June 3, 2013

Receptos

(RCPT-NASDAQ)

Stock Rating: **Outperform**
Industry Rating: **Outperform**

Biotechnology

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Initiating With Outperform

Investment Thesis

We are initiating coverage of Receptos (RCPT) with an Outperform rating and $22 price target. Our favorable rating is driven primarily by expectations for RPC1063, a potential best-in-class oral S1P1 receptor modular, in phase 2/3 development for patients with relapsing multiple sclerosis (RMS) and inflammatory bowel disease (IBD). Following success of the less selective oral S1P modulator GILENYA in establishing a $1.5B-plus run rate in just two years, and with more recent launch of oral TECFIDERA in establishing a steeper adoption with cleaner labeling, we expect significant interest in proof-of-concept data for RPC-1063 in RMS by mid-2014. Additional upside potential could emerge from RPC-1063 proof-of-concept data in ulcerative colitis (UC) as well as increasing visibility on an earlier stage program for IL-13 inhibitor RPC-4046 in eosinophilic esophagitis (EoE). Overall, we believe that RCPT is attractively valued relative to an opportunity estimated for RPC-1063 at $1.8B globally as second-line option in RMS alone.

Forecasts

We estimate 2013-2018 per share losses of $(2.12), $(4.63), $(2.73), $(4.09), $(3.53), and $(2.11), respectively. Our forecast calls for RCPT to become profitable in 2019 with EPS of $0.86, increasing to $2.49 in 2020, our valuation year.

Valuation

Our $22 price target is based on 25x 2020 EPS of $2.49, discounted 20%. We believe that the multiple appropriately reflects growth prospects for RCPT and that the 20% discount rate adequately reflects risk to our estimates.

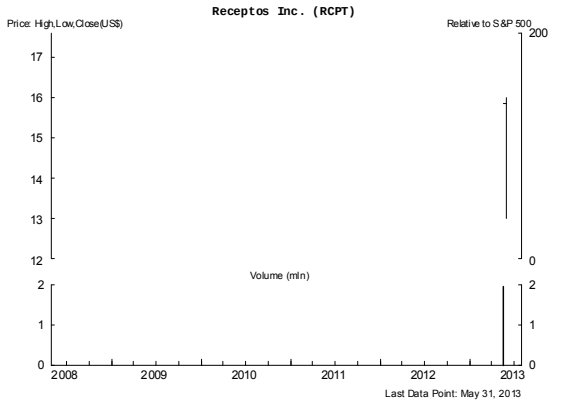
Recommendation

We rate shares of RCPT stock as Outperform.

Securities Info

Price (31-May)	**$15.87**	**Target Price**	**$22**
52-Wk High/Low	$15/$13	Dividend	--
Mkt Cap (mm)	$284	Yield	--
Shs O/S (mm, BASIC)	17.9	Float O/S (mm)	4.8
Options O/S (mm)	na	ADVol (30-day, 000s)	133

Price Performance



Valuation/Financial Data

(FY-Dec.)	2011A	2012A	2013E	2014E
EPS GAAP	-$1.04	-$0.28	-$2.12	-$4.63
P/E			nm	nm
First Call Cons.				
FCF	$1.20	-$18.40	-$10.30	-$30.80
P/FCF			nm	nm
EBITDA ($mm)	-$6	-$18	-$38	-$96
EV/EBITDA			nm	nm
Rev. ($mm)	$9	$9	$0	$0
EV/Rev			na	#DIV/0!

Quarterly EPS	**1Q**	**2Q**	**3Q**	**4Q**
2012A	na	na	na	na
2013E	-$0.45A	-$0.50	-$0.56	-$0.61

Balance Sheet Data (na)

Net Debt ($mm)	-$98	TotalDebt/EBITDA	nm
Total Debt ($mm)	$0	EBITDA/IntExp	na
Net Debt/Cap.	na	Price/Book	24.8x

Notes: Quarterly EPS may not sum due to share count. All values in US$.

Source: BMO Capital Markets estimates, Bloomberg, Thomson Reuters, and IHS Global Insight.

Investment Thesis

We rate Receptos (RCPT) at Outperform with ~50% upside potential to our $22 price target. Our valuation is driven solely by prospects for selective S1P1 modulator RPC-1063 as a second-line treatment option behind Biogen Idec's TECFIDERA, and could see significant upside on confirmation of a more selective profile than first-generation S1P modulator GILENYA. With focus on phase 2 proof-of-concept data in both relapsing multiple sclerosis (RMS) and ulcerative colitis (UC) by mid-2014 we believe that lymphocyte reductions already observed should support efficacy and that favorable cardiac safety and short half-life should establish a favorable profile to GILENYA and potentially competitive profile with TECFIDERA. While not a primary driver of valuation we do see incremental upside potential from the pipeline, in particular IL-13 inhibitor RPC-4046 for patients with eosinophilic esophagitis (EoE), and an oral GLP-1 agonist for type 2 diabetes.

Key Investment Highlights

- RCPT has a potential best-in-class, highly selective S1P1 modulator, in RPC-1063, that should differentiate favorably from approved first-generation S1P modulator GILENYA and position competitively with expected oral brand leader TECFIDERA, in patients with relapsing multiple sclerosis (RMS).
- With phase 2 proof-of-concept data expected for RPC-1063 in both RMS and ulcerative colitis (UC), we believe that reductions in lymphocyte count of ~70% will translate into clinical efficacy across both indications.
- With GILENYA establishing a run rate of >$1.5 billion in global sales despite major limitations on first-dose monitoring for bradycardia and extended half-life and prolonged lymphocyte suppression, we believe that significant upside potential exists for a more selective S1P1 modulator with lesser effect on heart rate, absent QTc effect, and much shorter half-life and reversibility of lymphocyte suppression.
- With more recent launch of Biogen Idec's TECFIDERA achieving TRx's in the first seven weeks of launch of ~2000, a level only seen after 30 weeks with GILENYA, we believe that the value of a cleaner label has been validated and provides a window into the substantial upside potential for RPC-1063 if a competitive profile can be achieved.
- Our RPC-1063 estimates only assume second-line use after TECFIDERA (estimates for ~20-30% discontinuation in year one) and still approach $900 million in the US and similar levels ex-US. We estimate a probability adjusted NPV of ~$20/share with 40%-55% probability of success assumed on this second-line opportunity alone.
- We believe that ulcerative colitis (UC), and more broadly inflammatory bowel disease (IBD), represents a large category with greater unmet need where sales could approach $1 billion ultimately and where this would be incremental to our current RPC-1063 estimates.

Valuation

Our $22 price target is based on 25x 2020 EPS of $2.49, discounted 20%. We believe that the multiple appropriately reflects growth prospects for RCPT and that the 20% discount rate adequately reflects risk to our estimates. Separately, we estimate a probability-adjusted NPV for RCPT today of $20/share assuming 55% likelihood of success for RPC-1063 in RMS in the US and 40% likelihood of success for RPC-1063 in RMS ex-US.

Exhibit 1. RCPT Comps

RECEPTOS COMPARABLES						
Company	**Ticker**	**Market Cap (M)**	**Cash (M)**	**EV (M)**	**Therapeutic Focus**	**Stage of Development**
Acadia Pharmaceuticals	ACAD	$1,053.8	$108.0	$945.8	CNS	Phase 3
Acorda Therapeutics	ACOR	1,577.3	234.2	1,348.5	CNS	Market
Alnylam Pharmaceuticals	ALNY	1,487.9	122.8	1,365.1	Orphan Disease	Phase 2
Arena Pharmaceuticals	ARNA	1,816.0	165.8	1,725.1	Metabolic	Market
Cempra	CEMP	156.9	70.1	96.6	Infectious Disease	Phase 3
Corcept Therapeutics	CORT	186.7	101.6	115.6	Metabolic	Market
Cytokinetics	CYTK	194.8	75.6	119.2	CNS/CV	Phase 2
Amicus Therapeutics	FOLD	170.2	99.1	71.8	Orphan Disease	Phase 3
Idenix Pharmaceuticals	IDIX	517.1	232.9	284.1	HCV	Phase 2
Lexicon Pharmaeuticals	LXRX	1,174.8	206.8	991.8	Cancer/GI	Phase 2
Neurocrine Biosciences	NBIX	795.2	173.0	622.2	CNS/Endocrine	Phase 3
Rigel Pharmaceuticals	RIGL	413.9	298.2	115.7	Inflammation	Phase 3
Repros Therapeutics	RPRX	374.2	24.2	350.0	Endocrine	Phase 2
Sangamo Biosciences	SGMO	568.2	76.3	491.9	Infectious Disease	Phase 2
Targacept	TRGT	148.6	125.0	25.6	CNS	Phase 2
Tetraphase Pharmaceuticals	TTPH	149.0	9.1	151.5	Infectious Disease	Phase 2
Mean		$674.0		$551.3		
Median		465.5		317.1		
Receptos	RCPT		$85.4	N/A		

RECEPTOS SUM-OF-THE-PARTS					
Target	**Indication**	**Launch Year**	**Peak Sales ($M)**	**Probability**	**NPV ($M)**
RPC1063	MS	2018	$906.0	55%	$199.0
RPC1063	MS	2018	906.0	40%	144.7
Total					$343.8

Source: Company reports, Thomson Reuters, and BMO Capital Markets.

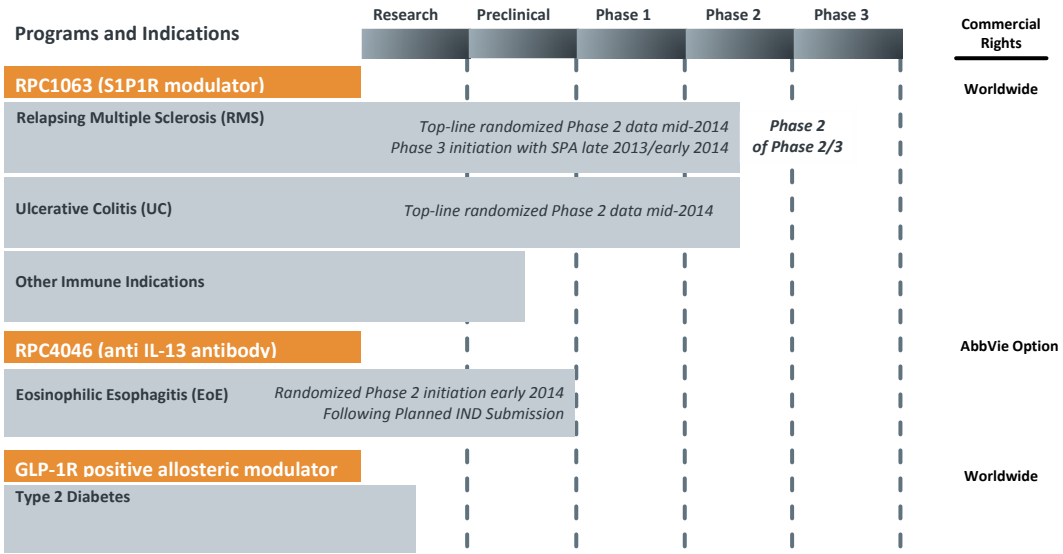
Overview

Receptos is a development-stage biopharmaceutical company focused on novel therapeutics for immune disorders, including Relapsing-Remitting Multiple Sclerosis (RRMS), Ulcerative Colitis (UC), and Eosinophilic Esophagitis (EoE). The company's lead compound is RPC1063, a S1P1 modulator being developed for the treatment of RMS and UC. Developed with a broad S1P1 modulator patent licensed from The Scripps Research Institute, RPC1063 is currently being evaluated in a phase 2/3 RRMS study, RADIANCE, and in a phase 2 UC study, TOUCHSTONE. Top-line results for RADIANCE phase 2 and for TOUCHSTONE are expected in mid-2014. Another compound in development is RPC4046, a recombinant anti-IL13 monoclonal antibody licensed from AbbVie. Receptos plans to initiate a phase 2 study of RPC4046 in EoE, an orphan disease, in 1H14.

One other very important asset of the company is a proprietary GPCR structure-based drug discovery and design technology platform, and the company is using this platform to develop oral, small molecule positive allosteric modulators (PAMs) of the GLP-1R receptor for the treatment of Type 2 Diabetes. Receptos has enacted several collaborations based on the GPCR platform, including an ongoing collaboration with Ono Pharmaceutical Co., a completed partnership with Ortho-McNeil-Janssen Pharmaceuticals, and a completed collaboration with Eli Lilly and Company.

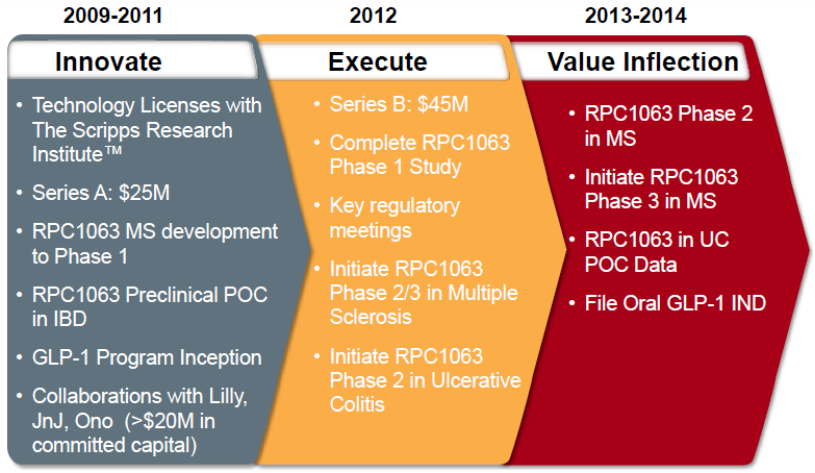
Receptos has gone through two rounds of venture capital financing, with a Series A at $25 million and a Series B at $45 million, and raised $72.8 million in an IPO in May 2013.

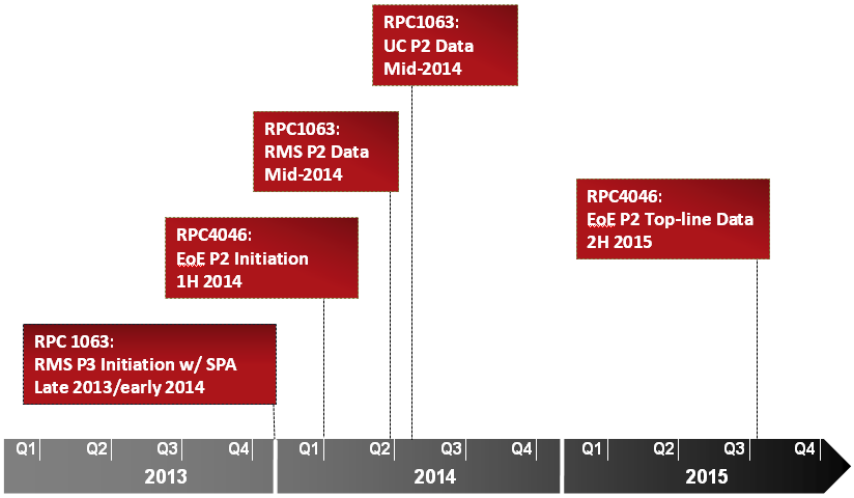
Exhibit 2. Receptos Pipeline



Source: Receptos.

Exhibit 3. Company Development Timeline and Future Milestones





Source: Receptos.

RPC1063 – A Modulator of Lymphocyte Trafficking

Receptos' RPC1063 is part of a new class of immune modulator that causes selective and reversible retention, or *sequestration*, of circulating lymphocytes (white blood cells) in peripheral lymphoid tissue, such as the lymph nodes, Peyer's patches, as well as in the thymus. The sequestration of lymphocytes could have a positive impact in the treatment of autoimmune diseases such as multiple sclerosis because it prevents autoreactive lymphocytes from entering circulation and reaching their target tissue or organ, thus preventing tissue destruction.

RPC1063 "puts a leash" on lymphocytes by targeting a key mediator of lymphocyte trafficking, sphingosine 1-phosphate (S1P), which controls the exit of lymphocytes from lymph nodes into blood circulation. Because S1P is synthesized by the lymphatic endothelium and degraded in

the lymph node parenchyma, a gradient of S1P concentration is established, with a high concentration in the lymphatic vessels and a low one in the lymph node. This S1P concentration gradient can be sensed by lymphocytes through a cell surface-expressed receptor, S1P receptor 1 (S1P1).

RPC1063 is an agonist of S1P1, and upon binding, RPC1063 causes the internalization of S1P1. Without S1P1, lymphocytes are unable to sense the S1P gradient and are therefore locked in lymph nodes.

S1P1 is one of five S1P receptors: S1P1, S1P2, S1P3, S1P4, and S1P5. The diversity of S1P receptors helps ensure tissue- and cell-type-specific responses to S1P, which is a versatile blood borne lipid mediator for many other biological processes besides lymphocyte trafficking. An extensive review of the biology of S1P and its receptors can be found in the *Deep Dive* section of this report (page 42).

The notion of using S1P receptor modulators to treat autoimmune diseases has been validated by Novartis' GILENYA, which is the first approved S1P receptor modulator. GILENYA has been approved for the treatment of RRMS.

A key difference between RPC1063 and GILENYA is that whereas GILENYA modulates four of the five S1P receptors (all but S1P2), RPC1063 binds specifically to S1P1. The increased specificity of RPC1063 reduces the possibility of unnecessarily triggering other S1P receptors and causing unwanted side effects.

RPC1063 Development in RRMS

Receptos is developing RPC1063 for two autoimmune disorders: Relapsing Remitting Multiple Sclerosis (RRMS) and Inflammatory Bowel Disease (IBD). RRMS's pathology, symptoms, disease course, and treatment options are described later in this report under *Multiple Sclerosis Overview* (page 38).

In preclinical animal studies with RPC1063, Receptos demonstrated dose-proportional lymphocyte count reduction with rapid lymphocyte recovery in multiple species. RPC1063 also demonstrated dose-proportional efficacy similar to that of GILENYA in a mouse model for RRMS (Experimental Autoimmune Encephalomyelitis, or EAE).

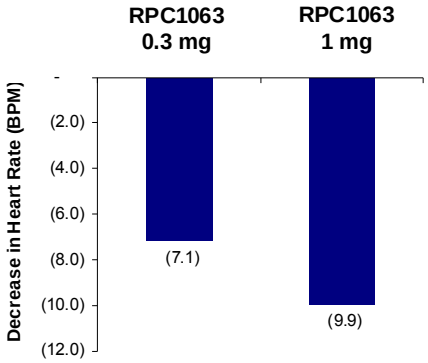
In chronic toxicology studies, oral daily dosing of six months in rodents and nine months in primates at doses up to 200-fold above the therapeutically relevant dose was achieved. Teratogenicity, or capability of causing fetal malformation, was found in Segment II (rat and rabbit) of RPC1063's genotoxicological and reproductive toxicological studies, consistent with findings on GILENYA. According to Receptos, animal studies with respect to human Ether-à-go-go Related Gene (hERG) inhibition demonstrated wide safety margins with no evidence of QTc prolongation *in vivo* in primates. Receptos also established a wide safety margin for RPC1063 for cardiac effects in primates and for respiratory effects in rodents.

A phase 1 study for RPC1063 has been completed and reported as having demonstrated adequate safety and tolerability, and linear pharmacokinetics (PK) for RPC1063. This single

center, randomized, double-blind, placebo-controlled, single and multiple dose escalation study evaluated the safety, tolerability, pharmacokinetic and pharmacodynamic effects of RPC1063 administered orally to 88 healthy adult volunteers, 68 of whom were treated with RPC1063. RPC1063 was administered as single doses of 0.3 to 3.0 mg, as well as multiple doses of 0.3 to 2.0 mg daily for 7 days or 0.3 to 1.5 mg daily for 28 days. RPC1063 was also administered in a dose titration regimen as multiple daily doses from 0.3 to 2.0 mg for 10 days.

Upon the first dose administration of RPC1063, a dose-dependent drop in heart rate was observed. (See Exhibit 4.) The largest difference from the placebo group (both in terms of absolute heart rate as well as change from baseline) occurred within the first six hours and then the effect gradually attenuated over time. The drop in heart rate was mitigated by the use of a dose titration regimen.

Exhibit 4. Dose-Dependent Decrease in Heart Rate Upon First Dose Administration of RPC1063



Source: Receptos and BMO Capital Markets.

Overall, RPC1063 was well tolerated in phase 1 experience. There was one Grade 2 serious adverse event (considered a pre-existing condition and unrelated to RPC1063 by treating physician), no Grade 3 or higher adverse events, and no dose-limiting toxicities. Serious infections or side effects that have been associated with GILENYA, such as macular edema or hepatotoxicity, were not observed in the RPC1063 study.

The phase 1 study has also demonstrated a dose-dependent reduction in lymphocyte count, which Receptos considers to be a biomarker that will correlate with clinical efficacy in phase 2 studies. The rationale of using lymphocyte count reduction as a biomarker is based on the observation that several S1P1 modulator compounds demonstrated *MRI efficacy* at doses reaching threshold levels of lymphocyte count reduction of ~50% to 70%, and that these compounds demonstrated *relapse efficacy* at doses reaching threshold levels of lymphocyte count reduction of ~60% to 70%. (See Exhibit 5.) (*MRI efficacy* refers to the reduction in new lesions as measured by MRI brain scans. *Relapse efficacy* refers to the reduction in Annualized Relapse Rate, or ARR).

Exhibit 5. Peripheral Lymphocyte Count Reduction of 60%-70% Correlates Strong MRI and ARR Efficacy Outcomes for the S1P1 Modulator Class

	Gilenya® versus Placebo	Ono-4641 versus Placebo		Ponesimod versus Placebo		Siponimod versus Placebo	
	0.5 mg	0.1 mg	0.15 mg	20 mg	40 mg	2 mg	10 mg
Lymphocyte Count Reduction	~70%	~60%	~65%	~65%	~70%	~70%	>70%
Reduction in Mean Number of Gd+ T1 Lesions (as measured by MRI)	~80%	90%	89%	83%	77%	76%	85%
Reduction in Annualized Relapse Rate (ARR)	54%	70%	39%*	21%*	52%	66%	48%*
	Phase 3 Outcomes	Phase 2 Outcomes					

* not significant; Phase 2 studies not powered to show significant reduction in ARR outcomes

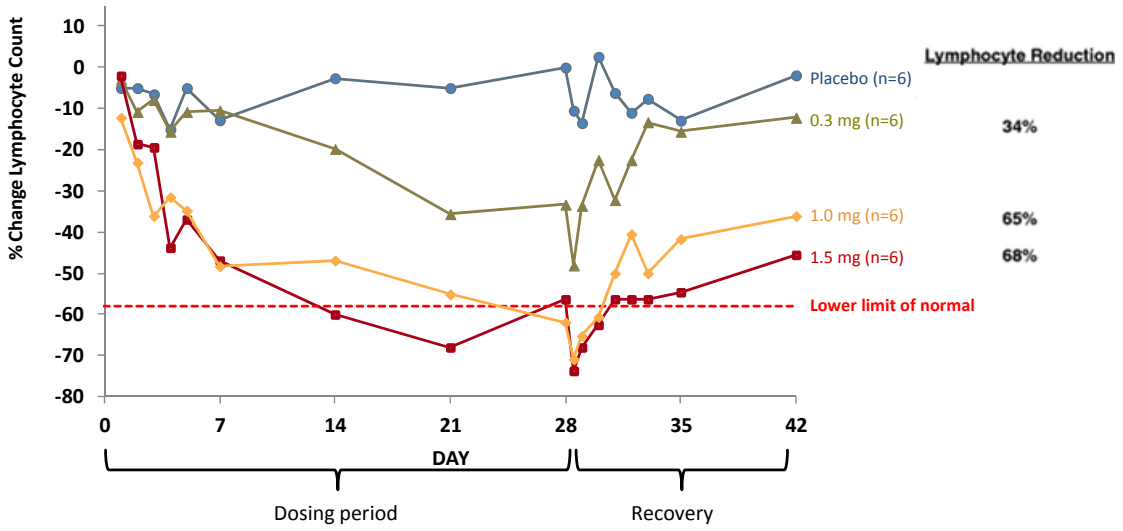
Source: Receptos.

