com



Jean Perreault

Boston

617.946.3967

jean.perreault@cowen.com

Steve Scala is a senior analyst covering global big cap pharmaceutical companies for over 20 years, his entire career with Cowen.

Kathy Miner is a vice president covering the major pharmaceuticals sector. She rejoined Cowen in 2013 after working as a consultant.

Jean Perreault is an associate covering the major pharmaceuticals sector. She joined Cowen in 1996 following 20+ years on the buy side.

Reaching Cowen

Main U.S. Locations

New York

599 Lexington Avenue
New York, NY 10022
646.562.1000
800.221.5616

Boston

Two International Place
Boston, MA 02110
617.946.3700
800.343.7068

Cleveland

20006 Detroit Road
Suite 100
Rocky River, OH 44116
440.331.3531

San Francisco

555 California Street, 5th Floor
San Francisco, CA 94104
415.646.7200
800.858.9316

Atlanta

3399 Peachtree Road NE
Suite 417
Atlanta, GA 30326
866.544.7009

Chicago

181 West Madison Street
Suite 1925
Chicago, IL 60602
312.577.2240

International Locations

Cowen International Limited

London
1 Snowden Street - 11th Floor
London EC2A 2DQ
United Kingdom
44.20.7071.7500

Cowen and Company (Asia) Limited

Hong Kong
Suite 1401 Henley Building
No. 5 Queens Road Central
Central, Hong Kong
852 3752 2333



@CowenResearch



Cowen and Company

Addendum

Analyst Certification

Each author of this research report hereby certifies that (i) the views expressed in the research report accurately reflect his or her personal views about any and all of the subject securities or issuers, and (ii) no part of his or her compensation was, is, or will be related, directly or indirectly, to the specific recommendations or views expressed in this report.

Important Disclosures

This report constitutes a compendium report (covers six or more subject companies). As such, Cowen and Company, LLC chooses to provide specific disclosures for the companies mentioned by reference. To access current disclosures for the all companies in this report, clients should refer to <https://cowen.bluematrix.com/sellside/Disclosures.action> or contact your Cowen and Company, LLC representative for additional information.

Cowen and Company, LLC compensates research analysts for activities and services intended to benefit the firm's investor clients. Individual compensation determinations for research analysts, including the author(s) of this report, are based on a variety of factors, including the overall profitability of the firm and the total revenue derived from all sources, including revenues from investment banking. Cowen and Company, LLC does not compensate research analysts based on specific investment banking transactions.

Disclaimer

This research is for our clients only. Our research is disseminated primarily electronically and, in some cases, in printed form. Research distributed electronically is available simultaneously to all Cowen and Company, LLC clients. All published research can be obtained on the Firm's client website, <https://cowenlibrary.bluematrix.com/client/library.jsp>.

For important disclosures regarding the companies that are the subject of this research report, please contact Compliance Department, Cowen and Company, LLC, 599 Lexington Avenue, 20th Floor, New York, NY 10022. In addition, the same important disclosures, with the exception of the valuation methods and risks, are available on the Firm's disclosure website at <https://cowen.bluematrix.com/sellside/Disclosures.action>.

Price Targets: Cowen and Company, LLC assigns price targets on all covered companies unless noted otherwise. The price target for an issuer's stock represents the value that the analyst reasonably expects the stock to reach over a performance period of twelve months. The price targets in this report should be considered in the context of all prior published Cowen and Company, LLC research reports (including the disclosures in any such report or on the Firm's disclosure website), which may or may not include price targets, as well as developments relating to the issuer, its industry and the financial markets. For price target valuation methodology and risks associated with the achievement of any given price target, please see the analyst's research report publishing such targets.

Notice to UK Investors: This publication is produced by Cowen and Company, LLC which is regulated in the United States by FINRA. It is to be communicated only to persons of a kind described in Articles 19 and 49 of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005. It must not be further transmitted to any other person without our consent.

Copyright, User Agreement and other general information related to this report

© 2014 Cowen and Company, LLC. Member NYSE, FINRA and SIPC. All rights reserved. This research report is prepared for the exclusive use of Cowen clients and may not be reproduced, displayed, modified, distributed, transmitted or disclosed, in whole or in part, or in any form or manner, to others outside your organization without the express prior written consent of Cowen. Cowen research reports are distributed simultaneously to all clients eligible to receive such research reports. Any unauthorized use or disclosure is prohibited. Receipt and/or review of this research constitutes your agreement not to reproduce, display, modify, distribute, transmit, or disclose to others outside your organization the contents, opinions, conclusion, or information contained in this report (including any investment recommendations, estimates or price targets). All Cowen trademarks displayed in this report are owned by Cowen and may not be used without its prior written consent.

Cowen and Company, LLC. New York (646) 562-1000 **Boston** (617) 946-3700 **San Francisco** (415) 646-7200 **Chicago** (312) 577-2240 **Cleveland** (440) 331-3531 **Atlanta** (866) 544-7009 **London** (affiliate) 44-207-071-7500

COWEN AND COMPANY RATING DEFINITIONS

Cowen and Company Rating System effective May 25, 2013

Outperform (1): The stock is expected to achieve a total positive return of at least 15% over the next 12 months

Market Perform (2): The stock is expected to have a total return that falls between the parameters of an Outperform and Underperform over the next 12 months

Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

Outperform (1): Stock expected to outperform the S&P 500

Neutral (2): Stock expected to perform in line with the S&P 500

Underperform (3): Stock expected to underperform the S&P 500

Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

Cowen Securities, formerly known as Dahlman Rose & Company, Rating System until May 25, 2013

Buy – The fundamentals/valuations of the subject company are improving and the investment return is expected to be 5 to 15 percentage points higher than the general market return

Sell – The fundamentals/valuations of the subject company are deteriorating and the investment return is expected to be 5 to 15 percentage points lower than the general market return

Hold – The fundamentals/valuations of the subject company are neither improving nor deteriorating and the investment return is expected to be in line with the general market return

Cowen And Company Rating Definitions

Distribution of Ratings/Investment Banking Services (IB) as of 09/30/14

Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
Buy (a)	440	59.95%	105	23.86%
Hold (b)	278	37.87%	10	3.60%
Sell (c)	16	2.18%	0	0.00%

(a) Corresponds to "Outperform" rated stocks as defined in Cowen and Company, LLC's rating definitions. (b) Corresponds to "Market Perform" as defined in Cowen and Company, LLC's ratings definitions. (c) Corresponds to "Underperform" as defined in Cowen and Company, LLC's ratings definitions.

Note: "Buy", "Hold" and "Sell" are not terms that Cowen and Company, LLC uses in its ratings system and should not be construed as investment options. Rather, these ratings terms are used illustratively to comply with FINRA and NYSE regulations.