Based on the above observations, Receptos concluded that a lymphocyte count reduction in the range of 50%-70% correlates with MRI and relapse efficacy outcomes. In the RPC1063 phase 1 study, a dose-related decreases in lymphocyte count was observed. (See Exhibit 6.) For dose levels of 0.3 mg, 1.0 mg, and 1.5 mg, the median decreases in lymphocyte count after 28 days of dosing were 34%, 65%, and 68%, respectively, and lymphocyte reduction appeared to approach steady state by the 28th day of dosing.

Notably, the circulating lymphocyte levels returned to above lower limit of normal within three days in all patients. (See Exhibit 6.) In contrast, following chronic administration of GILENYA, it can take 4-8 weeks for lymphocyte counts to return to the normal range.

Based on the phase 1 data and additional modeling, Receptos selected 0.5 mg and 1.0 mg doses (projected to lead to approximately 50% and 70% lymphocyte count reduction, respectively) for the phase 2 and 3 clinical studies in RRMS. According to Receptos, the FDA has agreed with this dose selection.

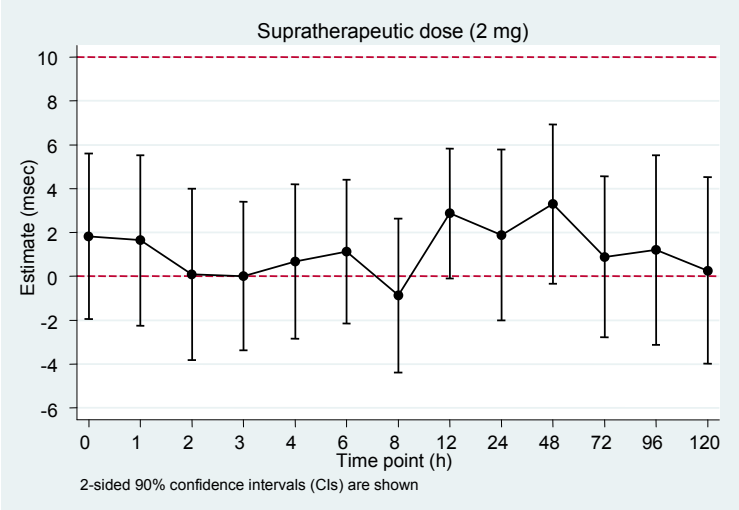
Exhibit 6. Phase 1 RPC1063 Lymphocyte Count Reductions



Source: Receptos.

The effects of RPC1063 on QT interval were assessed in a thorough QT study involving approximately 120 patients. The study evaluated the therapeutic dose of 1 mg RPC1063 and supra-therapeutic dose of 2 mg RPC1063. There was no significant effect on the QT interval with RPC1063 at a dose of 2 mg, with the upper bound of the 90% confidence interval well below 10 milliseconds. (See Exhibit 7.)

Exhibit 7. RPC1063 Thorough QT Study – QT Interval for the Superatherapeutic Dose of 2 mg



Source: Receptos.

In GILENYA's QT interval study, a mild but statistically significant prolongation of the QTc interval was reported at supra-therapeutic doses of 1.25 or 2.5 mg (with upper bound of the 90% confidence interval at 14.0 milliseconds).

The RPC1063 phase 1 thorough QT/QTc study also aims to assess heart rate, utilizing the same dose titration regimen for RPC1063 as in the phase 2 study and incorporating continuous 24-hour ambulatory electrocardiogram (ECG) monitoring on the day before first dosing, the first day of dosing, and on each day of dose escalation during the dose titration regimen.

Receptos is conducting a phase 2/3 trial for RPC1063 in RRMS. This study, called RADIANCE (RPC01-201), consists of a placebo-controlled portion (phase 2) and an active comparator-controlled portion (phase 3).

Receptos is currently enrolling the phase 2 portion and will enroll up to 210 patients. The phase 2 portion is a randomized, double-blind comparison of 0.5 mg and 1.0 mg of RPC1063 versus placebo and will characterize the short-term safety and efficacy of RPC1063 in RRMS. The primary objective of this study is to demonstrate a reduction in the cumulative number of total gadolinium-positive (Gd+ve) T1 lesions determined by MRI brain scans from week 12 to week 24 of study treatment.

Gd+ve T1 lesions refer to new, active lesions identified as bright spots on brain MRI scans using contrast material gadolinium and T1 weighting. It is estimated that lesions will enhance (i.e., become brighter) with gadolinium for six weeks or less. MRI-based readouts have increasingly become a surrogate for clinical efficacy in MS clinical trials. Other types of clinical readouts, such as relapse rates or disability assessment, require a much longer study time frame and therefore are not practical primary endpoints in phase 2 trials.

Enrollment for the phase 2 portion of RADIANCE is expected to complete in 2H13, and top-line primary endpoint results are expected in mid-2014.

The phase 3 portion of RADIANCE, which will enroll up to 900 patients, is a randomized, double-blind, double-dummy comparison of RPC1063 (0.5 mg or 1.0 mg, twice daily oral) to an active comparator, AVONEX (30 μg weekly intramuscular injection), administered for 24 months in patients with RRMS. The primary objective will be to assess whether RPC1063 is superior to IFNβ-1a in reducing the rate of relapse at 24 months of treatment. Patient enrollment for the phase 3 portion of RADIANCE is scheduled to start in late 2013 or early 2014, subject to ongoing Data Monitoring Committee (DMC) oversight during the phase 2 portion of RADIANCE.

Receptos plans to initiate a second phase 3 trial of RPC1063 in RRMS given positive phase 2 study results. The company has obtained a Special Protocol Assessment (SPA) agreement from the FDA on its clinical trial design for the phase 3 potion of RADIANCE as well as for the second phase 3 study. Receptos expects to file an NDA to the FDA in 2017 for the use of RPC1063 in patients with RRMS.

The Competitive Landscape of S1P Receptor Modulators

With Receptos seeking to establish proof-of-concept in its ongoing phase 2/3 study of RPC1063, it is worthwhile considering precedent data for approved S1P receptor modulator GILENYA, along with that of other S1P1 modulators in development.

GILENYA's Phase 2 and Phase 3 Development

Novartis's GILENYA (fingolimod, formerly FTY-720) is the only marketed S1P receptor modulator and was approved in the US in 2010 and in EU in 2011. A comparison of the US and European labels for GILENYA illustrates that European regulators take a more proactive role in clarifying when and how GILENYA should be used. Whereas in the US GILENYA can be used in relapsing forms of the disease irrespective of prior therapy, use of GILENYA in Europe is restricted to subjects with documented failure of a 12-month course of an interferon. European regulators further document failure with respect to relapse number and lesion load. Only in the US label do claims for reducing the frequency of relapses and accumulation of disability exist.

As noted in Exhibit 8, both labels detail the FREEDOMS and TRANSFORMS trials, with the European label including details of the second two-year placebo controlled trial FREEDOMS II; recall GILENYA was approved in 2011 versus 2010 in the US. The efficacy described from the trial is comparable with the notable exception that the European label contains a description of the brain volume changes observed over two years. In all three studies, GILENYA reduced the loss of brain volume compared to placebo or AVONEX.

Both the US and EU labels contain detailed sections on contraindications, warnings and precautions that are largely overlapping. Both labels also contain selected information about preclinical data. The US label focuses on lung toxicity, while the EU label notes toxicity associated with lymphoid organs, heart changes, and lung toxicity. The US label notes that at all doses tested in chronic studies, lung toxicity was observed but that the lowest dose tested led to an exposure roughly 20x above the exposure expected in humans. In contrast, the EU label notes that the vasculopathy signal in rats occurred at 4x the expected human exposure.

Exhibit 8. Comparison of US and EU GILENYA Label

	Gilenya - US label		Gilenya - EU label		
Status	Approved 2010 Treatment of relapsing MS Reduce frequency of clinical exacerbation Reduce accumulation of physical disability		Approved 2011 Use in highly active disease- Failed to respond to full and adequate course of beta interferon, patients should have at least 1 relapse and 9 T2-hyerintense lesions or at least 1 Gd+ve lesion OR patients with rapidly evolving severe relapsing remitting MS defined by 2 or more disabling relapse in 1 year with 1 or more Gd+ve lesions on and significant increase in T2 lesion load as compared to a previous recent MRI.		
Efficacy	**FREEDOMS**	**TRANSFORMS**	**FREEDOMS**	**FREEDOMS2**	**TRANSFORMS**
ARR	0.18 vs. 0.4	0.16 vs. 0.33	0.18 vs. 0.4	0.21 vs. 0.4	0.16 vs. 0.44
Risk reduction	55%				
Relapse free at yr2	70% vs. 46%	83% vs. 70%	70% vs. 46%	71.5% vs. 52.7%	83% vs. 71%
Risk Reduction	0.7	0.71			
Disability Progression at 2yr			17% vs. 24%	25% vs. 39%	6% vs. 8%
Hazard ratio/ Risk Reduction	0.7	0.71	0.7	0.83	0.71
MRI					
New/enlarging T2 lesion number	Mean 2.5 vs. 9.8; median 0 vs. 5	Mean 1.6 vs. 2.6; Median 0 vs. 0	Median 0 vs. 5	Median 0 vs. 4; mean 2.3 vs. 8.9	Median 0 vs. 1.0; mean 1.7 vs. 2.6
No of Gd+ve lesions	Mean 0.2 vs. 1.1; median 0 vs. 0	Mean 0.2 vs. 0.5; median 0 vs. 0	Median 0 vs. 0	Median 0 vs. 0; mean 0.4 vs. 1.2	Median 0 vs. 0; mean 0.2 vs. 0.5
% change in brain volume			Median -0.7 vs. -1; mean -0.8 vs. -1.3	Median -0.71 vs. -1.02; mean -0.86 vs. -1.28	Median -0.2 vs. -0.4; mean -0.3 vs. -0.5
Safety					
Contraindication	Recent (within 6 months) occurrence of: myocardial infarction, unstable angina, stroke, transient sichemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure History of presence of 2nd or 3rd degree AV block or sick sinus syndrome unless patient has a pacemaker Baseline QTc interval of ≥500mS		Known immunodeficiency syndrome Increased risk for opportunistic infection, including immunocompromised patients including those receiving immunosuppressive therapies of those immunocompromised by prior therapy Severe active infection, active chronic infection (HCV, TB) Known active malignancy except basal cell carcinoma Severe liver impairment Hypersensitivity to the active substance or to any of the excipients		
Warnings	Bradycardia Atrioventricular block Infection Macular edema Respiratory effects Hepatic effects Fetal risk Blood pressure effects Immune system effects following discontinuation		Bradycardia QT interval Infection Macular edema Liver function Interference with serological testing Blood pressure effects Respiratory effects Prior treatment with immunosupressants Stopping therapy		
Pre-clinical safety - rat, dog and monkey	Lung toxicity in rat, dog and monkey increase lung weight, associated with smooth muscle atrophy, hyperdistension of the alveoli, and/or increased collagen. Insufficient or lack of pulmonary collapse at necropsy Rat and monkey lung toxicity observed all oral doses tested in chronic studies; lowest doses tested ~ 20x recommended human dose		Lymphopenia and lymphoid atrophy Increased lung weight, smooth muscle atrophy at the bronchiolar junction Heart - negative chronotropic effect, increase in blood pressure, perivascular changes and myocardial degeneration; vasculopathy in rats at 0.15mg/kg an ~4x margin of exposure vs. human dose		

Source: FDA, EMA, and BMO Capital Markets.

It is interesting that the European label details changes in brain volume, but no claim or clinical benefit is suggested. Novartis has identified a role for S1P receptor modulation on neuronal cells and, by inference, the potential for decreasing or even reversing MS related neuronal cell damage. Such brain volume data are absent from the US label, yet the label contains a claim for a reduction in disability accumulation for which one could assume that brain volume, as a surrogate for overall brain health, may be a proxy. In short both the US and EU label contain data that go beyond treating the clinical symptoms associated with the disease.

The pathology associated with the lung, heart, and lymphatic changes provide an opportunity of differentiation for RCP1063. If RCP1063's more selective profile reduces toxicity, we would expect improved chronic toxicity.

Novartis is currently conducting a phase 3 trial of GILENYA in 940 subjects with a more severe form of MS, primary progressive MS (PPMS), with data expected 3Q14. Novartis is also evaluating a dose of GILENYA that is 50% lower than the currently approved dose in RRMS.

GILENYA Phase 2

Efficacy of GILENYA in RRMS was established by three randomized studies including the D2201 phase 2 trial and the 2-year FREEDOM and 12-month TRANSFORMS trial. In addition, the FDA reviewed long-term efficacy and safety from the D2201 trial, which included up to 60 months of data. The D2201 trial randomized 281 subjects to 1.25 mg or 5.0 mg GILENYA or placebo once daily for six months. The primary endpoint was total number of Gd+ve T1 lesions determined at monthly intervals over six months. Secondary endpoints included additional MRI analyses (including total volume of Gd+ve lesions per patient, the proportion of patients with Gd+ve lesions, the total number of new lesions per patient on T2-weighted images, changes in lesion volume on T2-weighted images, and brain volume from baseline to month six), clinical relapse rates and safety, which included pulmonary function testing (PFT) and at some sites intensive cardiac monitoring. An extension study allowed subjects to continue dosing between months 7 and 12, during which placebo patients were randomized to one of the two GILENYA doses under evaluation.

Subjects enrolled in D2201 were in their late 30s, predominantly female, ranged 8.4-9.5 years since documentation of first symptoms of MS and had a baseline EDSS of 2.5-2.7. (EDSS, or the Expanded Disability Status Scale, is a method of quantifying disability in MS). On average, enrolled subjects had a history of 1.8-1.9 relapses in the prior two years with 1.2-1.3 in the previous 12 months. At baseline 50-60% of subjects had a Gd+ve T1 lesion with an average of three lesions per patient.

Key MRI efficacy data are summarized in Exhibit 9, and suggest that GILENYA reduced the cumulative number of Gd+ve lesions over six months as well as the lesion burden at month six. Specifically the cumulative number of Gd+ve lesions was reduced from approximately 15 in the placebo group to 6-8 in the GILENYA cohorts. At the six-month landmark, in patients with Gd+ve lesions, the average number of lesions was just over two for the control, one for the low dose, and around 0.3 for the higher dose. An additional metric for efficacy was the proportion of subjects free of Gd+ve lesions at six months that also favored GILENYA. Approximately 50% of subjects in the placebo cohort remained Gd+ve lesion free over the six months trial, compared to 80% in the two GILENYA cohorts. During the six-month trial, the proportion of subjects free from Gd+ve lesions in the placebo cohort did not change from baseline; however, in both GILENYA cohorts a significant increase in the proportion of patients free from Gd+ve lesions was observed between months one and three before a plateau effect was reached.

Exhibit 9. Key MRI Efficacy Data from GILENYA Phase 2 Trial D2201

	Placebo	Gilenya 1.25mg	Gilenya 5mg
n	81	83	77
Total Gd+ve Lesions	14.8	8.4	5.7
No. at 6 mo.	2.21	1.29	0.27
% Gd+ve lesion free	47%	77%	82%

Source: Kappos et al. NEJM 355(11), 1124-40, 2006 and BMO Capital Markets.

Confirmed clinical relapses were noted in 34 of 92 subjects in the placebo cohort compared to 16 of 93 and 16 of 92 subjects in the GILENYA cohorts, equating to a 53-55% relative reduction. In addition, the time to first clinical relapse was delayed in the GILENYA cohorts with the cumulative relapse curves separating at around month two.

The extension phase of the trial between months 7 and 12 provided additional evidence of GILENYA efficacy as noted in Exhibit 10. Subjects crossed over from placebo to one of two doses of GILENYA at month six showed a significant decrease in Gd+ve lesion burden over six months while those continuing GILENYA continued to benefit from a low lesion burden.

Exhibit 10. Key MRI Efficacy Data from GILENYA Phase 2 Trial D2201 Extension

	Placebo > 1.25mg	Placebo > 5mg	Gilenya 1.5mg	Gilenya 5mg
n	28	32	62	65
Gd+ve Lesion No. m. 6	2.9	1.6	1.2	0.3
No. at mo. 12	0.2	0.4	1	0.2
Relative reduction	93%	75%	17%	33%
% Gd+ve lesion free	86%	69%	85%	88%
ARR 0-6mo.	0.7	0.69	0.36	0.32
ARR 6-12mo.	0.21	0.1	0.29	0.23
Relative Reduction	70%	86%	19%	28%

Source: Kappos et al. NEJM 355(11), 1124-40, 2006 and BMO Capital Markets.

Similarly, subjects switching from placebo to GILENYA at month six experienced a significant drop in clinical relapse rates consistent with a 70-80% decrease in the extrapolated annual rate.

Over the first six months of the trial adverse event rates were higher in the 5 mg GILENYA cohort than the 1.25 mg cohort with an excess of dyspnea and nasopharyngitis. Compared to placebo, headache, diarrhea, and nausea were more commonly reported in the GILENYA cohorts. Discontinuation of study medication was noted in four, five, and eight subjects in the placebo low and high dose GILENYA cohorts, respectively. Serious adverse events of interest were more commonly observed in the 5 mg cohort including three cases of bradycardia, two cases of chest pain, and one case of dyspnea. Overall, serious cardiac adverse events included: bradycardia (n=4), palpitations (n=1), arrhythmia (n=1), AV block (first degree) (n=1), extrasystoles (n=1) and ventricular extrasystoles (n=1). In addition, eight transient second-degree AV blocks occurred in eight patients on day one of GILENYA dosing. During the extension study, two serious infectious events were observed including a case of facial herpes zoster in a patient switching from placebo to 5 mg GILENYA and a case of enterocolitis in a patient switching from placebo to 1.25 mg.

Increases in alanine aminotransferase (ALT) to 3x above the upper limit of normal (ULN) were observed more commonly in subjects receiving GILENYA at a rate of 10-12% versus placebo at 1%. In 26 subjects with an elevated ALT who received GILENYA, levels fell below 3x ULN in 13 subjects including normalization in 5 subjects with continued treatment while in 13 subjects GILENYA was halted. In subjects discontinuing GILENYA for liver function test (LFT) elevation, ALT normalized and three of four patients were re-challenged successfully. Across both core and six-month extension studies, GILENYA was permanently discontinued in two subjects owing to LFT changes.

Within six hours after the first dose of GILENYA, heart rate was reduced by an average of 13.8 and 16.6 beats per minute in the low- and high-dose GILENYA cohorts, respectively. Symptomatic bradycardia was reported in a single subject at 1.25 mg following switch from placebo and in three subjects receiving GILENYA at a dose of 5 mg. Transient day one second degree AV block was noted in four subjects receiving GILENYA at a dose of 1.25 mg and five receiving 5 mg. An acute 5-6 mmHg decrease in blood pressure after GILENYA dosing normalized within 4-5 hours and was followed by a sustained 4-6 mmHg increase after two months of treatment with no further increase during the extension cohort. Pulmonary function tests showed a GILENYA dose-dependent reduction in forced expiratory volume in one second (FEV_1) over six months of 2.8% and 8.8% versus 1.9% for placebo. With respect to forced vital capacity (FVC) changes over six months, a 4.3% increase in the placebo cohort was noted versus a 0.8% and 3.2% decrease for the GILENYA cohorts. No further changes were noted during the extension phase.

Following the initial NEJM publication of the core and six-month extension, two- and three-year updates have been published: "Oral fingolimod (FTY720) in multiple sclerosis: two-year results of a phase II extension study." O'Connor *et al. Neurology*. 2009 Jan 6;72(1):73-9.

- Patients receiving 5 mg GILENYA switched to 1.25 mg at 15 months.
- 250/289 (89%) entered extension phase with 189 (75.6%) completing two year.
- Four cohorts: placebo to 1.25 mg (P1), placebo to 5 mg then 1.25 mg (P5), 1.25 mg to 1.25 mg and 5 mg to 5 mg then 1.25 mg.
- AE most common reason for withdrawal at 10.4%.
- Two subjects discontinued GILENYA for lymphopenia.
- SAE rates were 8% for 1.25 mg continuous, 15% for 5 mg continuous, 5% for P1 and 9% for P5.
- Nasopharyngitis, influenza, lymphopenia and URI more common in 5 mg continuous cohort than 1.25 mg.
- ALT >3XULN 15% P1, 12% P5, 16% 1.25 continuous and 15% 5 mg continuous – No cases of Hy's law.
- Blood pressure remained stable from 6-24 months with an increase of 4.1-6.3mm Hg over baseline.
- No clinically relevant changes in FVC observed between 6 and 24 months.
- No confirmed cases of macular edema between 6 and 24 months.
- 24mo Gd+ve lesion free – 79-91% and 66-74% T2 lesion free.
- At 24 months 75-77% of original GILENYA subjects relapse free and 54-59% for those switched to GILENYA at six months.

The phase 3 results are summarized below. "Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results." Comi *et al*. *Mult Scler*. 2010 Feb;16(2):197-207

- 69% of subjects entering the extension phase of D2201 completed three years.
- SAE rate was 16% (n=46) including 4 SIEs: Dengue fever, herpes zoster, otitis extema and salpingitis; in total six cases of herpes zoster were reported over 36 months (~15/1000 subject years)
- Following three cases of skin cancer in the first 24 months, dermatologist assessment introduced leading to detection of four additional skin cancers in months 24-36, including two cases of melanoma, one squamous, and one basal carcinoma.
- Between month 12 and 36 FEV_1 increased 3.37% and FVC 2.47%.
- Mean number of Gd+ve lesions at month 36 was 0.2, ranging from 0.1-0.3 across the four subgroups.
- 88-89% of patients in the continuous and placebo-switch groups were free from Gd+ve lesions at three years
- ARR ranged from 0.2/0.21 in the continuous to 0.31 in the placebo switch cohorts.
- 68-73% of continuous GILENYA subjects relapse free at 36 mo vs. 51% in the switch group.

GILENYA Phase 3 Program – FREEDOMS I and Its Follow-Up

Novartis's phase 3 program comprised three trials, FREEDOMS I and II, both placebo-controlled trials of 24 months duration, and TRANSFORMS, a 12-month trial comparing GILENYA versus AVONEX. Owing to slow recruitment of FREEDOMS II, regulatory filings were based on FREEDOMS I and TRANSFORMS; data from FREEDOMS II confirmed the data from FREEDOMS I.

FREEDOMS I randomized 1272 subjects with RRMS to 1.25 mg or 0.5 mg/d of GILENYA or placebo. Subjects were approximately 37 years of age with a symptom history of 8 to 8.4 years, and a mean EDSS of 2.3-2.5 at baseline. In the preceding two years, subjects reported approximately two relapses, with 1.4-1.5 occurring in the past 12 months. Approximately 40% of subjects had Gd+ve lesions at baseline with an average lesion burden of 1.3-1.8 lesions per subject.

In total, 1,033 subjects (81.2%) completed 24 months of dosing, and, at study end, 74.3% of patients were still receiving drug. Study drug discontinuation was higher in the placebo and 1.25 mg cohorts (27.5% and 30.5%, respectively) than in the 0.5 mg cohort (18.8%). Patient disposition is summarized in Exhibit 11. More subjects discontinued GILENYA at the 1.25 mg dose than the 0.5 mg with higher rates of adverse events and unsatisfactory efficacy noted. In total, 333 and 369 subjects completed the study in the GILENYA cohorts including 35 (10.5%) and 24 (6.5%) not receiving study drug.

Exhibit 11. Patient Disposition in GILENYA Phase 3 FREEDOMS I Trial

	Gilenya 1.25mg	Gilenya 0.5mg	Placebo
N	429	425	418
Discontinued Study	96	56	86
AE	22	13	18
Efficacy	13	6	25
Discontinued Study Drug	131	80	115
AE	31	15	24
Efficacy	18	8	36

Source: Kappos et al., NEJM 362;5 387-402, 2010.

Selected efficacy measures are summarized in Exhibit 12, demonstrating that both doses of GILENYA reduced the risk for a relapse compared to placebo by 55-60% and increased the probability of being relapse free after two years by 35-40%. In addition GILENYA diminished the risk for sustaining confirmed disability by 36-45%.

Exhibit 12. Selected Efficacy Measures from FREEDOMS I

	Gilenya 1.25mg	Gilenya 0.5mg	Placebo
ARR	0.16	0.18	0.4
Relpase free	74.7%	70.4%	45.6%
Confirmed Disability (3mo.)	16.6%	17.7%	24.1%
Mean number of Gd+ve lesions	0.2	0.2	1.1
Gd+ve lesion free	89.80%	89.70%	65.10%

Source: Kappos et al., NEJM 362;5 387-402, 2010.

With respect to MRI measures, the mean number of Gd+ve T1 lesions was reduced from 1.1 lesions per subject in placebo to 0.2 lesions in the GILENYA cohorts. This was driven in part by the number of patients lesion-free at 24 months, which was roughly 27% higher in the GILENYA cohorts than placebo.

Adverse events leading to study drug discontinuation were twice as common in the 1.25 mg GILENYA cohort as either of the two other cohorts at 14.2% versus 7.5-7.7%. Serious AEs were reported in equal number of patients but differed in nature. Seven cases of serious bradycardia were observed in the GILENYA cohorts, including three cases at 1.25 mg and four cases at 0.5 mg, versus one case for placebo; only one of the seven cases in the GILENYA cohorts was symptomatic. In total, bradycardia was reported in 9 and 14 subjects receiving GILENYA 1.25 and 0.5 mg vs. three in the placebo cohort. In total, six cases of bradycardia were symptomatic and two subjects received treatment for bradycardia. Heart rate decreases started two hours after dosing reaching a nadir after 4-5 hours of 8-10 beat per minute (bpm).

The use of ECG monitoring identified 20 subjects with first-degree AV block at the 0.5 mg dose of GILENYA, 37 subjects at the 1.25 mg dose and six subjects in subjects receiving placebo. Of these, five, two, and two were described as serious respectively. Second degree AV block was identified by ECG in one subject receiving GILENYA 5 mg and four at the 1.25 mg dose, one of whom was symptomatic. Mean systolic blood pressure at 12 and 24 months increased 1.9 and 0.7 mmHg and 3.6 and 2.1 mmHg, respectively, for the 0.5 mg and 1.25 mg GILENYA cohorts versus a 0.4 and 0.5 mmHg decline for placebo.

Of the seven cases of macular edema, three cases were described as serious, all of which occurred in the 1.25 mg GILENYA cohort. Five of these cases occurred within the first three months and six cases resolved within one to six months of discontinuing therapy. Increases in ALT to ≥3X ULN occurred more frequently at the higher dose of GILENYA (12.5% vs. 8.5%). Two subjects in the 1.25 mg GILENYA cohort had LFT changes categorized as serious; however, in the NEJM manuscript by Kappos *et al.* regarding the FREEDOMS I trial, one subject in the 0.5 mg cohort had an LFT elevation >10X ULN. While lymphopenia was expected and not listed as an AE, the average decrease in peripheral blood lymphocytes was 73% and 76% for the two doses of GILENYA; two subjects in the 1.25 mg cohort were categorized as meeting criteria for severe lymphopenia ($<0.2^9$/L)

No significant imbalance in infections was observed, although there was a trend to more lung infections in the GILENYA cohorts. Only two serious infections, both UTIs, were noted in the low-dose GILENYA cohort and while herpes zoster infections occurred in all three cohorts, the two serious cases HZV both occurred in the GILENYA cohorts. Eight neoplasms were observed in the placebo cohort including 5 basal cell carcinomas and 1 melanoma, compared with 10 neoplasms in the placebo cohort, including 3 cases of basal and 1 case of melanoma.

Long Term Follow-Up of FREEDOMS I

At the 2013 AAN meeting, data for a 12-month follow-up from FREEDOMS I was presented. At month 24.5, subjects were randomized to either 0.5 mg or 1.25 mg GILENYA and subsequently all patients were switched to the 0.5 mg dose. From the original core trial, 217 of 272 subjects, 203 of 251 subjects, and 212 of 255 subjects elected to enter the extension trial from the 0.5 mg, 1.25 mg, and placebo cohorts, respectively, for a total of 632 subjects. As shown in Exhibit 13, approximately 84% remained on study without significant difference between the cohorts; similarly, adverse events led to a roughly 5% study discontinuation rate, and a slightly higher study drug discontinuation rate. Despite having received 24 months of GILENYA, patients discontinued both the study and study drug owing to an adverse event, at the same rate as subjects switching from placebo. Further, discontinuation due to a serious adverse event was more common in subjects continuing into their third year of GILENYA, versus those switching at year two.

Exhibit 13 : Selected Adverse Event Data From 12-Month Extension of FREEDOMS I Trial

Study/Drug Discontinuation

	Placebo > 0.5mg	Placebo > 1.25mg	Gilenya 0.5mg	Gilenya 1.25mg
n	107	105	217	203
Completed 12 months	**88**	**89**	**180**	**172**
AE - Discontinue study	5	3	9	13
AE - Discontinue study drug	**8**	**5**	**11**	**17**
SAE - Discontinue study drug	0	1	4	5
MS Relapse	**0**	**1**	**0**	**1**
Cardiac Disorder	0	3	0	1
Bradycardia	**0**	**2**	**0**	**0**
Lab AE - Discontinue study drug	2	2	2	4

Selected AEs of Interest

	Placebo > 0.5mg	Placebo > 1.25mg	Gilenya 0.5mg	Gilenya 1.25mg
Cardiac AE	5 (4.7%)	5 (4.8%)	5 (2.3%)	9 (4.4%)
Palpitation	**3 (2.8%)**	**2 (1.9%)**	**3 (1.4%)**	**4 (2.2)**
Bradycardia	0	2 (1.9%)	0	0
AV Block				
First	1 (0.9%)	1(1%)	0	1 (0.5%)
Second	**0**	**1(1%)**	**0**	**0**

Source: Rammohan et al. and BMO Capital Markets.

Focusing on selected AEs of interest in the FREEDOMS I trial, cardiac AEs occurred in approximately 5% of all subjects irrespective of duration of GILENYA exposure; however, the only two cases of bradycardia occurred in subjects switching from placebo to 1.25 mg GILENYA. Similarly the only case of second-degree AV block occurred in a subject switching from placebo to 1.25 mg GILENYA.

During year three of the FREEDOMS I study, no increase in infections or severe infections was observed, with a single severe case of herpes zoster in a subject from the 1.25 mg continuous cohort. Three additional cases of squamous cell skin carcinoma were reported during year three, two in the 1.25 mg cohort, and one in the 0.5 mg cohort, where an additional case of basal cell carcinoma was also reported. Macular edema was restricted to two cases in the placebo switch subjects, one at each GILENYA dose. Elevations in LFTs were stated to improve with continuous dosing as was the case for blood pressure.

GILENYA versus AVONEX – the TRANSFORMS Trial

The second phase 3 trial Novartis used for registration was TRANSFORMS, a 12 month head to head trial of GILENYA versus AVONEX in 1292 subjects with RRMS. The trial evaluated the same two doses of GILENYA as FREEDOMS I versus weekly AVONEX. The primary endpoint of annualized relapse rate was statistically significantly lower for the GILENYA cohorts at 0.16-0.20 versus AVONEX at 0.33. The overall safety profile of GILENYA in the TRANSFORMS trial mirrored that from the FREEDOMS I trial with the exception that two fatal herpetic infections occurred at the 1.25 mg dose, a case of disseminated varicella zoster and a case of herpes encephalitis.

Our View

GILENYA establishes that modulation of S1P is efficacious in the treatment of RRMS. The presumed mechanism of action is based primarily on a sequestration of pathogenic T and B cells in lymphoid tissue leading to a depletion of these cells from the brain. The reduction in pathogenic immune cell burden correlates with a rapid reduction in inflammatory activity in the brain, as evidenced by MRI. Specifically the ability of gadolinium to cross the blood brain barrier at sites of active inflammation is reduced. A high degree of correlation exists between short-term, but stable, decreases in gadolinium signal and a reduction in clinical activity of the disease as assessed by annualized relapse rate. Less clear is a mechanism of action based interpretation for some of the hypothesis generating MRI data; however, S1P receptor distribution in the brain is ubiquitous and preclinical studies suggest that modulation of S1P receptors on neural cells may be beneficial.

The TRANFORMS data establishes that GILENYA has a more robust effect on reducing annualized relapse rates than AVONEX and this has led to GILENYA creating a rung on the therapeutic ladder above the interferons and Copaxone but below TYSABRI.

The phase 2 and 3 data suggest that GILENYA is associated with an increase in the risk for a number of acute and chronic side effects. First dose bradycardia is common and while symptomatic bradycardia or atrioventricular block is rare, FDA updated the GILENYA label in 2012 to introduce strict requirements for first dose monitoring. Macular edema is another rare event that generally occurs with in the first few months of dosing, often leading to study drug discontinuation. The data also suggest that GILENYA resets the setpoint for blood pressure as BP rises rapidly before reaching a plateau, which appears to be maintained while the patients continues to receive drug. While the precise mechanisms of action for many of the adverse events observed during the GILENYA trial program are unclear, there is often a dose dependency, which led Novartis to discontinue evaluation of the 1.25 mg dose. In fact, the entire MS dataset suggest to us that Novartis has yet to establish a minimally effective dose of GILENYA in MS. This in part because GILENYA was first evaluated for the indication of solid organ transplantation, and that program concluded GILENYA was not sufficiently immunosuppressive at the doses tested. As the MS program progressed, successively lower doses of GILENYA were evaluated, but with an approximately 70% reduction in lymphocyte counts for both the 0.5 mg and 1.25 mg doses of GILENYA in the TRANSFORMS I trial,

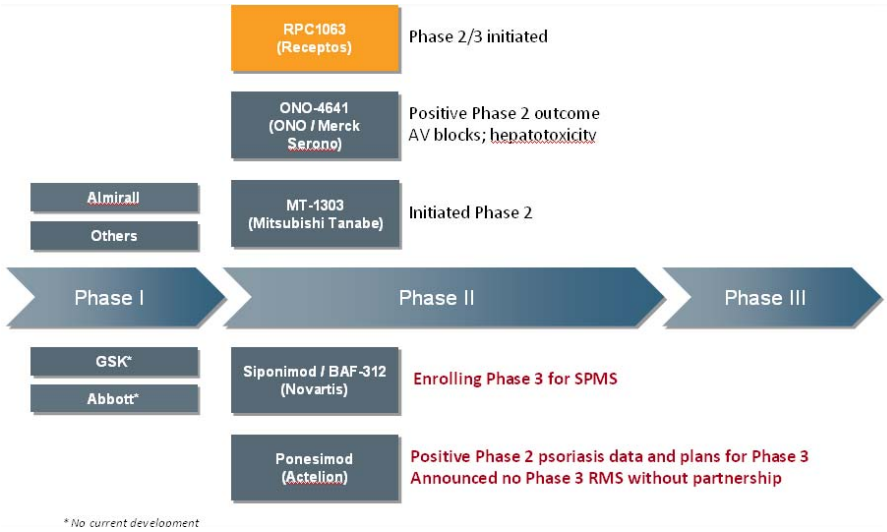
Novartis has obviously yet to establish a minimally efficacious dose. Novartis is currently conducting the D2312 trial, which will compare the licensed 0.5 mg dose of GILENYA to a dose of 0.25 mg with COPAXONE as an active control. The trial will enroll 2,550 subjects and the primary endpoint is annualized relapse rate over 12 months of dosing with data expected 4Q17.

Assessing long-term safety of GILENYA is problematic as there is no longer a control group, and patients who continue on study to three years and beyond are those in whom GILENYA is tolerated and efficacious. However, the three-year FREEDOMS I data are informative as they suggest to us that SAEs leading to study drug discontinuation continue to occur with continuous GILENYA dosing. While precise details of the events leading to study drug discontinuation are lacking, and perhaps therefore suggesting that the events are not associated with events of interest such as cardiac, the possibility of cumulative toxicity exists.

Other S1P Receptor Modulators in Development

In addition to Receptos' RPC1063, three other late-stage S1P receptor modulator drugs are currently under development: Novartis' siponimod, Actelion's ponesimod, and Merck Serono and Ono Pharmaceutical's ONO-4641. A common theme among all four compounds, which aims to drive differentiation from GILENYA, is a shorter half-life and higher selectivity for S1P1.

Exhibit 14. Competitive Landscape for S1P1 Modulating Compounds



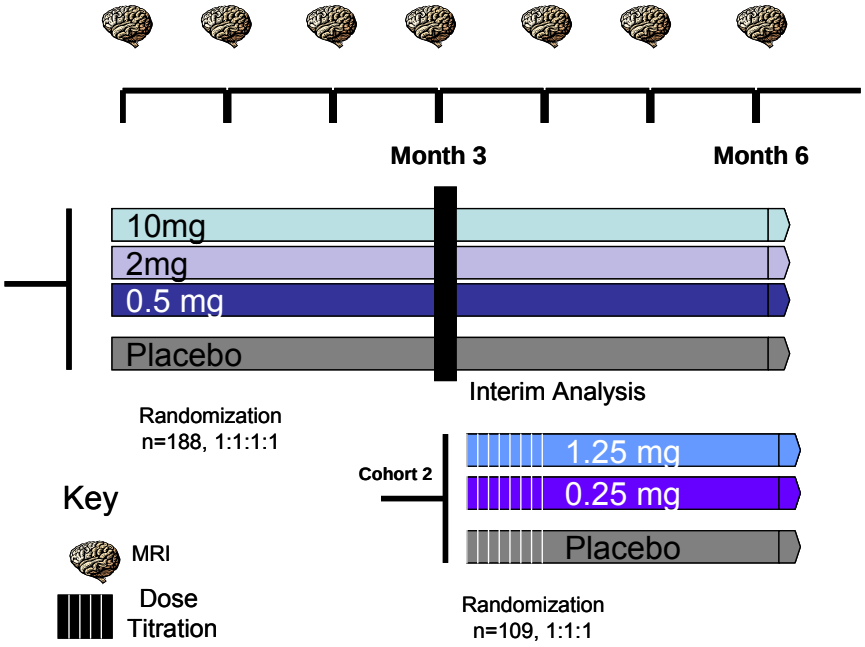
Source: Receptos.

Siponimod

Siponimod (formerly BAF-312) is a second-generation S1P receptor modulator developed by Novartis as a life-cycle extension strategy to the first generation product GILENYA. Siponimod is more selective than GILENYA with activity restricted to S1P1 and S1P5.

In phase 1 testing, Novartis established that siponimod has a serum half life of approximately 30 hours and that siponimod is eliminated from the body after approximately six days. Following phase 1 testing, Novartis conducted the BOLD trial to establish proof-of-concept for safety and efficacy of siponimod. BOLD is a randomized double-blind, placebo-controlled, dose ranging study. In total, 297 MS patients were randomized to either placebo or one of five dose levels of siponimod ranging from 0.25 mg/day to 10 mg/day. As shown in Exhibit 15, the trial was conducted in two separate stages with a second cohort added after the interim analysis of cohort 1. The second cohort expanded the dose escalation by adding a lower dose, 0.25 mg and a 1.25 mg dose intermediate between the 0.5 mg and 2 mg doses. Beginning in parallel to the addition of this second cohort, Novartis added a dose titration schema to subjects enrolled in both cohort 2 and the original cohort who continued into what Novartis described as period 2 of the trial. The purpose of the dose escalation was to mitigate first-dose bradycardia observed during period 1 of the trial. The primary end point of the BOLD trial was the number of combined unique active lesions (CUAL) on MRI at month three, defined as the number of unique new or enlarging Gd+ve T1 lesions or T2 lesions. Secondary endpoints included annualized relapse rates and of course safety. The study design is summarized in Exhibit 15.

Exhibit 15. Siponimod BOLD Trial Study Design



Source: ECTRIMS 2012 and BMO Capital Markets.

Subjects enrolled in BOLD were aged in their mid-30s, had a disease duration of approximately eight years, a baseline EDSS of 2.2, and a history of one relapse per year over the prior two years. Approximately 40-50% of subjects had active Gd enhancing T1lesions at baseline with 1-2 active lesions each for five of the six cohorts. The 43 subjects in the 0.5 mg cohort had an average of 3.7 lesions at baseline.

As presented at the 2011 and 2012 ECTRIMS meetings, siponimod met the primary endpoint of the trial by demonstrating a statistically significant dose response relationship as measured by the number of CUAL in the five-dose groups of siponimod and in the placebo group. Siponimod reduced the number of CUAL on MRI at month 3 by 35%-82% versus placebo. The number of CUAL between baseline and week 12 ranged from 1.5 in the placebo cohort to 0.2-1.0 in the siponimod cohorts. Annualized relapse rate data (ARR) over six months was available for cohort 1 with 13 relapses each noted for placebo and 0.5 mg cohorts versus 5 relapses and 9 relapses for the 2 mg and 10 mg cohorts. As a percent relative reduction versus placebo, the two higher doses were associated with a 47.6% and 66% reduction in ARR at 10 mg and 2 mg doses, respectively.

Siponimod also caused a decrease in peripheral lymphocyte counts in the blood, as can be expected from the compound's mechanism of action. Lymphocyte counts were taken at baseline, day seven, and months one, three, and six. Novartis modeled the lymphocyte dose response curve, suggesting a very steep dose response curve up to a siponimod dose of ~ 1 mg, before flattening through 4 mg and then reaching a plateau.

Exhibit 16. Results of the BOLD Study

	Siponimod					
	10 mg	2 mg	1.25 mg	0.5 mg	0.25 mg	placebo
Mean CUAL at (Month 3)	0.4	0.5	0.2	1	0.8	1.5
SD	0.99	1.07	0.65	2.65	1.45	3.27
Relative reduction in lesions vs placebo (Month 3)	85%	76%	93%	63%	59%	0%
ARR (Month 6)	0.3	0.2		0.61		0.58
p-value	0.15	0.04		0.9		
Mean reduction in lymphocyte counts vs placebo (Month 3), 109/L	1.5	1.4	1.1	1	0.5	0

Source: ECTRIMS 2011, 2012 and BMO Capital Markets.

Adverse events and serious adverse events were more commonly observed in the siponimod groups; however, the only SAE to occur in more than one patient was second-degree AV block. As indicated previously, Novartis modified the BOLD trial design to expand dose ranging and also to test the hypothesis that dose escalation would reduce first-dose bradycardia side effects in the second period of the trial when compared to the first period. The dose escalation schema used a 0.25 mg dose of siponimod on days one and two increasing by 0.25 mg on day three with subsequent increases thereafter such that the dose escalation period was bracketed at 3 days for a target dose of 0.5 mg/d and 10 days for a target dose of 10 mg/d. In the first period of the trial, four cases of second degree AV block occurred after the first dose of drug, one in the 10 mg cohort, and three in the 2 mg cohort. During the second period, no cases of second degree AV block were observed. Four cases of less serious first degree AV block were also observed, with three occurring in the 10 mg cohort and one in the 0.5 mg cohort. Beyond cardiovascular (CV) events, siponimod dose associated changes in liver transaminase levels were observed in the

BOLD trial with ALT > 3XULN noted in 4.3% of subjects dosed at 10 mg and 2 mg, 2.4% of subjects at 1.25 mg and 0% and 2% at 0.5 mg and 0.25 mg, respectively. Novartis also noted small changes in mean arterial blood pressure and forced expiratory volume.

At the 2013 AAN meeting data from a 12-month extension of BOLD was presented. At the end of six months of dosing for the subjects in cohort 1 and at the end of three months of dosing for those in cohort 2, dosing was interrupted. Because of the trial design all subjects receiving 0.5 mg, 2 mg, and 10 mg had a dose interruption of >3 months, while two-thirds to three-quarters of the subjects at a dose of 0.25 mg or 1.25 mg/d had a dose interruption of at least one week and 20-25% at least one month. Following initiation of the extension study, patients continued on their originally assigned dose of siponimod, or if they were receiving placebo, randomized to one of the five siponimod dose levels under investigation. As introduced in period 2, all subjects underwent a dose escalation during the first 10 days of the extension. Of the 184 patients who entered the extension study, 163 (89%) completed 12 months of treatment. Overall siponimod was well tolerated with no cases of bradycardia or AV bock reported. A total of six patients discontinued owing to AEs, including MS activity at the 0.25 mg dose and LFT abnormalities and or headache at the 2 mg and 10 mg doses. Exhibit 17 summarizes both adverse events leading to siponimod discontinuation and serious laboratory adverse events.

Exhibit 17. Safety of Siponimod in Long-Term BOLD Extension Study

	Siponimod				
	10 mg	2 mg	1.25 mg	0.5 mg	0.25 mg
AE leading to Siponimod D/C					
ALT	0	1	0	0	0
GGT	0	1	0	0	0
CNS Lesion	0	0	0	0	1
Headache	1	1	0	0	0
MS Relapse	0	0	0	0	2
Laboratory Abnormalities					
ALT >3XULN/5XULN	0/0	2/1	1/0	1/0	0/0
AST >3XULN/5XULN	0/0	1/1	0/0	0/0	0/0
GGT >3XULN/5XULN	6/1	6/1	0/0	1/0	2/1
ALC $<0.2x10^9$/L	13	5	4	0	0
ANC $\leq 1x10^9$/L	1	1	0	0	0

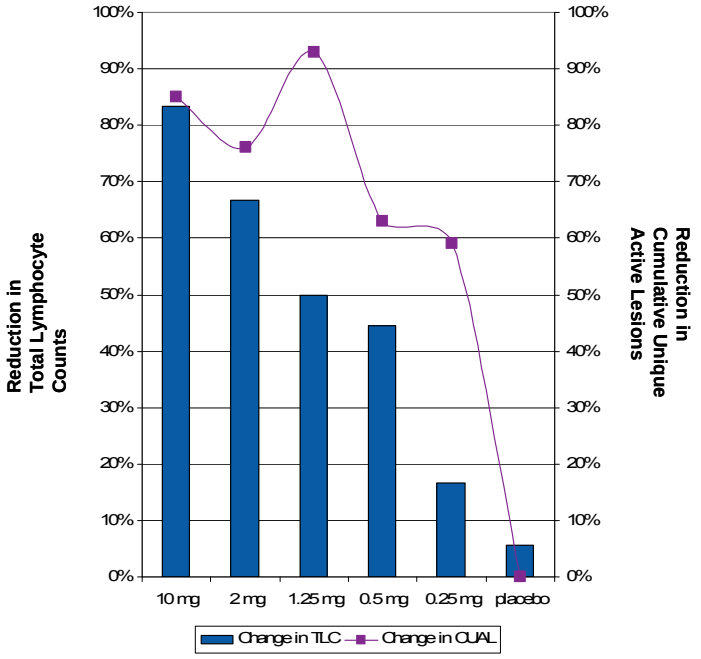
Source: AAN 2013 and BMO Capital Markets.

Our View

In modeling lymphocyte changes in the BOLD trial, Novartis demonstrated that changes in lymphocyte count were very sensitive to small changes in siponimod dose. Circulating lymphocyte counts decreased close to 50% with an increase in siponimod dose from 0.25 to 0.5 mg. At a siponimod dose of 2 mg the dose response curve flattened, indicating that further dose escalation will not achieve additional reduction in circulating lymphocytes. To correlate

lymphocyte change with changes in MRI-assessed lesion burden, Novartis conducted further modeling suggesting that both with and without the presence of Gd+ve T1 lesions at baseline decreasing lymphocyte count correlated with a decrease in Gd+ve T1 lesion burden. Interestingly the magnitude of Gd+ve lesion protection benefit was greater in subjects with Gd+ve T1 lesions at baseline than those without, and for those with lesions at baseline, Novartis's modeling suggested a plateau of benefit was reached at a dose of 1.25 mg/d. Recalling that the 0.5 mg cohort of patients had approximately twice as many Gd+ve T1 lesions at baseline as the other cohorts, our own simplistic analysis shown in Exhibit 18 suggests that a significant change in Gd+ve T1 lesion burden occurs at a lower dose than does a significant decrease in circulating lymphocytes. To put this another way, small changes in circulating lymphocytes may be amplified into larger changes in reduction of Gd+ve T1 lesion burden.

Exhibit 18. Correlation of Lymphocyte Count Changes and MRI lesion Burden in the BOLD Trial



Source: ECTRIMS 2011 and BMO Capital Markets.

The safety of siponimod with respect to first dose effects was improved with the use of a 10-day dose escalation phase, which for the phase 3 siponimod dose of 2 mg actually lasts six days. Beyond amelioration of acute effects, however, many of the adverse events associated with GILENYA are still present including LFT changes, pulmonary function test changes, and at least one case of macular edema has been reported. Absent head to head data it is difficult to assess if siponimod has significantly changed the risk profile of GILENYA.

As noted above, Novartis has elected to pursue the 2 mg siponimod dose into phase 3 testing. Based on BOLD results with siponimod, the safety of the 2 mg dose appears to be inferior to the 1.25 mg dose, which produced pronounced lymphocyte count reduction and MRI benefit. Perhaps one reason for Novatris's selection of a 2 mg siponimod dose is that Novartis has elected to evaluate siponimod in secondary progressive MS. Given the absence of any effective therapy in SPMS, the tolerance for side effects is considerably higher than it is for RRMS. In addition subjects with SPMS have moved beyond the relapsing phase of the disease and are at higher risk from accumulating disability due to irreversible loss of neuronal function. Novartis has ascribed a re-myelinating benefit to $S1P_5$ modulation, which would be highly relevant in this population if it translated to a clinically significant reduction in disability.

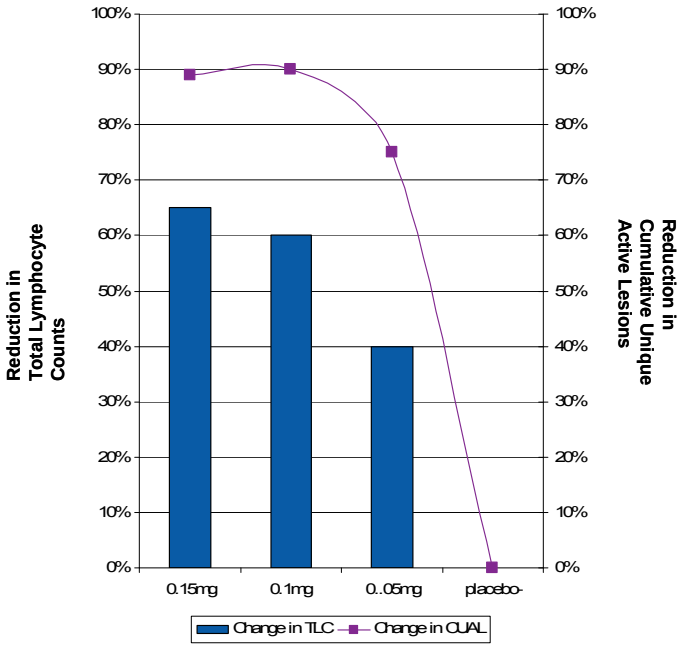
ONO-4641

Ono Pharmaceuticals and Merck KGaA's ONO-4641 is a selective S1P1/S1P5 agonist that has completed phase 2 clinical testing in RRMS. At the 2012 ECTRIMS meeting, Ono presented data from the 360 patient DreaMS trial. DreaMS randomized 407 patients to placebo or ONO-4641 at doses of 0.05 mg, 0.1 mg or 0.15 mg per day for 26 weeks.

The primary efficacy endpoint was cumulative unique new or enlarging Gd+ve T1 lesions between weeks 10 and 24. In the placebo cohort the average number of Gd+ve lesions was 5.65 versus 1.41 (0.05 mg), 0.57 (0.1 mg) and 0.63 for the 0.15 mg cohort. In terms of relative reduction versus placebo, the 0.05 mg dose reduced the incidence of Gd+ve lesions by 75%, increasing to 90% for the two higher doses of ONO-4641. The cumulative number of new/enlarging T2 lesions showed a very similar pattern

Changes in absolute lymphocyte counts showed a 40% decrease at the lowest dose by week two, which remained stable for the duration of the study. Increasing the dose of ONO-4641 to 0.1 or 0.15 mg decreased lymphocyte counts by 60-65%. Within four weeks of follow-up after the end of dosing, lymphocyte counts had returned to normal. ONO had shown in previous phase 1 testing that lymphocyte counts returned to 80% of baseline levels within three weeks of stopping dosing.

Exhibit 19. Correlation of Lymphocyte Count Changes and MRI Lesion Burden in the ONO-4641 DreaMS Trial



Source: BMO Capital Markets.

Ponesimod

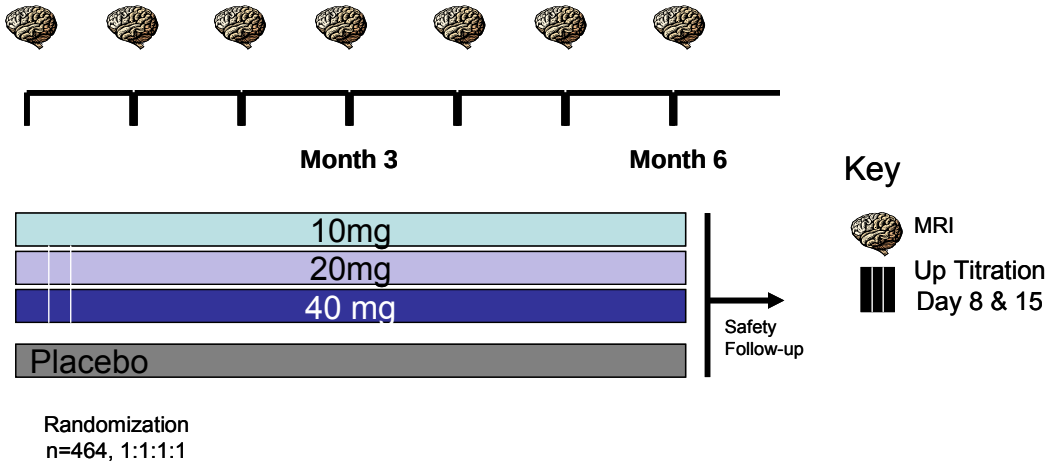
Ponesimod is a S1P1 and S1P5 specific modulator being developed by Swiss biopharmaceutical company Actelion. Actelion has completed two phase 2 trials of ponesimod, including one in RRMS and the other in psoriasis.

In preclinical studies, ponesimod demonstrated effectiveness in reducing inflammation in a delayed-type hypersensitivity (DTH) model in mouse and an adjuvant-induced arthritis model in rat.

In a phase 1 study (published in April 2013), single doses of ponesimod up to 75 mg were well tolerated, and the half-life of ponesimod was found to be approximately 30 hours.

The phase 2b study for ponesimod in RRMS was completed in July 2011. In this multicenter, double-blind, dose-ranging study, 464 patients were randomized in a 1:1:1:1 ratio to 10 mg, 20 mg, 40 mg ponesimod or placebo, administered orally once daily for 24 weeks. For higher doses, up-titration was performed on day 8 and day 15. The primary endpoint was the mean cumulative number of new Gd+ve T1 lesions detected on monthly MRI scans at weeks 12, 16, 20, and 24 after study drug initiation. The secondary endpoint was ARR and time to first confirmed relapse within 24 weeks of study drug imitation. The study design is summarized in Exhibit 20.

Exhibit 20. Ponesimod Phase 2b Study Design

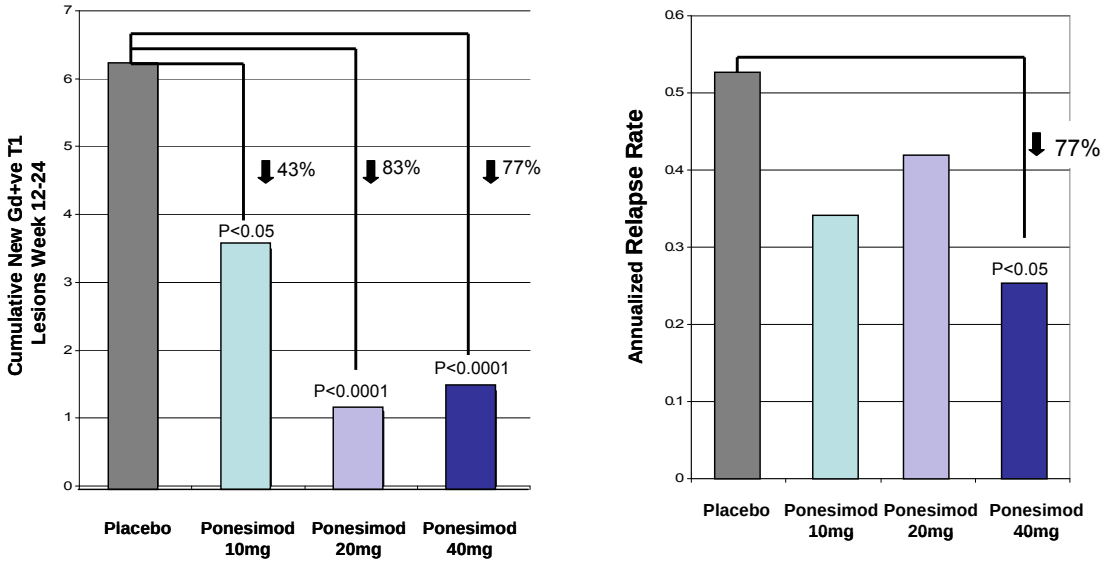


Source: ECTRIMS 2012 and BMO Capital Markets.

Baseline characteristics were well balanced across groups. The mean age was approximately 36 years and the mean disease duration was approximately 8 years. At the baseline, the mean number of Gd+ve T1 lesions was between 1.7 and 2.5. Approximately 50-60% of the patients were free of Gd+ve T1 lesions at baseline.

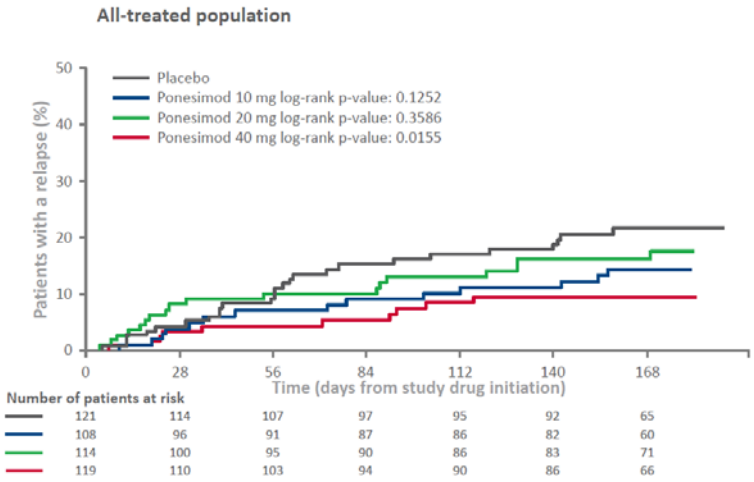
Compared to placebo, the cumulative number of new Gd+ve T1 lesions detected on four monthly MRI scans (weeks 12, 16, 20, and 24) decreased 43% ($p<0.05$), 83% ($p<0.0001$), and 77% ($p<0.0001$) with ponesimod 10 mg, 20 mg, and 40 mg, respectively, and a significant dose relationship was observed, as shown in Exhibit 21 (left hand panel). The mean ARR was lower with ponesimod, with a maximum reduction of 52% in the 40 mg group versus placebo ($p<0.05$), as shown in Exhibit 21 (right hand panel). The reductions in ARR in the 10 and 20 mg dose groups were not statistically significant. In addition, the time to first clinical relapse was delayed in the ponesimod cohorts. (See Exhibit 22.)

Exhibit 21. Reduction of Accumulative New Active Lesions (Primary Endpoint) and Annualized Relapse Rate (Secondary Endpoint)



Source: ECTRIMS and BMO Capital Markets.

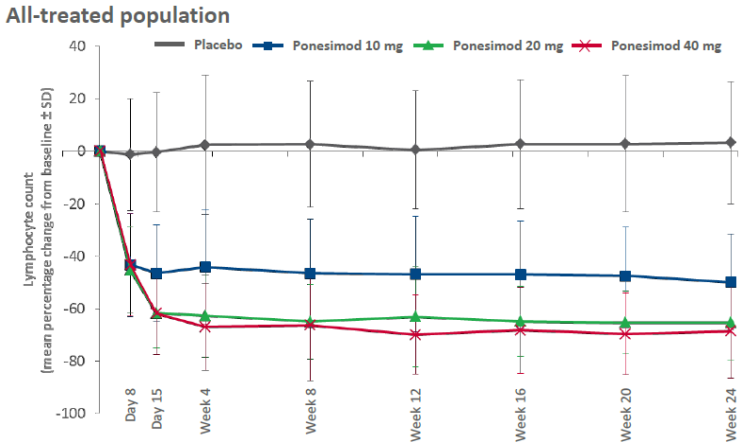
Exhibit 22. Increase in the Time to First Confirmed Relapse (Secondary Endpoint)



Source: Actelion Presentation at 2012 ECTRIMS.

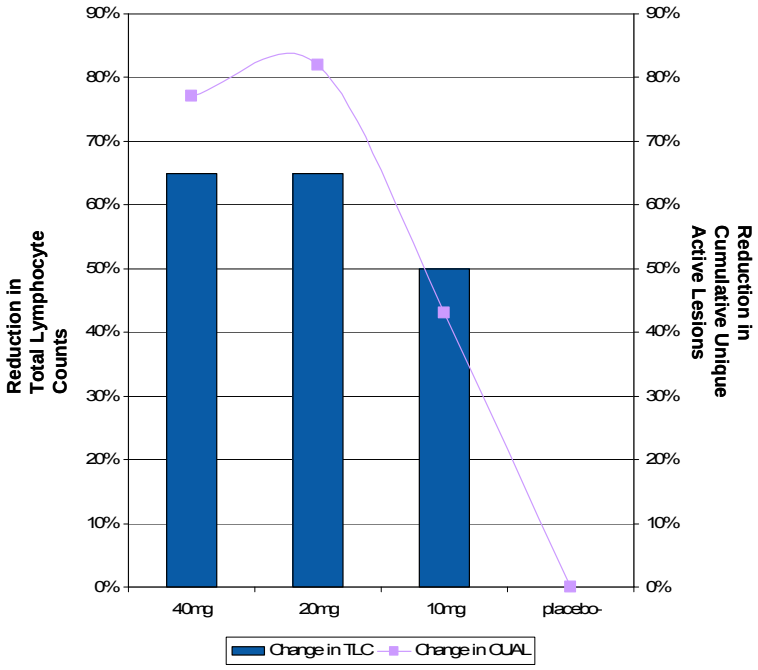
Lymphocyte count was rapidly reduced after treatment initiation and was this reduction was maintained throughout the treatment period. There was a big increase in steady-state lymphocyte count reduction between 10 and 20 mg dose groups (approximately 45% reduction versus 65% reduction), which appeared to correlate with MRI efficacy readouts. (See Exhibit 23 and Exhibit 24.) In a subgroup of patients not entering a subsequent extension study, lymphocyte count returned to normal ranges within 7 days after end of treatment.

Exhibit 23. Change in Lymphocyte Count During Treatment Period



Source: Actelion Presentation at 2012 ECTRIMS.

Exhibit 24. Correlation of Lymphocyte Count Changes and MRI Lesion Burden in the Ponesimod Phase 2 Trial



Source: ECTRIMS 2012 and BMO Capital Markets.

Ponesimod was generally well tolerated at doses of 10 and 20 mg, with signs of reduced tolerability at 40 mg. Treatment-emergent adverse events, reported with higher incidence in the ponesimod 40 mg group, included dyspnea (difficulty in breathing), cough, peripheral edema, and dizziness. Seven patients discontinued owing to dyspnea, including six from the 40 mg group. One case of macular edema occurred with 20 mg ponesimod and resolved on discontinuation. Cardiac AEs associated with first dose of ponesimod included AV block first and second degree (1.2% and 0.9%, respectively) and bradycardia (2%) and were minimized by dose titration. Liver enzyme increases (≥3x ULN) occurred in 2.8-4.5% patients on ponesimod and none on placebo. Approximately 11%, 5%, and 13% of patients treated with 10 mg, 20 mg, and 40 mg ponesimod, respectively, discontinued treatment prematurely due to adverse events, compared to 2.5% in the placebo group.

We see ponesimod as a promising contender in the S1P1 modulator arena, given the strong data on its ability to reduce T1 Gd+ lesions. The half-life of 30 hours, although slightly longer than that of RPC1063 (19 hours), still leads to a relatively rapid lymphocyte count recovery upon ponesimod treatment withdrawal (seven days). However, ponesimod's ARR efficacy seems weaker than that of the competition, especially at lower dose levels. This is of course with the caveat that the ARR was obtained from a relatively small study over a relative short period of six months. At the high dose level of 40 mg, adverse reactions may become an issue for ponesimod.

Actelion has also conducted a phase 2 trial in psoriasis. In that trial, 46-48% of subjects achieved a PASI 75 response at week 16 compared to 13% of subjects treated with placebo. After 16 weeks subjects in the ponesimod arms were randomized to continue ponesimod or switch to placebo. Actelion notes that 71-77% of subjects achieving a PASI 50 response after 16 weeks of ponesimod achieved a PASI 75 response at week 28 with continued ponesimod treatment.

Actelion is planning a phase 3 program for psoriasis, but the future development in RRMS is less certain and Actelion is seeking partnership on RRMS development.

KRP203

KRP203 is a structural analog of GILENYA developed by Kyorin Pharmaceuticals and licensed exclusively to Novartis. Compared to GILENYA, KRP203 has 5-fold greater selectivity for binding to S1P1 versus S1P3 and 100-fold greater selectivity over S1P2 and S1P5.

Novartis initiated two phase 2 trials of KRP203 in 2011, one in subjects with cutaneous lupus and one in subjects with moderate to severe refractory ulcerative colitis (UC). In March and April of 2013, Novartis changed the status of these trials on clinicaltrials.gov as terminated. Also in April a phase 2 trial for KRP203 in subjects undergoing stem transplant for hematologic malignancy was listed.

MT-1303

MT-1303 is another second generation S1P receptor modulator. It is being developed by Mitsubishi Tanabe Pharma and the company is currently conducting a phase 2 dose ranging trial of three dose levels of MT-1303 in 400 subjects with RRMS in Europe and Russia. The primary endpoint is the total number of Gd+ve lesions at 24 weeks with data expected 1Q15. Mitsubishi Tanabe Pharma has also initiated a phase 1 single dose trial of MT-1303 in 24 subjects with inflammatory bowel disease, with data expected 3Q13.

RPC1063's Points of Differentiation

The success of GILENYA as the first approved oral disease modifying therapy for RRMS and the first S1P receptor agonist has attracted numerous competitors, the most advanced of which have now entered phase 3 testing. Including Receptos, all the GILENYA follow-on S1P receptor agonists, have a more selective profile than GILENYA and to a varying extent different pharmacodynamic properties. Exhibit 25 summarizes some key features of the S1P receptor agonist competitive landscape. RCP1063 is the most specific S1P receptor agonist with activity restricted to $S1P_1$. Actelion, Novartis, and Ono/Merck Serono have conducted phase 2 trials of their respective S1P receptor agonists. Actelion has committed to a phase 3 trial in psoriasis and intends to partner development in MS. Novartis elected to conduct a trial of siponimod in secondary progressive MS (SPMS) while Ono and Merck/Serono have yet to communicate next steps for Ono-4641.

Exhibit 25. Selected S1P Receptor Agonist Properties

	RPC1063 0.3mg	RPC1063 1.0mg	GILENYA 0.5mg	Ponesimod 20mg	Siponimod 2mg	Ono-4641
Specificity	$S1P_1$	$S1P_1$	$S1P_{1,3,4,5}$	$S1P_{1,5}$	$S1P_{1,5}$	$S1P_{1,5}$
EC50 (nM)						
$S1P_1$	0.16	0.16	0.27	0.25	0.21	
$S1P_2$	>10,000	>10,000	>10,000	>10,000	>10,000	
$S1P_3$	>10,000	>10,000	7.8	980	>10,000	
$S1P_4$	>7,865	>7,865	344	>10,000	920	
$S1P_5$	11	11	0.5	87	0.4	
Status	P2/3	P2/3	Approved; 0.25mg P3	On-hold -RRMS Phase 3* PsO	P3 SPMS	P2 complete
Half Life (h)	19	19	168	30	30	
Time to lymphocyte recovery	3d	3d	6-8wk	3-6d	<1wk	
Cmax (nM)		0.36nM	0.89nM	286nM	31.9nM	
Time to Cmax (h)		10	6	4	4	
1st dose heart rate decrease	7.1	9.9	12.2	16.6	17.3	
Dose Titration	Y	Y	Y (0.25x2)	Y	Y	N
Time to lymphocyte recovery	3d	3d	6-8wk	3-6d	<1wk	
≥3X ULN AST/ALT	TBD	TBD	8%	2.8-4.5%	4.30%	5.9-14.2%

Source: BMO Capital Markets. *Planned.

Available phase 1 clinical data suggest to us that RCP1063 has a differentiated pharmacokinetic profile from GILENYA and competitors:

RPC1063 has a considerably shorter half life than GILENYA, and a shorter half life compared to other development stage S1P receptor agonists for which data have been presented. The most obvious corollary of the difference in half life between RPC1063 and GILENYA is duration of lymphopenia following termination of therapy. While lymphocytes return to normal levels three days after stopping RPC1063; it can take 6-8 weeks for lymphocytes to return to normal levels following termination of GILENYA. This has many ramifications:

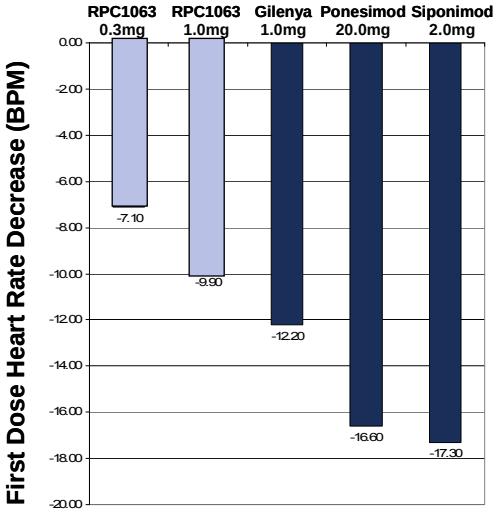
- If GILENYA needs to be stopped for inadequate efficacy or a safety signal, the prolonged immunosuppressive effects leads to caution in selecting and or starting a course of an alternative therapy especially if the clinical course suggests stepping up to TYSABRI, for example.
- As a pregnancy category C drug, GILENYA has shown adverse effects in animal reproductive studies. Thus it would be inadvisable for a woman to become pregnant while taking GILENYA and the label states that women should use reliable contraception while taking GILENYA and for two months after stopping GILENYA. While RPC1063 is also likely to be a category C drug, the shorter half life would place less onerous contraception requirements after stopping therapy and potentially also reduce the risk for fetal harm if accidental pregnancy occurred while taking drug.

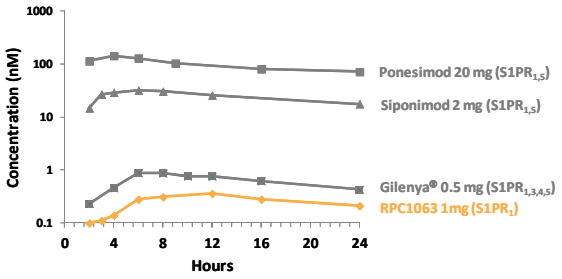
One advantage of a drug with a long half life is that a missed dose is not associated with a high risk for therapeutic failure. In fact we understand that for patients with high out-of-pocket costs for GILENYA some neurologists recommend every other day dosing. While RPC1063 has a much shorter half life than GILENYA, it is still long enough to provide good coverage for a missed dose.

RCP1063's differentiated PK profile may also be the reason why the drug appears to have a differentiated profile with respect to bradycardia. As shown on the left hand panel of Exhibit 26, RCP1063 has the lowest first dose heart rate effect at a 7-9 beat per minute (BPM) decrement. Notably, both siponimod and ponesimod have a more pronounced first dose heart rate effect than GILENYA at >15 BPM reduction versus ~ 12BPM for GILENYA. The PK profile chart shown on the right hand side of Exhibit 26 may provide an explanation for the heart rate observations since RCP1063 has both a lower post first dose maximal serum concentration (Cmax) and a longer time to Cmax than GILENYA, ponesimod, or siponimod.

Maximal first-dose heart rate effects with GILENYA are seen at roughly six hours post dosing, which coincides with Cmax, and, further, the magnitude of heart rate decrease is dose dependent. From first principles therefore one would expect that all other things being equal a drug with a lower Cmax would lead to a reduction in first-dose heart rate effects. In addition, an increase in time to Cmax may allow for a more muted effect as compensatory mechanisms for bradycardia have more time to develop. To further improve patient outcomes upon initial dose administration, Receptos has also implemented a dose titration regime by first exposing patients to a subtherapeutic dose and over time adjusting the dose upward.

Exhibit 26. Comparative First-Dose Heart Rate and PK Profiles of RPC1063 and Other S1P Receptor Agonists





Sources: Receptos and BMO Capital Markets.

While the evidence for RCP1063 having a superior lymphopenia and bradycardia profile, what remains to be determined is whether or not RPC1063 has a differentiated safety profile either for toxicities thought to be associated with S1P receptor selectivity or for toxicity not thought to be associated with S1P receptor selectivity.

Preclinical studies conducted by Actelion suggested that the profibrotic response observed for GILENYA could be blunted by using the $S1P_3$ sparing ponesimod, but could only be neutralized by a specific $S1P_1$ receptor agonist. Both the US and EU product labels for GILENYA make note of the pro-fibrotic toxicities associated with chronic GILENYA use, and while to date there has not been a rash of irreversible changes in pulmonary function associated with long-term GILENYA use reported in the literature, MS is a disease that requires management over decades and long-term safety is thus critical.

RPC1063's low Cmax also helps it to spare $S1P_5$. Although RPC1063 is relatively selective for $S1P_5$ from an EC_{50} perspective (EC_{50}=11nM, Exhibit 25), the low Cmax (0.36nM, see Exhibit 25) of RPC1063 ensures that there will be little triggering of $S1P_5$. This contrasts with ponesimod, which has a much higher Cmax (286nM, see Exhibit 25) and therefore is likely to trigger $S1P_5$ (EC_{50}=87nM, see Exhibit 25).

Moving to non-S1P receptor mediated toxicity, the most common off-target laboratory abnormality associated with GILENYA is liver toxicity. Data from phase 2 trials of other S1P receptor agonists suggest that the rate of liver toxicity noted for GILENYA is at the upper end of the range when comparing GILENYA with ponesimod, siponimod and ONO-4641. The liver toxicity profile of RPC1063 has yet to be determined, but we are encouraged that GILENYA appears to close to the high water mark for an S1P receptor agonist.

While improved receptor specificity may lead to improved safety, there is also the possibility that broad activity may be associated with the so far unquantifiable but claimed neuroprotective activity observed with GILENYA. As noted earlier, the brain atrophy data are included in the EU label for GILENYA and to be broadly competitive all S1P receptor agonists will need to show evidence of neuroprotection.

Precedent Data for Other Oral Agents for RRMS

Following the approval of the first oral RRMS therapy, GILENYA, another two oral therapies have been approved. Sanofi's AUBAGIO (teriflunomide) was approved in both the US and EU, and Biogen Idec's TECFIDERA (BG-12) was approved in the US and is currently under review in EU. Teva's oral therapy, laquinimod, has completed phase 3 testing in RRMS and is under regulatory review in Europe. Laquinimod will need another phase 3 study before applying for US approval.

Exhibit 27 summarizes the US labels from placebo-controlled trials of AUBAGIO, TECFIDERA, and GILENYA. In two-year placebo controlled trials, GILENYA and TECFIDERA reduced annual relapse rates by 50% versus placebo suggesting a higher level of efficacy than AUBAGIO, which reduced ARR by 30% versus placebo, comparable with what has been reported with the interferons. There is a suggestion that the patients in the AUBAGIO trial had more active disease since the relapse rate for the placebo arm was higher, in that trials at 0.54 relapses/year versus 0.4 for the TECFIDERA and GILENYA trials. Another measure of efficacy is the proportion of patients that remain relapse-free after two years of treatment, which was 55% for AUBAGIO, 73% for TECFIDERA, 70% for GILENYA, and 46% for the placebo arms of all three trials. TECFIDERA and AUBAGIO labels also report the proportion of subjects with confirmed disability after two years, which was 20% for AUBAGIO, 16% for TECFIDERA, and 27% for the placebo arms of both trials. In terms of MRI-based assessment of activity, the only metric reported by each of the three trials was the mean number of Gd+ve lesions after two years of treatment. Across the placebo groups, patients had 1.1-1.8 Gd+ve lesions versus 0.1-0.2 lesions per patient for TECFIDERA and GILENYA and 0.26 lesions per patient for the 14 mg dose of AUBAGIO and 0.57 lesions per patient for the low dose of AUBAGIO.

Exhibit 27. Comparison of Key Features for AUBAGIO, TECFIDERA, and GILENYA

	Aubagio	Tecfidera	Gilenya
Sponsor	Sanofi	BiogenIdec	Novartis
Status - US	Approved for relapsing MS in 2012	Approved for relapsing MS in 2013	Approved for relapsing MS in 2010
Approved Dose	7mg or 14mg once daily	120mg twice daily maintenance dose after 7 days 240mg twice daily	0.5mg/d
Mechanism of Action	Pyrimidine synthesis inhibitor	Nrf2 activator	S1P receptor agonist
Efficacy			
ARR	0.37 vs. 0.54	0.17 vs. 0.36	0.18 vs. 0.4
Risk reduction	31%	53%	55%
Relapse free at yr2	54-56% vs. 46%	73% vs. 46%	70% vs. 46%
Risk Reduction		49%	
Disability Progression at 2yr	20-22% vs. 27%	16% vs. 27%	
Hazard ratio/ Risk Reduction	0.7-0.76	38%	0.7
MRI			
T2 and T1 hypointense lesion volume	0.34-0.75 vs. 1.13		
New/enlarging T2 lesion number		2.6 vs. 17	2.5 vs. 9.8
Percent with no new/newly enlarging lesions		45% vs. 17%	
Mean no of Gd+ve lesions	0.26-0.57 vs. 1.33	0.1 vs. 1.8	0.2 vs. 1.1
Safety			
BW	Yes - hepatotoxicity and teratogenicity	No	
Pregnancy Category	X	C	C
Warnings	Hepatotoxicity WBC count decrease Infection Risk/TB Peripheral neuropathy Acute renal failure Hyperkalemia Skin reactions Blood Pressure Increase Respiratory Effects	Lymphopenia Flushing	Bradycardia Atrioventricular block Infection Macular edema Respiratory effects Hepatic effects Fetal risk Blood pressure effects Immune system effects following discontinuation
Aes - Other than Warnings		Gastrointestinal Hepatic transaminases Eosinophilia	

Source: US FDA and BMO Capital Markets.

With respect to safety, a comparison of the labels' Warnings section suggests a greater level of concern from the FDA toward AUBAGIO and GILENYA than TECFIDERA. AUBAGIO carries a black box warning for hepatotoxicity and teratogenicity. In considering AUBAGIO's approval, the FDA considered the safety database of the rheumatoid arthritis drug ARAVA because AUBAGIO is the active ingredient of ARAVA. Thus many of the comments in the Warnings section of AUBAGIO's label rely on ARAVA's database. The package insert describes a procedure for elimination of AUBAGIO because, without this procedure, up to eight months are required for drug levels to reach a level that confers minimal teratogenicity risk.

In summary, AUBAGIO appears to be less effective than either GILENYA or TECFIDERA, and the second placebo-controlled trial of AUBAGIO, TOWER showed very similar efficacy data to the TEMSO trial detailed in the package insert. GILENYA and TECFIDERA appear to have comparable efficacy, and while GILENYA has the advantage of daily dosing, the requirement for intensive monitoring of the first dose and lengthy safety issues put it at a disadvantage to TECFIDERA.

Market Opportunity in RRMS

Multiple Sclerosis Overview

MS is a chronic autoimmune disorder characterized by recurring episodes of neurological symptoms such as numbness, difficulty walking, visual loss, lack of coordination, and muscle weakness. These symptoms are caused by the destruction of the myelin sheath of neurons in the brain and spinal cord by autoreactive lymphocytes. Myelin is an insulating layer that wraps around the axon of a neuron. Insulation by the myelin sheath increases the speed at which neural impulses propagate along nerve fibers. Damage to the myelin sheath, also known as demyelination, impairs the conduction of signals in nerve fibers, leading to deficiency in sensation, movement, cognition, or other functions.

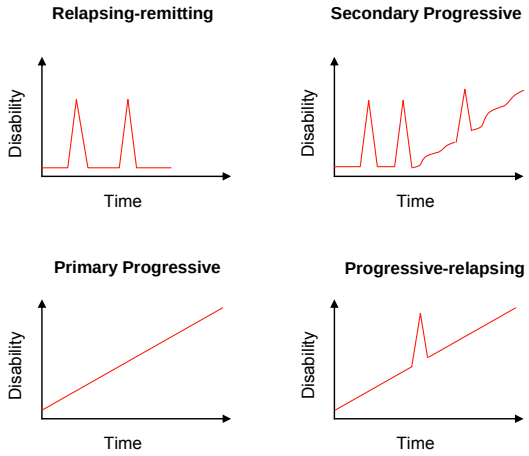
The majority of MS patients are diagnosed between the ages of 20 and 40, but MS may also occur in young children and older adults. In the US, the prevalence of MS is estimated to be 100 per 100,000; in Europe, the prevalence is 83 per 100,000 and the incidence rate is 4.3 cases per 100,000. As with many autoimmune diseases, MS affects women more than men, with two-thirds of MS patients being women.

The disease course of MS is characterized by episodes of neurological dysfunction followed by periods of remission during which the symptoms resolve to a variable extent. MS can be categorized into four subtypes according to the pattern of disease progression. (See Exhibit 28.)

- Relapsing remitting MS (RRMS) is characterized by clearly defined acute attacks (relapses) with full recovery or with sequelae and residual deficit upon recovery. There is no disease activity or progression between the acute attacks, and these quite periods of remission could last from a few months to years. RRMS describes the initial disease course for 85% of MS patients and is associated with better prognosis than other MS subtypes.
- Secondary-progressive MS (SPMS) starts with an initial RRMS disease course followed by progressive neurologic decline between acute attacks without any definite periods of remission. Within 6-10 years of disease onset, 30-40% of patients with RRMS have progressed to SPMS. The median time between disease onset and conversion from RRMS to SPMS is 19 years.
- Primary-progressive MS (PPMS) is characterized by steady neurologic decline from onset without any definite periods of acute attacks or remissions. This subtype describes 10-15% of MS patients. The mean age of onset for PPMS is 40.
- Progressive-relapsing MS (PRMS) is characterized by steady neurologic decline from onset as well as clearly superimposed acute attacks. This is the lease common of all subtypes.

Receptos' compound, RPC1063, is for the treatment of RRMS. Receptos estimates that there are 500,000 RRMS patients worldwide.

Exhibit 28. Disease Courses of MS Subtypes



Source: Cleveland Clinic (Adapted from Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology* 1996;46:907-911) and BMO Capital Markets.

Current Treatments for RRMS and Their Limitations

The first-line therapy for RRMS traditionally includes four injectables collectively know as ABCR: AVONEX (interferon (IFN) β-1a, weekly intramuscular injection), REBIF (IFNβ-1a, three times-weekly subcutaneous injection), BETASERON (IFNβ-1b, alternate-day subcutaneous injection), and COPAXONE (glatiramer acetate, daily subcutaneous injection). Interferon therapies are recombinant forms of human IFNβ-1 protein, an immunomodulatory cytokine produced in response to viral infection and other biological inducers. Glatiramer acetate is a mixture of random polymers of four amino acids based and is antigenically similar myelin basic protein, a component of the myelin sheath. Although the mechanisms of action differ, interferon and glatiramer acetate have similar efficacy for treating RRMS.

Although ABCR therapies have become the standard of care for the treatment of RRMS, these agents have limitations. The reduction in annualized relapse rate (ARR) versus placebo, a primary measure of efficacy for RRMS therapies, is quite moderate at approximately 30%. In addition, each ABCR agent is effective in only a subset of patients, thus requiring patients to cycle through these agents. ABCR agents are also associated with unfavorable tolerability profiles. The interferon therapies cause flu-like symptoms following an injection, and glatiramer acetate requires daily injections, which may lead to injection-fatigue.

Recently, the FDA approved three new RRMS therapies, all of which are oral drugs: Novartis' GILENYA (fingolimod, once daily), Sanofi's AUBAGIO (teriflunomide, once daily), and Biogen Idec's TECFIDERA (dimethyl fumarate, twice daily). GILENYA is an S1P modulator that has demonstrated a reduction in ARR of 54%-60% versus placebo and a reduction of 52%

versus AVONEX. For the most part GILENYA is well tolerated, with most frequent adverse reactions mild in nature, including headache, influenza, diarrhea, back pain, liver transaminase elevations, and cough. In addition, warnings and precautions in GILENYA's label include risks of abnormal slowing of heart rate (bradyarrhythmia), atrioventricular (AV) blocks, infection, macular edema, respiratory effects, hepatic effects, fetal risk, blood pressure effects, and long lymphocyte recovery time (one to two months) following therapy discontinuation. It is thought that certain of these adverse events may be a result of GILENYA's non-selectivity for S1P receptors.

Sanofi's AUBAGIO is the second oral treatment approved for RRMS. AUBAGIO is an inhibitor of dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de-novo pyrimidine synthesis. AUBAGIO is the active metabolite of Sanofi's approved rheumatoid arthritis drug, ARAVA. The exact mechanism of action of AUBAGIO in MS is unknown, but may involve a reduction in the number of activated lymphocytes in CNS. AUBAGIO demonstrated a reduction in ARR of 31% versus placebo. The most common adverse reactions include risk of alanine aminotransferase increases, hair loss, diarrhea, influenza, nausea, and paresthesia. AUBAGIO's label carries a black box warning for both hepatotoxicity and teratogenicity.

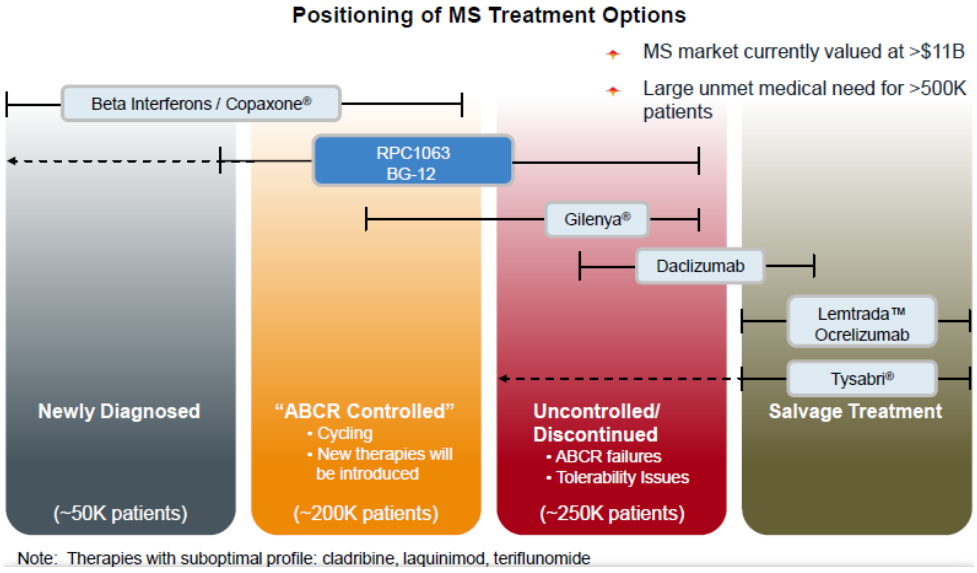
Biogen Idec's TECFIDERA, or dimethyl fumarate (DMF), is the most recently approved MS drug. DMF is the principal component of BIIB's psoriasis drug, FUMIDERM, which has been available in Germany since 1994. It is unclear how DMF exerts its therapeutic effect in MS. DMF and its metabolite, monomethyl fumarate (MMF), have been shown to activate the nuclear factor-like 2 (Nrf2) pathway, and this pathway is involved in the cellular response to oxidative stress. TECFIDERA demonstrated a 44% reduction in ARR versus placebo and a 52% reduction versus AVONEX. The most common adverse reactions for TECFIDERA include flushing, abdominal pain, diarrhea, and nausea. TECFIDERA's label also includes warnings and precautions for risks of lymphopenia and flushing.

Second-line therapies are used when patients stop responding to or become intolerant of ABCR therapies. Second-line drugs for RRMS include mitoxantrone and TYSABRI (natalizumab). Mitoxantrone is a cytostatic agent and is approved for use in severe forms of RRMS, but cumulative dose-related cardiac toxicity and a risk of secondary leukemia limit the total amount that can be administered. TYSABRI is a monoclonal antibody against the $\alpha 4$ subunit of the integrin $\alpha 4\beta 1$ on lymphocytes. TYSABRI demonstrates a reduction in ARR of 67%, but it may cause serious side effects including increased risk of progressive multifocal leukoencephalophaty (PML), a rare and potentially fatal viral disease. TYSABRI is indicated for patients unable to tolerate or respond well to other therapies, and is available only to this defined patient group through a special restricted distribution program.

Products that are in registration for the treatment of RRMS include Sanofi's LEMTRADA (anti-CD52 mAb injectable) and Teva Pharmaceuticals' laquinimod (oral immune modulator). In addition, two phase 3 drug candidates, daclizumab (anti-IL2R-α mAb injectable) from Biogen Idec/Abbvie and ocrelizumab (anti-CD20 mAb intravenous infusion) from Genentech, are expected to file for approval before 2018.

In terms of market opportunities for RPC1063, the second-line uncontrolled and discontinued patient population represents the most promising. Patients that have discontinued treatment are expected to re-enter treatment with the availability of new therapies. In addition, a proportion of newly diagnosed patients and some first-line patients undergoing ABCR cycles may also be candidates for a safe, oral therapy.

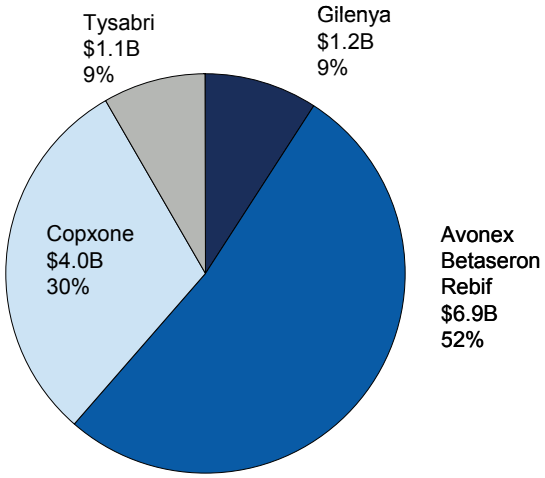
Exhibit 29. RRMS Therapies and the Positioning of RPC1063



Source: Receptos.

In 2012, the annual RRMS market for branded therapeutic treatments was approximately $13 billion worldwide, increasing by 18% over 2011. A breakdown of sales of various branded drugs is shown in Exhibit 30. Notably, GILENYA achieved worldwide sales of $1.2 billion in 2012, its second full year of commercial launch. This highlights the unmet need in the RMS market for efficacious, orally administered therapies.

Exhibit 30. 2012 RRMS WW Sales (~$13 billion)



Source: Receptos and BMO Capital Markets.

Deep Dive - the Biology of S1P and Its Receptors

Sphingosines are derived from cell membranes and are thus ubiquitous. Specifically, sphingosines can be phosphorylated by specific kinases to produce signaling molecules, one of the most important of which is spingosine-1-phosphate or S1P. S1P mediated signaling has been associated with a variety of cell properties including: proliferation, migration, contraction and intracellular mobilization of calcium. The activity of S1P is mediated by G-protein coupled receptors of which there are 5: $S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$, and $S1P_5$. Binding of S1P to an S1P receptor activates specific signaling pathways dependent on engagement of G-protein signaling proteins and it is the repertoire of G-proteins that dictate diverse signaling effects of S1P. Indeed the diversity, and differential tissue distribution of, S1P receptors, combined with a broad repertoire of G-protein mediators dictates specific cellular responses despite the ubiquitous presence of S1P. In the context of tissue distribution of S1P receptors, $S1P_1$, $S1P_2$, and $S1P_3$ are widely expressed whereas $S1P_4$ and $S1P_5$ are limited to the immune and nervous system.

Given the ubiquitous distribution of sphingosine and the pleiotrophic effects of SIPR signaling, dysregulation of the S1P pathway has been associated with a broad variety of diseases as depicted in Exhibit 31 and, in fact, the literature is replete with data suggesting utility of S1P modulation in many of these conditions.

Exhibit 31. Role of Sphingosine-1-Phosphate in Human Disease

Source: BMO Capital Markets.

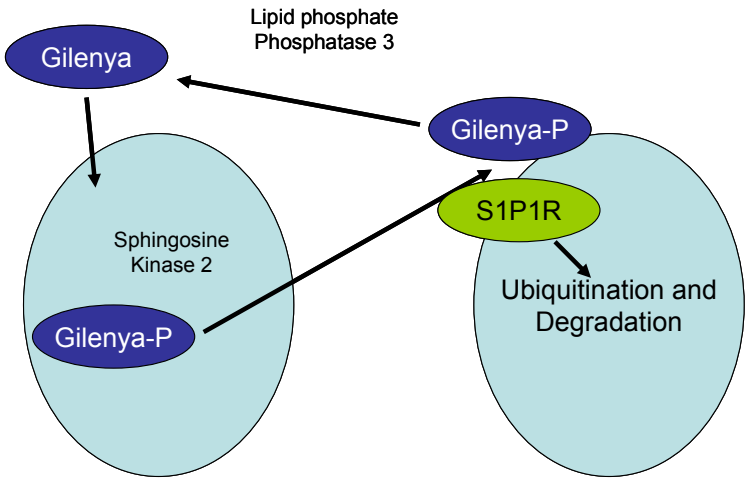
S1P and Multiple Sclerosis

Because autoreactive T cells trafficking to the brain may be responsible for tissue destruction associated with MS, efforts have been made to search for ways to stop T cells from crossing the blood-brain barrier. One incarnation was Biogen Idec's Tysabri, which blocked a key adhesion molecule used by T cells to cross the blood brain barrier. An alternate approach was pioneered by Novartis with the development of the archetypal S1P agonist, GILENYA. Pathogenic T cells, for example, enter lymph nodes as part of their immune surveillance where they encounter an S1P gradient. S1P concentrations are sensed by the S1P receptor (S1PR) and cells migrate through an S1P gradient eventually exiting the lymph node and re-entering circulation. However, if T cell and B cell subsets encounter a suitable antigen in the lymph node, expression of S1PR is down-regulated. This allows these cells to reside in the lymph node and be educated, after which S1PR is upregulated and the cells can then respond to the S1P gradient that allows them to egress from the lymph node. S1P agonist drugs such as RPC1063 take advantage of this elegant biology by causing drug-related downregulation of the S1PR, in this case $S1P_1$ in the lymph node.

As noted GILENYA is the archetypal S1P modulator and while much has been published on its biology, the mechanistic investigations are common to other S1P modulators such as RPC1063. GILENYA is a pro-drug, which, like sphingosine is phosphorylated intracellularly by sphingosine kinase 2. Phosphorylated GILENYA is released from the cell where it can bind to S1P receptors. This binding leads to internalization of the complex followed by separation of the ligand and degradation of the receptor. The released phosphorylated GILENYA can either remain phosphorylated or become de-phopsphorylated by lipid phosphate phosphatase as

depicted in Exhibit 32. GILENYA does not exactly mimic human S1P biology as when S1PR-S1P complexes are internalized both are re-cycled, suggesting that GILENYA changes the fate of the S1P receptor.

Exhibit 32. Schematic Diagram Depicting GILENYA Mechanism of Action on the Lymph Node



Source: BMO Capital Markets.

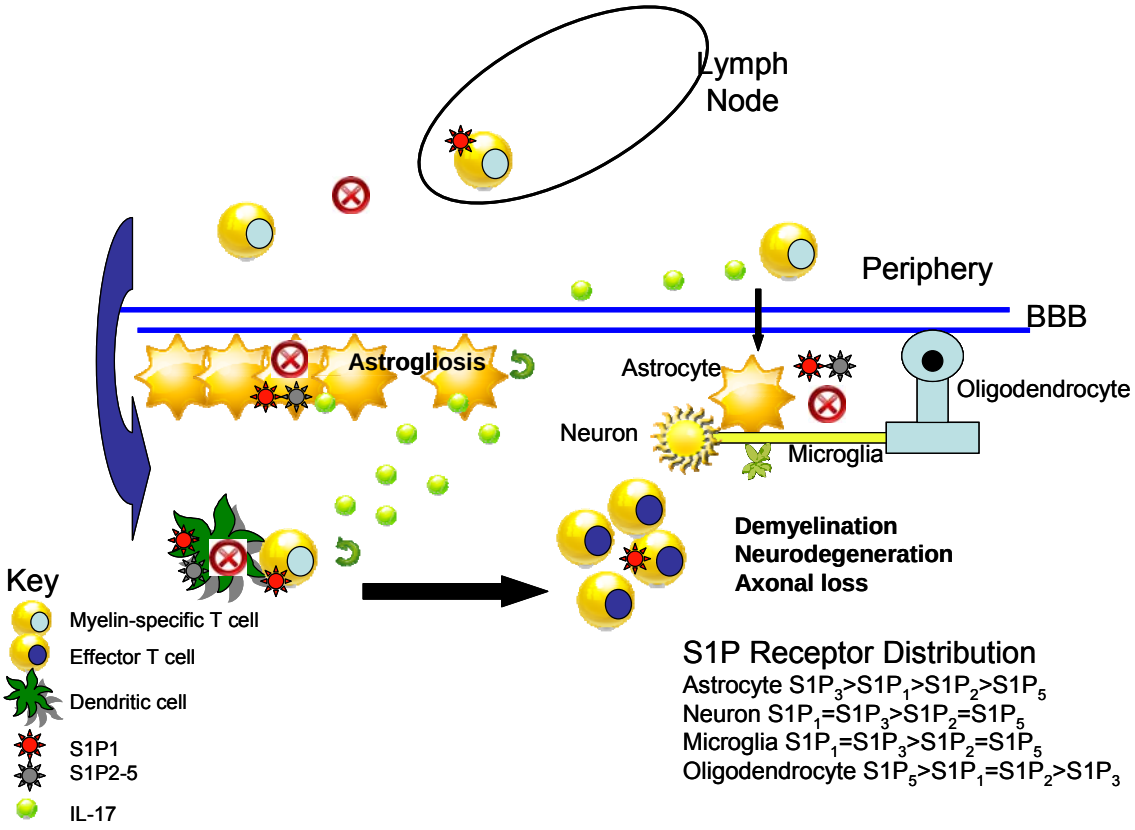
In the context of circulating B and T cells, S1PR agonism by phosphorylated GILENYA leads to loss of cell surface S1P receptors. Specifically for $S1P_1$, lymphocytes are unable to sense S1P, which is necessary for egress from lymphoid organ. In short, GILENYA locks lymphocytes in lymphoid tissues, preventing them from reaching and crossing the blood brain barrier.

Not all T cell subsets are equally affected by $S1P_1$ modulation. GILENYA leads to the reduction of CD4 and CD8 T cell counts by 60%-80%, and specifically affects naïve and central memory T cells that rely on trafficking through lymphoid organs. In contrast, CCR7-ve cells such as effector T cells do not traffic through lymphoid organs and are thus unaffected by GILENYA; in fact, their relative concentration in blood increases as CCR7+ve cells diminish in circulation. Importantly, GILENYA does not appear to affect lymphocyte function, suggesting that S1P is important for lymphocyte trafficking and not lymphocyte function. This has important implications for safety, as T and B cell responses to previously exposed pathogens remains intact and, in fact, serious infectious events in clinical trials of S1P agonists have been uncommon.

Beyond T and B cells, dendritic cells, which are responsible for presenting antigens to immune cells also express $S1P_1$ and $S1P_3$. GILENYA impairs the mobilization of dendritic cells from peripheral tissues to lymphoid tissues and efficacy of locally administered S1P agonists in models of asthma is thought to be related to impaired trafficking of dendritic cells from lungs to draining lymph nodes. Innate immunity is also important and it is noteworthy that NK cells express and use $S1P_5$. GILENYA is an agonist for $S1P_5$; however, it does not appear to alter peripheral levels of, or functionality of, NK cells.

Outside of the hematopoietic system and specific to neurological disease, certain neural cells are also known to express S1P receptors. This is relevant to discuss as preclinical data imply that GILENYA may have a direct effect on brain resident cells. The schematic diagram in Exhibit 33 depicts a sequence of events that leads to experimental autoimmune encephalitis, a mouse model of MS, onto which points of interdiction for an S1P1 agonist such as RCP1063 have been made.

Exhibit 33. Schematic Diagram of EAE Development and Possible S1P1 Sites of Interdiction



Source: BMO Capital Markets and Chun and Hartung, *Clinical Neuropharmacology*, 33(2) 91-101, 2010.

In the schematic diagram, myelin-specific TH17 memory T cells leave the lymph node and traffic to the brain crossing the blood brain barrier (BBB). Resident dendritic cells loaded with myelin antigen react with T cells, leading to stimulation of memory T cells to secrete cytokines such as IL-17. The memory T cells become effector T cells and amplification of the process occurs via attraction of other T, B, and NK lymphocytes. In addition, IL-17 activates astrocytes, which are immune-like cells resident in the brain for which both protective and pathogenic roles have been described. With respect to MS, S1P can induce the production of glial fibrillary

acidic protein or GFAP, which inhibits endogenous repair mechanisms associated with remyelination. In the context of damaged neurons, astrocyte numbers increase, a condition referred to as astrogliosis, leading to further pathogenic astrocyte involvement.

Superimposed on the proposed model of EAE are potential sites of S1PR agonist interaction beyond the previously described effects in lymphocyte egress from lymph nodes.

- Oligodendrocytes: Role of S1P varies with both the developmental stage of the cell and the receptor subtype involved. However, *in –vitro* data for GILENYA has been reported, suggesting it increases the number of both progenitor and mature oligodendrocytes, protecting them from cell death induced by cytokines or the withdrawal of growth factor.
- Neurons: As with oligodendrocytes, the role of S1P is complex and depends on the stage of cell differentiation, and S1P receptor subtype GILENYA has been shown in-vitro and in-vivo to increase the level of BNDF, a neuroprotectant for oligodendrocytes.
- Astrocytes: Express $S1P_1$, $S1P_2$, $S1P_3$, and S1P5; however, $S1P_1$ and $S1P_5$ are more highly expressed. S1P can induce astrocyte proliferation, migration, and astrogliosis.

As noted earlier in the introduction, S1P and S1PR are ubiquitous and some of the clinically and preclinically observed side effects associated with GILENYA are suggested to be mechanistically based; most notable are cardiac, fibrosis, and ocular toxicity.

S1P and Cardiovascular Biology

Activation of cardiac S1P receptors has been reported to affect cardiac contractility and heart rate, induce hypertrophy, provide protection from ischemia, and mobilize intracellular calcium. The observation of cardiovascular toxicity with GILENYA is consistent with the role of S1P in cardiovascular biology but offers the opportunity to dissect the relative roles of the $S1P_1$, $S1P_2$, and $S1P_3$ receptors. S1P1 receptor knockout mice show embryonic lethality due to the aberrant blood vessel development that results from loss of S1P receptors in vascular endothelial cells. In contrast $S1P_2$, $S1P_3$, or $S1P_{2,3}$ receptor knockout mice are viable and show only modest phenotypic changes.

In a review by Means and Brown titled "Sphingosine-1-phosphate receptor signaling in the heart," *Cardiovascular Research* (2009) 82, 193–200, the distribution and role of S1PR in the four principal cell types of the cardiovascular system is described. The relative distribution and importance of S1PR subtypes is summarized in Exhibit 34.

Exhibit 34. Relative Distribution of S1PR Subtypes in Cardiovascular Tissue

Tissue	Relative Expression of S1P Receptor Subtypes
Cardiac myocytes	$S1P_1$ >> $S1P_3$ > $S1P_2$
Cardiac fibroblasts	$S1P_3$ >> $S1P_1$ > $S1P_2$
Aortic smooth muscle cells	$S1P_2$ > $S1P_3$ >> $S1P_1$
Vascular endothelial cells	$S1P_1$ >> $S1P_3$ > $S1P_2$

Source: Means and Brown, *Cardiovascular Research*, 2009 and BMO Capital Research.

With respect to pharmaceutical intervention of S1PR and cardiovascular biology it is widely acknowledged that $S1P_3$ is implicated in regulating heart rate and that receptor activation leads to bradycardia, as GILENYA fails to induce bradycardia in an $S1P_3$ knockout mouse, Koyrakh *et al. Am J. Transpl.* 5: 529-536 2005. S1P is thought to be involved in cardioprotection and in the cardiomyocyte S1P effects are mediated by $S1P_1$ or $S1P_3$. With respect to vasoconstriction, this is primarily mediated by $S1P_3$ and the $S1P_3$ receptor is also found predominantly on cardiac fibroblasts compared to $S1P_1$ or $S1P_2$.

S1P and Fibrosis

S1P, S1PR, and the activating kinase SphK1 have been shown to be upregulated in serum, bronchoalveolar lavage and lung tissue of patients with the fibrotic lung disease idiopathic pulmonary fibrosis. Toxicology studies following chronic administration of GILENYA in rats and non-human primates reported fibrotic lung changes, including increased lung weight associated with smooth muscle hypertrophy and increased collagen deposition. In addition, insufficient or lack of pulmonary collapse at necroscopy, indicative of excessive collagen deposition consistent with fibrosis, was observed. Sobel and colleagues compared the pro-fibrotic responses of GILENYA with the more selective $S1P_1$, $S1P_5$ agonist and with a highly selective $S1P_1$ agonist in human lung fibroblasts ("S1PR agonist selectivity and pro-fibrotic potential", *Journal of Biological Chemistry*, in-press April, 2013). Sobel *et al.* show that GILENYA activated both $S1P_2$ and $S1P_3$, leading to robust synthesis of extracellular matrix (ECM), which is a pre-requisite for the fibrotic response. In contrast, the S1P1/S1P3 agonist led to a significant reduction in ECM production while the highly selective $S1P_1$ agonist was inactive in all pro-fibrotic readouts.

Our Take

GILENYA has validated that S1P agonism is an effective strategy in the treatment of MS, and arguably to date at least GILENYA is the most effective orally administered disease modifying therapy for MS. FDA's review of the GILENYA NDA and intensive research into the role of the five S1PR clearly suggests that inhibition of all five receptors increases the risk for unwanted toxicity; while GILENYA has been described as inactive against $S1P_2$, more recent data suggest it is active.

Perhaps the clearest need for an S1P agonist is to avoid or at least minimize bradycardia. In 2012, FDA strengthened the GILENYA label with a focus on the risk for bradycardia and atrioventricular (AV) block; selected changes include:

- Initiation of GILENYA is associated with heart rate reduction, usually within an hour of dosing, with maximal effect usually within 6h but can occur up to 24h after the first dose.
- Administration of GILENYA should be performed in a setting where management of symptomatic bradycardia can be managed.
- Patients with pre-existing cardiac disease should receive a cardiology consult; GILENYA is contra indicated in subjects with a recent serious cardiac event.
- Additional care is warranted if GILENYA is being added to drugs that slow heart rate or AV conduction.
- First dose precautions are required for re-introduction for breaks of 1 day or more during the first 2 weeks, 7 days during the first 2-3 weeks, and 14 days or longer after the first month.

Neither MS specialists nor general neurologist offices are mobilized to meet the strict cardiac monitoring requirements imposed by FDA for GILENYA use and this led Novartis to identify centers where neurologists can send patients for their first dose. Not surprisingly, the need for intensive first dose monitoring has become a barrier to GILENYA use and led to reduction in patient starts on GILENYA. Avoidance of $S1P_3$ would seem to be the most obvious way to minimize heart rate effects of S1P agonism and RCP1063 is the only S1P agonist in late stage development that does not bind to $S1P_3$.

With the exception of cardiac effects, the causative role of specific S1P receptors for other side effects noted in clinical trials is less precise. GILENYA clinical trials clearly suggested a dose-related decrease in pulmonary function as determined by FEV_1 and FVC. While these acute and self limiting changes may perhaps suggest a change in homeostatic set point, preclinical studies have established a role for $S1P_3$ in fibrosis, raising concern over long-term S1P suppression.

Our focus so far has been on reversing the negative effects of S1P signaling and evidence can be found suggesting a beneficial role for inhibition of S1P signaling such as for remyelination. However, much of this data derive from in-vitro and in-vivo testing in rodent models of MS and precisely how these data relate to human disease is unclear. Added to this is the uncertainty of how applicable two-year or even five-year data are for a therapy that will hopefully be used for decades. In summary we think it reasonable to propose that selective inhibition $S1P_1$ to limit lymphocyte trafficking to sites of inflammation provides the most balanced approach. Avoiding inhibition of S1P other than $S1P_1$ limits acute side effects of global S1P signaling inhibition such as bradycardia, and reduces concern for long-term negative effects of fibrosis, while preserving the opportunity for positive effects of S1P signaling, especially as they relate to tissue repair following injury.

RPC1063 in IBD

Receptos is also developing RPC1063 for the treatment of Inflammatory Bowel Disease (IBD), another autoimmune disease for which the company believes S1P1 modulation of lymphocyte trafficking may have a positive therapeutic impact. IBD encompasses a group of disorders characterized by chronic inflammation of the digestive tract. The two most common forms of IBD are ulcerative colitis (UC) and Crohn's Disease (CD). UC and CD share certain pathological characteristics, and therapies that work in one disease may work in the other. Receptos is currently focusing on developing RPC1063 for the treatment of UC only, but plans to expand its IBD program to include CD upon successful efficacy outcomes for UC.

In preclinical studies with RPC1063, Receptos demonstrated dose-proportional efficacy in two mouse models of IBD: naïve T-cell adoptive transfer-induced colitis and 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis. In the TNBS model, a correlation was observed between improvements in disease parameters and lymphocyte count reduction.

Receptos is currently enrolling TOUCHSTONE, a phase 2 study of RPC1063 in patients with moderately to severely active UC. TOUCHSTONE is a multi-national, multi-center, double-blind, randomized, placebo-controlled study investigating the clinical efficacy and safety of two doses of RPC1063 (0.5 mg and 1.0 mg) versus placebo. The study is designed to enroll ~180 patients in North America, Europe, and Asia Pacific. The primary endpoint of TOUCHSTONE is the induction of clinical remission eight weeks after treatment initiation. Secondary endpoints include clinical response, clinical remission, mucosal healing, and overall safety and tolerability of RPC1063.

Receptos expects to complete enrollment for TOUCHSTONE in 1H14 and plans to release top-line results, the proportion of patients in clinical remission at week eight, in mid-2014. TOUCHSTONE was designed with endpoints and a statistical analysis plan consistent with those of a phase 3 registration study. Although Receptos did not request an SPA for TOUCHSTONE, the FDA has indicated that if the results of the study are statistically and clinically persuasive, the study could be considered as a phase 3 study for RPC1063 in UC. For UC registration trials, the FDA typically requires two phase 3 studies for induction of clinical remission and one phase 3 study for maintenance of clinical remission.

Receptos believes an NDA for RPC1063 in UC may be submitted as early as 2018, potentially positioning RPC1063 as the first S1P1 receptor modulator approved in UC.

Market Opportunity in Ulcerative Colitis

Inflammatory Bowel Disease (IBD) represents a group of a chronic gastrointestinal inflammatory disorder, with symptoms such as abdominal pain, diarrhea, and weight loss. IBD is characterized by periods of active flares of disease followed by periods of remission in which there is little or no disease activity. The time between flare and remission can be anywhere from weeks to years. IBD is an autoimmune disorder with an unknown etiology. Both genetic disposition and environmental factors are thought to contribute to the dysregulation of the immune system.

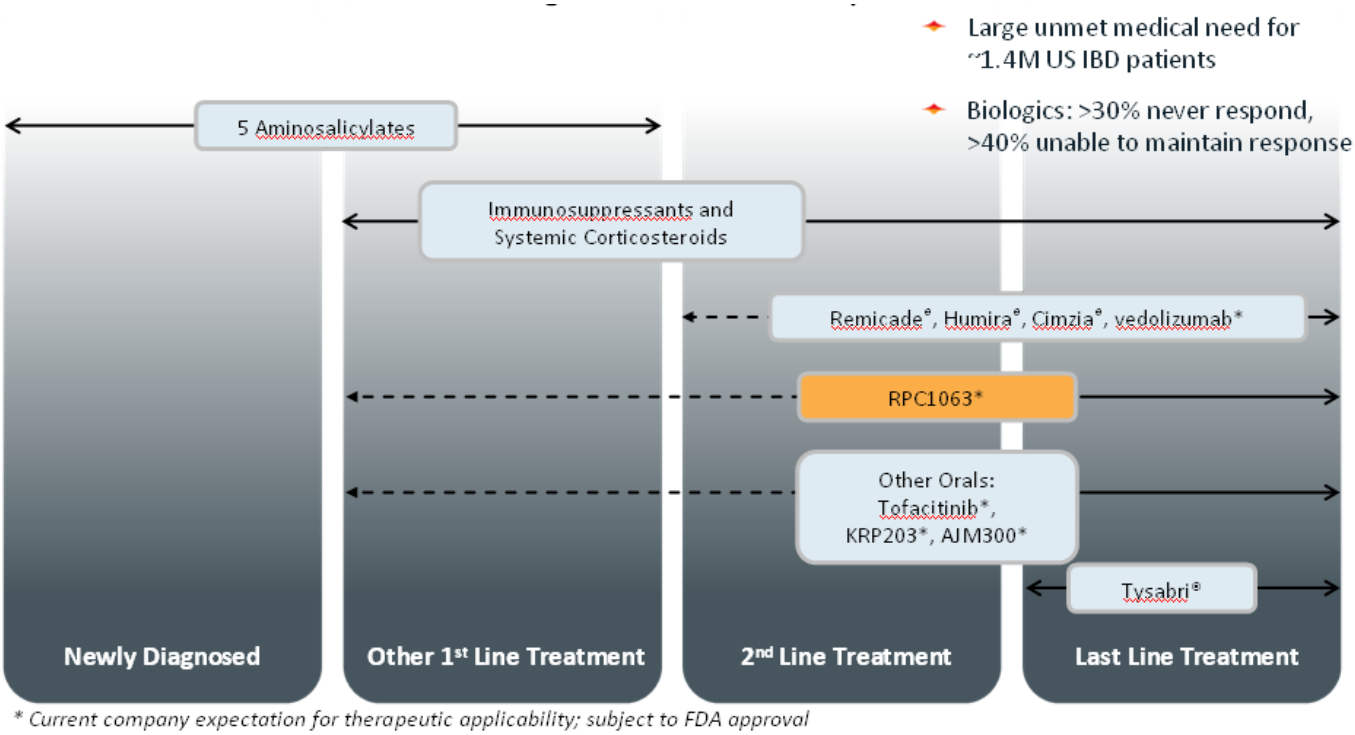
UC and CD are the most common forms of IBD, and have many symptoms in common, such as abdominal pain and diarrhea. The main distinction between UC and CD is that, while UC mostly affects the colon, CD can affect any part of the GI tract from the oral cavity to the anus.

UC affects an estimated 750,000 people in the US and affects men and women equally. Although UC can occur in people of any age, initial symptoms usually start between the ages of 15 and 30.

UC is characterized by a chronic course of remissions and exacerbations. Treatment for UC depends on the severity of the disease. Mild to moderate UC is commonly treated with 5-aminosalicyclic acid (5-ASA)-based oral anti-inflammatory agents. As an initial treatment, 5-ASA-based agents can keep 90% of mild to moderate UC patients in remission. However, over time half of these patients will progress to more severe disease and become nonresponsive to therapy.

For patients who do not respond to 5-ASAs, or those with more severe disease at diagnosis, the next line of therapy, corticosteroids, is used to induce clinical remission. However, longer-term use of corticosteroids has many adverse effects. In addition, approximately 45% of patients who initially responded to corticosteroids become steroid-dependent (i.e., unable to successfully taper corticosteroids without a return of symptoms) or require surgery after one year of treatment. Patients who have become nonresponsive or intolerant to corticosteroids may be treated with immunomodulating drugs azathioprine (AZA) and 6-mercaptopurine (6-MP), but the action of these treatments has a delayed onset of three months. The next line of treatment for UC includes three anti-TNFα biologics: REMICADE (infliximab), HUMIRA (adalimumab), and SIMPONI (golimumab). Lastly, some patients undergo surgery; within 10 years of diagnosis, 20% of adults with UC had undergone colectomy.

Exhibit 35. Treatment Options for IBD and RPC1063's Positioning



Source: Receptos.

Johnson & Johnson's REMICADE is a chimeric (75% human protein and 25% mouse protein) anti-TNF-α monoclonal antibody and the first of the anti-TNF class of biologics. REMICADE was approved for the treatment of UC in the US in 2005. AbbVie's HUMIRA is a fully human anti-TNF-α monoclonal antibody and was approved in the US for the treatment of UC in 2012.

TNF-α is a proinflammatory cytokine secreted by certain types of immune cells and a contributor in the pathogenesis of autoimmune diseases such as UC and CD. TNF-α is present in excess in the mucosa of IBD patients and is important for recruiting and activating many types of immune cells. Anti-TNFs work by blocking the activity of TNF-α.

In addition to being approved for UC, REMICADE and HUMIRA are also approved for the treatment of CD, along with another two biologics: CIMZIA (certolizumab, anti-TNF) and TYSABRI (natalizumab, anti-α4-integrin mAb).

Biologics require either intravenous or subcutaneous delivery, and therefore they are less convenient than oral drugs and may have infusion-related and injection-site reactions. Biologics may also have the issue of immunogenicity, in which the body's immune system generates neutralizing antibodies against the biologic agents, rendering them ineffective.

The phase 3 clinical trials for REMICADE and HUMIRA were similarly designed. Each program had two phase 3 trials: an 8-week trial and a longer trial of up to 54 weeks. The studies enrolled patients who had moderate to severe UC as determined by a Mayo score. The Mayo

score, a measure of UC activity based on clinical assessment and colonoscopy, ranges from 0 to 12 and has four subscales that are each scored from 0 (normal) to 3 (most severe), with four components: rectal bleeding, endoscopic findings, stool frequency, and a physician's global assessment. The HUMIRA trials enrolled patients with a Mayo score of 6 to 12 and an endoscopy subscore of 2 to 3. Patients in REMICADE trials received intravenous doses of REMICADE at weeks 0, 2, 6, and every 8 weeks thereafter, up to 46 weeks, whereas patients in HUMIRA trials received subcutaneous doses of HUMIRA every other week. The primary endpoint was clinical remission, defined as a Mayo score of 2 or less with no subscore greater than 1, at week 8 and/or week 54. Secondary endpoints included mucosal healing defined as endoscopy subscore of 0 or 1, and clinical response defined as a decrease in Mayo score of 3 or more points from baseline and decrease in Mayo score of 30% or greater from baseline and decrease in the rectal bleeding score of 1 or greater or an absolute rectal bleeding score of 0 or 1.

Key data from the trials are listed in Exhibit 36. Both REMICADE and HUMIRA demonstrated efficacy in inducing and maintaining clinical remission in patients with moderate to severe UC. Both drugs are well tolerated, with most common AEs including infections, infusion- or injection-related reactions, and headache. Both drug carry black box warnings on risks of serious infection and malignancies such as lymphoma.

Exhibit 36. Summary of Phase 3 Studies of REMICADE and HUMIRA in UC

		Remicade® (Study UC I – ACTI)		Humira® (Study UC II - ULTRA2)	
Mechanism of Action		Anti-TNF mAb		Anti-TNF mAb	
Indication		Moderate-to-Severe Ulcerative Colitis		Moderate-to-Severe Ulcerative Colitis	
Efficacy	***Induction** (week 8)*	Placebo	Remicade® (5 mg)	Placebo	Humira® (160/80 mg)
	Clinical Response*	37%	69%	34.6%	50.4%
	Clinical Remission**	15%	39%	9.3%	16.5%
	Mucosal Healing***	34%	62%	31.7%	41.1%
	***Maintenance** (week 52-54)*	Placebo	Remicade® (5 mg)	Placebo	Humira® (160/80 mg)
	Clinical Response*	20%	45%	18.3%	30.2%
	Clinical Remission**	17%	35%	8.5%	17.3%
	Mucosal Healing***	18%	45%	15.4%	25.0%
Safety		• SAE: Black box warning (malignancy and serious infection) • Immunogenicity: 10% • Infusion reactions: 20% • Contraindicated in patients with congestive heart failure		• SAE: Black box warning (malignancy and serious infection) • Immunogenicity: 5% • Injection reactions: 12.1% • Contraindicated in patients with congestive heart failure	
Route of Administration		• IV		• Prefilled syringe for self injection	

* Clinical response—a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1, at week 8; ** Clinical remission—a Mayo score of ≥ 2 points, with no individual subscore > 1, with a rectal bleeding subscore of either 0 or 1, at week 8, 30, or 54; *** Mucosal Healing—a Mayo endoscopy subscore of 0 or 1

Source: Receptos.

SIMPONI is Johnson & Johnson's next-generation, monthly subcutaneous injection anti-TNF. The safety and efficacy of SIMPONI were evaluated in two multicenter, randomized, double-blind, placebo-controlled clinical trials.

The first trial was an induction trial conducted in two parts (dose-finding and dose-confirming) in patients with moderate to severe UC. Subjects at the baseline had a Mayo score of 6 to 12, with an endoscopy subscore of 2 or 3, and were corticosteroid dependent or had an inadequate response to or had failed to tolerate at least one of the following: 5-ASAs, AZA, or 6-MP. Patients who received previous anti-TNF therapies were excluded. In the dose-finding part of the trial, patients were randomized to one of four treatment groups: 400 mg SIMPONI administered subcutaneously (SC) at week 0 and 200 mg at week 2, 200 mg SIMPONI at week 0 and 100 mg at week 2, 100 mg SIMPONI at week 0 and 50 mg at week 2, or placebo. In the dose-confirming part of the trial, 771 patients were randomized to receive either 400 mg SIMPONI SC at week 0 and 200 mg at week 2, 200 mg SIMPONI at week 0 and 100 mg at week 2, or placebo. Concomitant therapies with stable doses of 5-ASAs, oral corticosteroids, AZA, 6-MP, and/or methotrexate (MTX) were allowed. The primary endpoint was the percent of patients in clinical response at week 6. Clinical response was defined as a decrease in the Mayo score from baseline by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

The second SIMPONI trial was a maintenance trial in 463 patients who had clinical response to and tolerated SIMPONI treatment. Patients were randomized to receive 50 mg or 100 mg SIMPONI SC or placebo every four weeks. Concomitant therapies with 5-ASAs, AZA, 6-MP, and or MTX were allowed and corticosteroids were to be tapered at the start of the trial. The primary endpoint was the percent of patients maintaining clinical response through week 54.

In the first SIMPONI trial (induction trial), a greater portion of patients in the SIMPONI 200/100 mg group achieved clinical response, clinical remission, and improvement in endoscopic appearance of the mucosa at week 6 compared to the placebo group. (See Exhibit 37, left-hand panel.) The SIMPONI 400/200 mg group did not demonstrate additional clinical benefit over the 200/100 mg group.

In the second SIMPONI trial (maintenance trial), patients who had had clinical response to SIMPONI in the first trial were assessed by partial Mayo score every four weeks to confirm that the patient was still in clinical response. As shown in Exhibit 37 (right-hand panel), a greater proportion of patients in the SIMPONI 100 mg group maintained clinical response through week 54 compared to the placebo group.

Exhibit 37. Efficacy Outcomes in SIMPONI Induction and Maintenance Trials in UC

SIMPONI 6-Week Induction Trial			
	Placebo	SIMPONI 200/100 mg	Treatment difference (95% C.I.)
n	256	257	
Clinical response at week 6	30%	52%	22% (14%, 30%)
Clinical remission at week 6	6%	19%	12% (7%, 18%)
Improvement of endoscopic appearance of the mucosa at week 6	29%	43%	15% (6%, 23%)

SIMPONI 54-Week Maintenance Trial			
	Placebo	SIMPONI 100 mg	Treatment difference (95% C.I.)
n	156	154	
Clinical response through week 54	31%	51%	19% (8%, 30%)
Clinical remission at both week 30 and week 54	15%	29%	13% (4%, 22%)

Note: Clinical response was defined as a decrease from baseline in Mayo score of ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. Clinical remission was defined as a Mayo score ≤2 points, with no individual subscore >1. Improvement of endoscopic appearance of the mucosa was defined as a Mayo endoscopy subscore of 0 or 1.

Source: FDA and BMO Capital Markets.

SIMPONI is well tolerated, with most common AEs including upper respiratory tract infection, nasopharyngitis, and injection site reactions. SIMPONI carries a black box warning on risks of serious infection and malignancies such as lymphoma.

In addition to the approved and marketed UC drugs, there are several late-stage pipeline products for UC, including Takeda's vedolizumab and Pfizer's XELJANZ.

Vedolizumab is a humanized monoclonal antibody against the alpha-4-beta-7 integrin. It is being developed by Takeda as an intravenously infused inhibitor of lymphocyte trafficking. The alpha-4 beta-7 integrin is an adhesion molecule found on circulating memory T cells and it plays an important role in T cell recruitment into the gut. Under inflammatory conditions, blood vessels in the inflamed area in the gut greatly upregulate the expression of MAdCAM-1, the ligand for alpha-4 beta-7 integrin, and the interaction between alpha-4 beta-7 and MAdCAM-1 mediates the transmigration of memory T cells across the vascular endothelium into the intestinal tissue. Vedolizumab blocks the interaction and prevents T cell recruitment into the gut.

Takeda recently completed a phase 3 trial, GEMINI I, for vedolizumab in the treatment of UC. The trial enrolled 895 patients with moderate to severe UC who had failed at least one conventional therapy, including anti-TNF therapies. Patients were randomized to vedolizumab or placebo at week 0, 2, 6 for the induction of remission. Subsequently in the maintenance phase, those who responded to treatment were re-randomized to placebo or vedolizumab every 4 or 8 weeks for up to 46 weeks. The primary endpoint of the GEMINI I study was defined as the proportion of patients with a clinical response at week 6 and the proportion of patients in complete remission at week 52.

The GEMINI I trial demonstrated significant improvement in both induction and maintenance of clinical remission. (See Exhibit 38.) In the induction phase, 47.1% of patients receiving vedolizumab had a clinical response at week 6, versus 25.5% for placebo. In the maintenance phase, vedolizumab produced an improvement in clinical response of ~28-33% over the

placebo group, and this efficacy outcome compares favorably to HUMIRA, which produced an improvement of ~12% over placebo group in its ULTRA 2 phase 3 study.

The most common AEs reported in the trial are colitis, headache and nasopharyngitis.

Exhibit 38. Vedolizumab GEMINI I Phase 3 UC Trial Outcomes

		Induction	
		placebo	vedolizumab
Efficacy	Clinical Response*	25.5%	47.1%
	Clinical Remission**	5.4%	16.9%
	Mucosal Healing***	24.8%	40.9%

		Maintenance		
		placebo	vedolizumab Q8	vedolizumab Q4
Efficacy	Clinical Response*	23.8%	56.6%	52.0%
	Clinical Remission**	8.7%	20.5%	24.0%
	Mucosal Healing***	19.8%	51.6%	56.0%

*Clinical response was defined as a reduction in complete Mayo score by □30% and □3 points plus a decrease in rectal bleeding subscore of □1 or absolute rectal bleeding subscore of □ 1; ** Clinical remission was defined as complete Mayo score of □2 points, with no individual subscore >1; *** Mucosal Healing was defined as a Mayo endoscopy subscore of □1.

Source: Receptos.

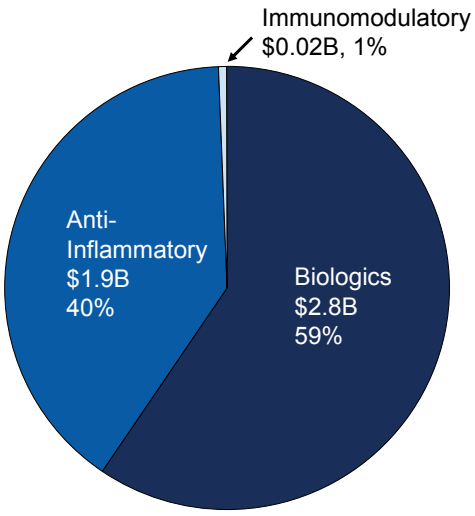
Although vedolizumab has a different mechanism of action than Receptos' RPC1063, both drugs affect lymphocyte trafficking and prevent lymphocytes, particularly T cells, from entering the brain. Another anti-integrin-based mAb, TYSABRI, has been approved for the treatment of CD as well as RRMS. However, owing to increased risk of progressive multifocal leukoencephalopathy (PML), TYSABRI is currently available only to a defined patient group through a special restricted distribution program. Nevertheless, the clinical studies for vedolizumab and TYSABRI in IBD contribute to growing evidence that supports efficacy for agents that inhibit lymphocyte trafficking, including RPC1063, in the treatment of IBD.

Pfizer's XELJANZ (tofacitinib) is a twice-daily oral janus kinase (JAK) inhibitor currently under development in CD and UC. In phase 2 studies in UC, XELJANZ caused dose-dependent clinical response in 32% to 78% of patients in the induction of clinical remission. There are several safety concerns for XELJANZ, including infections, cytopenias, and cholesterol elevations. Currently there are two phase 3 trials of XELJANZ open for enrollment in UC with expected outcomes in 2013 through 2016.

KRP203 is a S1P receptor modulator developed by Kyorin Pharmaceuticals and licensed exclusively to Novartis. KP203 is a structural analog of Novartis' GILENYA, and it has 5-fold greater selectivity for S1P1 over S1P3 and 100-fold greater selectivity over S1P2 and S1P5. Novartis recently reported completion of a European phase 2 trial examining a single dose of KRP203 in 35 UC patients. The primary endpoint is clinical remission rate after eight weeks of treatment. In March 2013, Novartis changed the status of the trial to "terminated" on clinicaltrial.gov. Receptos has studied KRP203 together with RPC1063 in a preclinical animal model of IBD and found that KRP203-treated animals had more active disease as measured by the amount of diseased tissue, or histopathology score, than did RPC1063-treated animals.

The total drug sales in IBD in 2012, including anti-inflammatory drugs (5-ASA and corticorsteroids), immunomodulators (AZA and 6-MP), and biologics (anti-TNFs and TYSABRI) were estimated to be $5 billion worldwide. (See Exhibit 39.)

Exhibit 39. Worldwide IBD Market



Source: Receptos, Datamonitor Group and BMO Capital Markets.

New therapeutics targeting lymphocyte trafficking, such as vedolimumab and RPC1063, could drive additional market growth. Compared to vedolimumab, RPC1063 has the advantage of being a more convenient, oral therapy. In patients with severe IBD, drug absorption in the GI tract may be affected and other routes of delivery, such as intravenous or subcutaneous, may be preferred. However, this may be more of a concern in CD than UC, because UC mostly affects the colon and not other parts of the GI tract.

Intellectual Property on RPC1063

As of March 2013, Receptos owned or had exclusive license from The Scripps Research Institute (TSRI) to two issued US patents, seven pending US patent applications, corresponding patents and patent applications in foreign countries, and a pending Patent Cooperation Treaty (PCT) application. Patents and patent applications in this portfolio are directed to compositions of matter for RPC1063 and multiple chemical scaffolds and certain of their metabolites, synthetic intermediates, manufacturing methods, and method of use. The composition of matter patent for RPC1063, if issued from the pending application, is expected to expire in 2029 and may be extended up to a maximum of five years under the Hatch-Waxman Act in the US and similarly extended in certain foreign countries upon regulatory approval. Other patents and patent applications in the portfolio, if issued, are expected to expire from 2030 to 2032.

Pipeline Review

RPC4046 for Eosinophilic Esophagitis

Receptos' second clinical product candidate is a recombinant anti-IL-13 antibody, RPC4046. Receptos plans to hold a pre-IND meeting with FDA by YE 13 and submit an IND in 1H14 for a phase 2 trial in subjects with eosinophilic esophagitis (EoE). RPC4046 was licensed from AbbVie for development in EoE and AbbVie retains opt-in rights for co-development after phase 2. If AbbVie does not elect to opt-in to RPC40406 development, Receptos would have an exclusive worldwide license for the development and commercialization of RPC4046, including in therapeutic areas outside of EoE.

Receptos envisions that the phase 2 trial will recruit approximately 90 subjects with confirmed active disease randomized to one of two doses of RPC4046 or placebo for 16 weeks with histologic improvement to assess eosinophil count at 12 weeks as the primary endpoint. Secondary endpoints will include clinical assessment of efficacy, patient reported outcomes, safety and biomarker evaluation.

IL-13 has long been known as an important target for inflammatory diseases and there is a long history of development of IL-13 antagonists or combined IL-4/IL-13 antagonists in eosinophilic asthma. Eosinophilic esophagitis as its name implies is an inflammatory disease associated with eosinophilic inflammation. Eosinophils are a type of white blood cell derived from myeloid precursors. Packed with protein granules, eosinophils traffic to sites of infection where they release the toxic payload of these granules in an attempt to kill the infectious agent. When dysregulated tissues mimic the cytokine/chemokine milieu of sites of infection, eosinophils traffic to these sites, triggering the release of their granule payload leading to inflammation and setting up a self perpetuating cycle. Eosinophils are sources of FGF-9, CCL18, and TGF-β1, all of which are considered pro-fibrotic. Proteins involved in eosinophil trafficking include the chemokine eotaxin and matrix protein periostin. Both these proteins are produced by epithelial cells in response to IL-13. Inflammation associated with the eosinophil is likely distinct from the more common IgE associated allergic inflammation where mast cells and basophils are involved in the inflammatory process along with eosinophils.

AbbVie conducted phase 1 trials of RPC4046 in both healthy volunteer and asthmatic populations, establishing safety of single dose IV and multiple SC doses. Receptos intends to use an IV loading dose of RPC4046 followed by SC maintenance in the planned phase 2 EoE trial.

Roche recently demonstrated proof-of-principle for IL-13 inhibition in the setting of eosinophilic asthma, and in the last month Regeneron's IL-13/IL-4 inhibitor was also shown to be effective in the setting of eosinophilic asthma. In the Roche trial, subjects with high serum periostin showed a more robust response than subjects with low serum periostin levels and, given that active EoE patients express high levels of periostin and eotaxin, one or both of these proteins may have utility as biomarkers for patient selection in future EoE.

Receptos estimates that the EoE market opportunity in the US encompasses more than 160,000 subjects in the US and approximately 145,000 subjects in the EU. As a recognized disease entity, EoE is relatively new, with the first case being described 30 years ago and the first clinical trial conducted in 1993. Clinically, the disease is manifest by esophageal dysfunction leading to difficulty swallowing, and, after GERD, it is the second most common cause of esophageal inflammation. As a disease, EoE is characterized by a bimodal age of onset, affecting pediatric and adult patients, suggesting that these represent two distinct diseases. The most commonly reported manifestations of EoE in pediatric patients are heartburn and abdominal pain/dyspepsia in 38% and 31%, respectively. Food impaction is the most common presenting symptom only in older children and adults. It is not unreasonable to suspect that EoE is mis-diagnosed in young patients as GERD and in the 4-5 years required for a correct diagnosis to occur, structural alteration of the esophagus lead to difficulty swallowing and food impaction, and sets the stage for irreversible fibrosis.

With no currently approved agents to treat EoE, the majority of patients receive dietary advice, proton pump inhibitor therapy and topical steroid treatment. Dietary therapies are aimed at eliminating the putative allergic triggers from the diet. Children receiving amino-acid based diets devoid of food allergens show clinical and endoscopic evidence of improvement. Removing food groups from diets has been shown to be successful and re-introduction of foods for a dietary Koch's postulate experiment allows for the development of a tailored diet to maximize nutritional value. In such experiments, cow's milk has been identified as the most prevalent cause of disease in adults and children, leading to a reoccurrence of symptoms in 70% of individuals following re-introduction to the diet. However, low sensitivity of allergy tests in predicting the causal food agent in the majority of patients who later undergo food reintroduction treatment suggests IgE-mediated allergies may not be the main pathophysiological mechanism in EoE; instead, a delayed hypersensitivity reaction against common, regularly consumed foods appears to be more likely. In addition, in many EoE patients aero-allergens play a role in the disease and while avoidance of these is more challenging than food allergens, identification and treatment where appropriate is important to optimal patient management. EoE is defined by a presence of persistent eosinophilic inflammation following proton pump inhibitor therapy. However, many subjects with EoE suffer from symptoms of GERD and PPI therapy may be beneficial in treating these symptoms. Additionally, while EoE is classically defined as PPI-resistant disease, there is increasing evidence of a subset of subjects who have PPI-sensitive EoE.

The mainstay of pharmacologic therapy for EoE is topical steroid use, with fluticasone and more recently budesonide as the predominant therapies. Topical steroids are highly efficacious, but the duration of benefit wanes rapidly after stopping therapy. Maintenance steroid use is practiced, but, absent data on side effects, concerns over long-term Hypothalamic-Pituitary-Adrenal (HPA) axis suppression abound. The most significant side effect associated with topical steroid use for EoE is pharyngeal-esophageal fungal infection.

Receptos' initial trials in EoE will focus on adult and adolescent populations, but an even larger unmet need is the pediatric population, where the inability to maintain adequate nutritional intake leads to a failure to thrive. It is also likely that long-term symptoms of eosinophilic inflammation lead to irreversible structural changes in the esophagus, such that neutralizing eosinophils has

limited clinical benefit, emphasizing to us the need to evaluate RPC4046 in a pediatric population. Combining the orphan disease status and unmet medical need, Receptos believes that an accelerated development and registration plan can be executed for RPC4046 in EoE.

Our View

While there are insufficient data to opine on RPC4046 as a compound, we are encouraged that Receptos has selected a compound that has a validated mechanism of action and an indication that has the potential for accelerated approval, orphan exclusivity, biomarker-based patient selection and avoids the intended direction of a major competitor. It is also noteworthy that in HUMIRA, AbbVie has a blockbuster compound in IBD and also a track record for developing highly successful compounds against established competition vis-à-vis Humira versus ENBREL and REMICADE. While the competitive landscape for developing therapies in EoE is minimal, biologics have been evaluated in eosinophilic disease, including two anti IL-5 monoclonal antibodies, mepolizumab and reslizumab.

Two small studies of mepolizumab in EoE have been reported in the literature.

- Strauman and colleagues reported the results of an 11-patient trial in 2010 - *Gut* 2010, 59:21-30. Eleven adults received either 750 mg mepolizumab (n=5) or placebo (n=6) as two infusions one week apart. Those not in complete eosinophilic response defined as less than five eosinophils per high power field (hpf) could receive two addition infusions four weeks apart of mepolizumab 1,500 mg or placebo. Eosinophil counts decreased 54% and 5% in the mepolizumab and placebo groups. However, no clinical symptom improvement was observed.

- Assa'ad and colleagues reported the results of a randomized double blind trial in 59 children - *Gastroenterology* 2011, 141(5): 1593-1604. Subjects received three infusions of mepolizumab at 0.55, 2.5 or 10 mg/kg over four weeks. Complete eosinophilic response (<5 eosinophils/hpf) was observed in 5 of 57 children, while reduced peak and mean eosinophil counts to <20/hpf were observed in 31.6% and 89.5% of children, respectively. No mepolizumab dose response was observed for eosinophils and, as in the Strauman study, no clinical benefit was observed.

The reslizumab trial enrolled 226 subjects with a mean four-year duration of moderate to severe symptoms of EoE and an esophageal biopsy specimen score of 80 eosinophils per hpf. Subjects were randomized to infusions of 1, 2, or 3 mg/kg reslizumab or placebo at weeks 0, 4, 8, and 12. The co-primary endpoints were change in peak eosinophil count and physician global assessment at week 15. Median reductions in end of treatment eosinophil counts were 59%, 67%, 64%, and 24% in the three reslizumab and placebo cohorts, respectively. PGA improvements were noted in all cohorts and not associated with change in eosinophil counts. In conclusion, the reslizumab trial both failed to show a consistent clinical improvement and a correlation between the reduction of eosinophil count and clinical outcomes.

We agree with Receptos' strategy to include adolescent subjects in the phase 2 trial since adult patients may have irreversible disease that will not show clinical symptom improvement. EoE is also a disease that is amenable to patient-reported outcomes. EoE patients develop strategies to

cope with their disease, including eating at a very slow pace, taking much longer than the rest of the family to complete a meal, holding food in the mouth, and prolonged chewing and usually drinking after each bite, especially in the case of more problematic foods such as dry rice and fibrous meat. Validation of improvement of these quality of life aspects will be required, however, as these disease-specific items are not captured by traditional quality of life tools.

The failed IL-5 trials provide some caution although the incomplete loss of eosinophils from the esophagus perhaps suggests that IL-5 inhibition is insufficient at clearing out eosinophils and those remaining perpetuate the disease. The authors also speculate that while eosinophils are the predominant cell, mast cells may also be involved and, in retrospect, should have been counted in the trial. The apparently random symptom improvement in the reslizumab trial may have been the result of patients modifying their diet despite instructions not to, emphasizing that trials in EoE are challenging to conduct.

We believe that RPC4046 could achieve break-through therapy designation and have a path for accelerated approval given the substantial morbidity associated with EoE and given the lack of available treatment options. Given the relatively limited experience of regulators with trials for EoE, we believe that there is an opportunity for sponsors, including Receptos, to work with regulators to establish relevant surrogates of clinical benefit.

Intellectual Property on RPC4046

Receptos in-licensed the patent portfolio for RPC4046 from AbbVie. As of March 2013, the portfolio consisted of one patent and one pending application in the US, and corresponding foreign pending patent applications in Europe, Japan, China, Canada, Australia, Mexico, Norway, Korea, Russia, and Costa Rica. The US composition of matter patent is expected to expire in 2028 and its term may be extended up to five additional years under the Hatch-Waxman Act, although AbbVie may choose not to pursue such extension – for example in case AbbVie chooses not enter into a global collaboration with Receptors on RPC4046 and would like to reserve the opportunity for an extension of that patent for a different drug. The pending foreign applications in the portfolio, if issued, are expected to expire in 2027 and their terms may similarly be eligible for extension, also subject to AbbVie's consent, upon regulatory approval.

Pipeline Review - Early Stage Assets

GLP-1R for Type 2 Diabetes

Receptos' third program involves preclinical small molecule agonists of glucagon-like peptide 1 receptor (GLP-1R). More specifically, Receptos focuses on positive allosteric modulators (PAMs) of GLP-1R using the company's proprietary GPCR target technology. The technology has been applied to programs with Eli Lilly and JNJ's Janssen and is the subject of an ongoing partnership with Ono Pharmaceuticals.

The first injectable GLP-1 was Amylin Pharmaceuticals' Byetta approved in 2005. Since then, Amylin's weekly GLP-1 Bydureon and Novo's daily GLP-1 Victoza have been approved, with Lilly and Sanofi in late-stage development. Novo estimates the value of the GLP-1 market at the end of 2012 to be close to $2.5 billion and growing rapidly. The development of oral GLP-1 agonists is focused on two areas, oral formulation of peptide-based compounds and small molecules.

- Novo is using Emisphere's Eligen technology to facilitate GLP-1 absorption from the gut. Novo initiated clinical development of NN9924 in 2010, NN9926 in 2011, and NN9927 in 2012. In 2Q13, Emisphere announced that the agreement with Novo had been amended to provide a $10 million payment ahead of the planned payment upon initiation of phase 2 and 3 testing.
- Oramed's ORMD-0901 is a capsulated formulation of exenatide, the active ingredient of Byetta/Bydureon. ORMD-0801 is Oramed's oral insulin currently in phase 2 testing, while a combination of ORMD-801 and ORMD-901 is in preclinical testing.
- Several publications on oral small molecules have been published but to date we are unaware of any small molecule GLP-1 agonists moving into the clinic.

Intellectual Property on GLP-1R PAMs

Receptos has pending patent applications directed to certain composition of matter of GLP-1R PAMs for multiple chemical scaffolds as well as certain method of use. As of March 2013, Receptos owned two pending patent applications in the US, the corresponding patent applications in Europe and Japan, and two pending PCT applications. The composition of matter patents in the US, if issued, are expected to expire from 2031 to 2032, and their terms may be extended to a maximum of five additional years under the Hatch-Waxman Act if a compound covered by these patents is selected for development and subsequently receives regulatory approval. The foreign applications in the portfolio, if issued, are expected to expire from 2031 to 2032 and their terms may similarly be extended upon regulatory approval.

Management

The management team at Receptos has substantial experience in drug discovery, development, and commercialization. Some members of the team have been involved in advancing therapeutics for RRMS and other immune-related diseases in their prior positions at other biotech and pharmaceutical companies.

Faheem Hasnain has been the president, chief executive officer, and a member of the board of directors since November 2010. From December 2008 to April 2010, Mr. Hasnain was the president and chief executive officer and a director at Facet Biotech Corporation, which was developing daclizumab for RRMS and was acquired by Abbott Laboratories in April 2010. From October 2008 to December 2008, Mr. Hasnain was President, Chief Executive Officer and a director of PDL BioPharma, until Facet Biotech was spun off from PDL BioPharma in December 2008. From October 2004 to September 2008, Mr. Hasnain was at Biogen Idec, most recently as executive vice president in charge of the oncology/rheumatology strategic business unit. Prior to Biogen, Mr. Hasnain held leadership roles at Bristol-Myers Squibb and GlaxoSmithKline. Mr. Hasnain has been chairman of the board of Ambit Biosciences Corporation since November 2010 and is a member of the board of directors of Somaxon Pharmaceuticals and Aragon Pharmaceuticals. Mr. Hasnain has also been chairman of the board of Sente, Inc. since 2008 and served as a member of the board of directors of Tercica, Inc. Mr. Hasnain received a B.H.K. and B.Ed from University of Windsor Ontario in Canada.

Graham Cooper joined Receptos as chief financial officer in February 2013. He was the executive vice president, finance and chief financial officer of Geron Corporation, a cancer-focused biopharma company, during 2012. From 2006 to 2011, Mr. Cooper was senior vice president, chief financial officer and treasurer of Orexigen Therapeutics, a biotechnology company focused on obesity. From 1999 to 2006, Mr. Cooper held positions of increasing responsibility including director of health care investment banking at Deutsche Bank Securities. From August 1992 to January 1995, he worked as an accountant at Deloitte & Touche. A certified public accountant, Mr. Cooper holds a B.A. in Economics from the University of California at Berkeley and an M.B.A. from the Stanford Graduate School of Business.

Marcus F. Boehm, Ph.D. is chief technology officer and has served in this role since October 2011. He was also vice president of chemistry from May 2009 to October 2011 and a co-founder. Prior to Receptos, Dr. Boehm was the Vice President of Chemistry for Apoptos, Inc. from 2007 until its acquisition by Receptos in 2009. From 2006 to 2007, Dr. Boehm worked at Biogen Idec as senior director of chemistry and served as the head of chemistry for the San Diego site. Prior to Biogen, Dr. Boehm served as vice president of chemistry at Conforma Therapeutics until its acquisition by Biogen in 2006. Previously, Dr. Boehm held positions with progressing responsibility in medicinal chemistry at Ligand Pharmaceuticals. Dr. Boehm holds a B.A. in Chemistry from the University of California, San Diego and a Ph.D. in Chemistry from State University of New York Stony Brook. He completed postdoctoral trainings at Columbia University.

Sheila Gujrathi, M.D. is chief medical officer and has served in this role since June 2011. From 2008 to 2011, she was vice president of the Global Clinical Research Group in Immunology Bristol-Myers Squibb. From 2002 to 2008, Dr. Gujrathi held roles of increasing responsibility in the Immunology, Tissue Growth and Repair clinical development group at Genentech. From 1999 to 2002, Dr. Gujrathi was a management consultant at McKinsey & Company in the healthcare practice. Dr. Gujrathi holds a B.S. in Biomedical Engineering and M.D. from Northwestern University in the accelerated Honors Program in Medical Education. She is board certified in internal medicine and completed Internal Medicine Internship and Residency at Brigham and Women's Hospital, Harvard Medical School. She completed additional training at University of California San Francisco and Stanford University in their Allergy and Immunology Fellowship Program.

Robert J. Peach, Ph.D. is chief scientific officer and has served in this role since October 2011. He was also vice president of biology from May 2009 to October 2011 and a co-founder. From 2007 to 2009, Dr. Peach co-founded and served as the vice president of biology for Apoptos, Inc., which was acquired by Receptos in 2009. From 2005 to 2007, Dr. Peach was senior director of oncology discovery at Biogen Idec. From 2001 to 2005, Dr. Peach was director of antibody discovery and tumor immunology at IDEC Pharmaceuticals and subsequently Biogen Idec, where he worked on developing new autoimmune therapeutics. From 1991 to 2000, Dr. Peach held research positions at Bristol-Myers Squibb. Dr. Peach holds a B.S. and M.S. from the University of Canterbury and a Ph.D. in Biochemistry from the University of Otago, New Zealand.

Chrysa Mineo is vice president, corporate development and has served in this role since July 2009. She is responsible for Receptos' collaborations with AbbVie, Ono, and Lilly and partnership with Janssen Pharmaceuticals. From 1997 to 2009, Ms. Mineo served roles of increasing responsibility in the biotechnology industry, leading to the position of senior director of business development at Neurocrine Biosciences. Prior to Neurocrine, Ms. Mineo played various roles in research, marketing, and business development at Amgen, DNAX Research Institute, Schering Plough, and Baxter Biotech. Ms. Mineo holds a B.S. in Zoology from the University of California, Davis and an M.B.A. from Duke University's Fuqua School of Business.

James R. Schmidt, CPA is vice president, finance and administration and has served in this role since May 2009. From 2007 to 2009, he was the senior director of finance and operations at Apoptos, Inc., which was acquired by Receptos in 2009. Previously, he was senior director of finance and operations at Conforma Therapeutics from 2001 to 2006 and assisted in the integration of companies when Conforma was acquired by Biogen in 2006. From 1986 to 2001, Mr. Schmidt served in various financial and operational roles, including chief financial officer for Kent SeaTech Corporation and controller for Medical Imaging Centers of America, Inc. He received his B.S. in Accounting and Corporate Finance from Drake University in Des Moines, Iowa.

Market

Our US market model for RPC1063 in MS is based on a prevalence of roughly 400,000, of which 75% is relapsing-remitting MS with an annual incidence of roughly 10,000, which represents the front-line population. We estimate that the ABCR drugs have 40% penetration, with a growing percent of those as oral patients. This group of new oral patients is the first of two subgroups that comprise RPC1063 patients. The second subgroup comprises patients who are on oral ABCR therapy and switch to RPC1063. We forecast pricing at $15,000 per patient in the US and expect that RCPT will partner the drug and receive a 15% royalty on sales. We forecast peak US sales of $900 million in 2024 and resulting in royalties of more than $130 million.

In terms of the ROW market, we believe that the addressable market is roughly double that of the US; however, with pricing that is likely to be half that in the US, we are forecasting peak ROW sales of $900 million in 2024, on par with that in the US. We believe that RPC1063 will also be partnered in ex-US markets and, at an estimated royalty rate of 15%, we forecast ROW royalties at greater than $130 million at peak.

Current BMO Capital Markets peak sales estimates of RPC1063 of $1.8 billion based on a probability-adjusted net present value (NPV) for RPC1063 of $19 per share. This NPV is based on 55% likelihood of success of RPC1063 in the US with an NPV of $11 and 40% likelihood of success of RPC1063 in ROW with an NPV of $8. We would note that existing US biotechnology product companies typically trade at a premium to risk-adjusted NPV estimates and are typically valued on a relative earnings or revenue multiple basis. Our $22 per share price target is based on a 25x multiple to 2020 EPS estimate of $2.49, discounted at 20%. We believe that the multiple is supported by expected EPS growth beyond 2020 and that the 20% discount rate adequately reflects risk to our estimates.

With its recent IPO, we believe RCPT's cash position has been bolstered to nearly $100 million, sufficient to fund operations into 2H14, at which time it may need to access the capital markets.

Forecasts

We estimate 2013-2018 per share losses of $(2.12), $(4.63), $(2.73), $(4.09), $(3.53), and $(2.11), respectively. Our forecast calls for RCPT to become profitable in 2019 with EPS of $0.86, increasing to $2.49 in 2020, our valuation year.

Valuation

Our $22 price target is based on 25x 2020 EPS estimate of $2.49, discounted 20%.

Exhibit 40. RCPT RPC1063 US Market

U.S. MARKET	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E
Multiple Sclerosis Prevalence	394,389	398,333	402,316	406,339	410,403	414,507	418,652	422,838	427,067	431,337	435,651	440,007	444,407
Growth 1.0%													
RRMS Prevalence	295,000	305,000	315,000	325,000	335,000	345,000	355,000	365,000	375,000	385,000	395,000	405,000	415,000
RRMS Incidence	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000
Front-Line Population													
Penetration of ABCR Drugs													
Front-Line ABCR Patients	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000
Penetration of Oral Drugs													
Front-Line Oral Patients	1,000	1,500	2,000	2,500	3,000	4,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000
RPC1063 Penetration Rate													
RPC1063 Patients	0	0	0	0	0	0	300	680	900	950	950	950	950
Front-Line Oral Patients	100	150	200	250	300	400	500	500	500	500	500	500	500
Prevalent patients on ABCR Therapy (80% of Prevalent Population)	206,751	199,697	193,506	188,047	183,196	178,856	172,284	169,304	166,293	170,161	174,318	178,606	182,953
Switch Rate to Orals													
Total ABCR Switches to Orals	33,080	47,927	61,922	75,219	87,934	100,159	113,707	125,285	136,360	139,532	142,941	146,457	150,021
RPC1063 Penetration Rate													
RPC1063 Patients	0	0	0	0	0	0	4,548	9,396	12,954	13,953	14,294	14,646	15,002
Total RPC1063 Patients	0	0	0	0	0	0	4,708	9,696	13,334	14,333	14,674	15,026	15,382
Pricing													
U.S. Sales (M)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$171.2	$475.5	$709.0	$840.9	$862.7	$884.4	$906.0
Royalty Rate 15.0%													
U.S. Royalties (M)	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$25.7**	**$71.3**	**$106.4**	**$126.1**	**$129.4**	**$132.7**	**$135.9**

Source: Company reports and BMO Capital Markets.

Exhibit 41. RCPT RPC1063 ROW Market

ROW MARKET	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E
Multiple Sclerosis Prevalence	788,778	796,665	804,632	812,678	820,805	829,013	837,303	845,676	854,133	862,674	871,301	880,014	888,814
Growth 1.0%													
RRMS Prevalence	590,000	610,000	630,000	650,000	670,000	690,000	710,000	730,000	750,000	770,000	790,000	810,000	830,000
RRMS Incidence	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000
Front-Line Population													
Penetration of ABCR Drugs													
Front-Line ABCR Patients	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000
Penetration of Oral Drugs													
Front-Line Oral Patients	2,000	3,000	4,000	5,000	6,000	8,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000
RPC1063 Penetration Rate													
RPC1063 Patients	0	0	0	0	0	0	600	1,360	1,800	1,900	1,900	1,900	1,900
Front-Line Oral Patients	200	300	400	500	600	800	1,000	1,000	1,000	1,000	1,000	1,000	1,000
Prevalent patients on ABCR Therapy (80% of Prevalent Population)	413,502	399,394	387,012	376,094	366,391	357,711	344,567	338,608	332,585	340,322	348,636	357,212	365,906
Switch Rate to Orals													
Total ABCR Switches to Orals	66,160	95,855	123,844	150,437	175,868	200,318	227,414	250,570	272,720	279,064	285,882	292,914	300,043
RPC1063 Penetration Rate													
RPC1063 Patients	0	0	0	0	0	0	9,097	18,793	25,908	27,906	28,588	29,291	30,004
Total RPC1063 Patients	0	0	0	0	0	0	9,417	19,393	26,668	28,666	29,348	30,051	30,764
Pricing													
ROW Sales (M)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$171.2	$475.5	$709.0	$840.9	$862.7	$884.4	$906.0
Royalty Rate 15.0%													
ROW Royalties (M)	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$25.7**	**$71.3**	**$106.4**	**$126.1**	**$129.4**	**$132.7**	**$135.9**

Source: Company reports and BMO Capital Markets.

Exhibit 42. RCPT Income Statement 2012A-2024E

INCOME STATEMENT ($M)	2012A	1Q13A	2Q13E	3Q13E	4Q13E	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E
REVENUES																	
Product Revenues	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 51.4	$ 142.6	$ 212.7	$ 252.3	$ 258.8	$ 265.3	$ 271.8
Collaborative Revenue	8.6	-	-	-	-	-	-	57.0	93.0	87.0	43.0	28.0	28.0	28.0	28.0	28.0	28.0
Milestones, grant revenue and other	-	-	-	-	-	-	-	50.0	50.0	50.0	-	-	-	-	-	-	-
TOTAL REVENUES	**$ 8.6**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ 115.0**	**$ 155.0**	**$ 145.0**	**$ 106.4**	**$ 182.6**	**$ 252.7**	**$ 292.3**	**$ 298.8**	**$ 305.3**	**$ 311.8**
EXPENSES (GAAP)																	
Cost of Goods Sold (COGS)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 2.6	$ 7.1	$ 10.6	$ 12.6	$ 12.9	$ 13.3	$ 13.6
R&D Expense	22.9	6.5	7.0	7.5	8.0	29.0	82.0	162.0	242.0	222.0	142.0	112.0	112.0	112.0	112.0	112.0	112.0
SG&A Expense	3.4	1.5	2.0	2.5	3.0	9.0	14.0	16.0	18.0	21.0	25.0	29.0	30.0	30.0	30.0	30.0	30.0
Other	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TOTAL EXPENSES	26.4	8.0	9.0	10.0	11.0	38.0	96.0	178.0	260.0	243.0	169.6	148.1	152.6	154.6	154.9	155.3	155.6
Operating Income	**(17.7)**	**(8.0)**	**(9.0)**	**(10.0)**	**(11.0)**	**(38.0)**	**(96.0)**	**(63.0)**	**(105.0)**	**(98.0)**	**(63.2)**	**34.5**	**100.1**	**137.7**	**143.9**	**150.0**	**156.2**
Depreciation and amortization	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EBIT	(17.7)	(8.0)	(9.0)	(10.0)	(11.0)	(38.0)	(96.0)	(63.0)	(105.0)	(98.0)	(63.2)	34.5	100.1	137.7	143.9	150.0	156.2
Interest and other income	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.4	0.6	0.8	1.1
Interest and other expense	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other Income (Expense)	(0.0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Interest and Other Income (Expense)	-	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.4	0.6	0.8	1.1
Pre-Tax Income	(17.7)	(8.0)	(9.0)	(10.0)	(11.0)	(37.9)	(95.9)	(62.9)	(104.9)	(97.9)	(63.1)	34.6	100.2	138.0	144.5	150.9	157.3
Income Taxes	-	-	-	-	-	-	-	-	-	2.4	-	8.6	25.1	34.5	36.1	37.7	39.3
Net Income (GAAP)	**$ (17.7)**	**$ (8.0)**	**$ (9.0)**	**$ (10.0)**	**$ (11.0)**	**$ (37.9)**	**$ (95.9)**	**$ (62.9)**	**$ (104.9)**	**$ (100.3)**	**$ (63.1)**	**$ 25.9**	**$ 75.2**	**$ 103.5**	**$ 108.3**	**$ 113.2**	**$ 118.0**
EPS (GAAP) (basic)	$ (0.28)	$ (0.45)	$ (0.50)	$ (0.56)	$ (0.61)	$ (2.12)	$ (4.63)	$ (2.73)	$ (4.09)	$ (3.53)	$ (2.11)	$ 0.86	$ 2.49	$ 3.41	$ 3.55	$ 3.70	$ 3.84
EPS (GAAP) (diluted)	**$ (0.28)**	**$ (0.45)**	**$ (0.50)**	**$ (0.56)**	**$ (0.61)**	**$ (2.12)**	**$ (4.63)**	**$ (2.73)**	**$ (4.09)**	**$ (3.53)**	**$ (2.11)**	**$ 0.86**	**$ 2.49**	**$ 3.41**	**$ 3.55**	**$ 3.70**	**$ 3.84**
Weighted average shares outstanding (diluted)	62.7	17.6	17.9	17.9	17.9	17.8	20.5	23.1	25.6	27.6	30.0	30.1	30.2	30.4	30.5	30.6	30.7

Source: Company reports and BMO Capital Markets.

Exhibit 43. RCPT Balance Sheet 2012A-2024E

BALANCE SHEET (M)	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E
Current Assets													
Cash and cash equivalents	$ 5.4	$ 64.5	$ 71.3	$ 11.0	$ 8.8	$ 11.1	$ 25.6	$ 54.2	$ 132.0	$ 238.1	$ 349.1	$ 464.8	$ 585.5
Short-term investments	-	-	-	-	-	-	-	-	-	-	-	-	-
Total cash, cash equivalents, and short-term investments	$ 5.4	$ 64.5	$ 71.3	$ 11.0	$ 8.8	$ 11.1	$ 25.6	$ 54.2	$ 132.0	$ 238.1	$ 349.1	$ 464.8	$ 585.5
Accounts Receivables	-	-	-	-	-	-	-	-	-	-	-	-	-
Restricted Cash	-	-	-	-	-	-	-	-	-	-	-	-	-
Inventories	-	-	-	-	-	-	-	-	-	-	-	-	-
Prepaid and other current assets	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Total Current Assets	$ 6.2	$ 65.3	$ 72.1	$ 11.8	$ 9.6	$ 11.9	$ 26.4	$ 54.9	$ 132.7	$ 238.9	$ 349.9	$ 465.6	$ 586.2
Leasehold improvements	-	-	-	-	-	-	-	-	-	-	-	-	-
Property and equipment, net	0.5	(2.1)	(4.7)	(7.3)	(9.9)	(12.6)	(15.2)	(17.8)	(20.4)	(23.1)	(25.7)	(28.3)	(30.9)
Patents and licensed technology	-	-	-	-	-	-	-	-	-	-	-	-	-
Intangibles, net	-	-	-	-	-	-	-	-	-	-	-	-	-
Other assets	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
TOTAL ASSETS	**$ 6.9**	**$ 63.4**	**$ 67.5**	**$ 4.6**	**$ (0.3)**	**$ (0.6)**	**$ 11.3**	**$ 37.3**	**$ 112.4**	**$ 216.0**	**$ 324.3**	**$ 437.5**	**$ 555.4**
Current Liabilities													
Accounts payable	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Accrued payroll	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Accrued expenses	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
Accrued interest	-	-	-	-	-	-	-	-	-	-	-	-	-
Payables to related parties	-	-	-	-	-	-	-	-	-	-	-	-	-
Income taxes payable	-	-	-	-	-	-	-	-	-	-	-	-	-
Current portion of other long-term obligations	-	-	-	-	-	-	-	-	-	-	-	-	-
Current portion of convertible notes payable	-	-	-	-	-	-	-	-	-	-	-	-	-
Current portion of deferred revenue	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
Other current liabilities	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Total Current Liabilities	$ 6.1	$ 6.1	$ 6.1	$ 6.1	$ 6.1	$ 6.1	$ 6.1	$ 6.1	$ 6.1	$ 6.1	$ 6.1	$ 6.1	$ 6.1
Convertible notes payable	-	-	-	-	-	-	-	-	-	-	-	-	-
Accrued interest on convertible notes payable	-	-	-	-	-	-	-	-	-	-	-	-	-
Other long-term obligations, less current portion	-	-	-	-	-	-	-	-	-	-	-	-	-
Deferred revenue, less current portion	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Deferred rent	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Other liabilities	-	-	-	-	-	-	-	-	-	-	-	-	-
TOTAL LIABILITIES	$ 7.1	$ 7.1	$ 7.1	$ 7.1	$ 7.1	$ 7.1	$ 7.1	$ 7.1	$ 7.1	$ 7.1	$ 7.1	$ 7.1	$ 7.1
Shareholder's Equity													
Series A convertible preferred stock	27.3	27.3	27.3	27.3	27.3	27.3	27.3	27.3	27.3	27.3	27.3	27.3	27.3
Series B convertible preferred stock	12.6	12.6	12.6	12.6	12.6	12.6	12.6	12.6	12.6	12.6	12.6	12.6	12.6
Common stock, at par	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Additional paid-in capital	7.6	102.0	202.0	202.0	302.0	402.0	477.0	477.0	477.0	477.0	477.0	477.0	477.0
Deferred compensation	-	-	-	-	-	-	-	-	-	-	-	-	-
Notes receivable from shareholders	-	-	-	-	-	-	-	-	-	-	-	-	-
Unrealized gains (losses) on short-term investments	-	-	-	-	-	-	-	-	-	-	-	-	-
Accumulated other comprehensive income	-	-	-	-	-	-	-	-	-	-	-	-	-
Accumulated deficit	(47.6)	(85.5)	(181.4)	(244.3)	(349.1)	(449.4)	(512.6)	(486.6)	(411.4)	(307.9)	(199.6)	(86.4)	31.5
TOTAL SHAREHOLDER'S EQUITY (DEFICIT)	$ (0.2)	$ 56.3	$ 60.5	$ (2.4)	$ (7.3)	$ (7.6)	$ 4.3	$ 30.2	$ 105.4	$ 208.9	$ 317.2	$ 430.4	$ 548.4
TOTAL LIABILITIES AND SHAREHOLDER'S EQUITY	**$ 6.9**	**$ 63.4**	**$ 67.5**	**$ 4.6**	**$ (0.3)**	**$ (0.6)**	**$ 11.3**	**$ 37.3**	**$ 112.4**	**$ 216.0**	**$ 324.3**	**$ 437.5**	**$ 555.4**

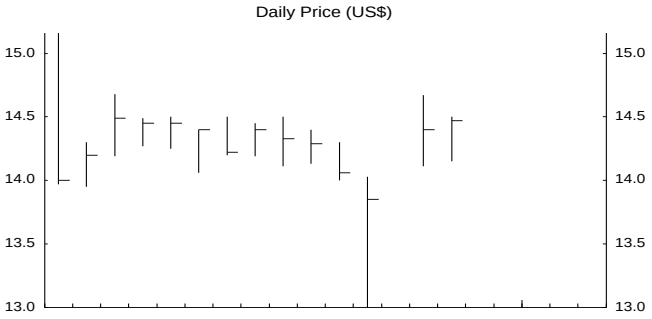
Source: Company reports and BMO Capital Markets.

Exhibit 44. RCPT Cash Flow Statement 2012A-2024E

CASH FLOW STATEMENT (M)	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E
Cash Flow From Operating Activities													
Net Income	$ (17.7)	$ (11.0)	$ (31.4)	$ (19.5)	$ (30.0)	$ (33.5)	$ (4.4)	$ 12.0	$ 23.7	$ 26.9	$ 28.1	$ 29.2	$ 30.4
Adjustments to reconcile net income to cash from operations													
Depreciation & amortization	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Deferred revenue	(2.2)	-	-	-	-	-	-	-	-	-	-	-	-
Stock-based compensation	0.2	-	-	-	-	-	-	-	-	-	-	-	-
Deferred rent	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Deferred income taxes	-	-	-	-	-	-	-	-	-	-	-	-	-
Other	-	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Working Capital Adjustments													
Prepaids and other assets	(0.3)	-	-	-	-	-	-	-	-	-	-	-	-
Accounts payable	0.7	-	-	-	-	-	-	-	-	-	-	-	-
Accrued payroll	0.2	-	-	-	-	-	-	-	-	-	-	-	-
Accrued expenses	-	-	-	-	-	-	-	-	-	-	-	-	-
Accrued interest	-	-	-	-	-	-	-	-	-	-	-	-	-
Payables to related parties	-	-	-	-	-	-	-	-	-	-	-	-	-
Income taxes payable	-	-	-	-	-	-	-	-	-	-	-	-	-
Deferred revenue	-	-	-	-	-	-	-	-	-	-	-	-	-
Deferred rent	-	-	-	-	-	-	-	-	-	-	-	-	-
Other assets and liabilities, net	-	-	-	-	-	-	-	-	-	-	-	-	-
Total Working Capital Increase (Decrease)	$ 0.6	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
TOTAL CASH FROM OPERATIONS	**$ (18.4)**	**$ (10.3)**	**$ (30.8)**	**$ (18.8)**	**$ (29.3)**	**$ (32.8)**	**$ (3.7)**	**$ 12.6**	**$ 24.3**	**$ 27.6**	**$ 28.7**	**$ 29.9**	**$ 31.1**
Cash From Investing Activities													
Purchases of short-term investments	(0.2)	-	-	-	-	-	-	-	-	-	-	-	-
Maturities and sales of short-term investments	-	-	-	-	-	-	-	-	-	-	-	-	-
Purchases of property and equipment	-	-	-	-	-	-	-	-	-	-	-	-	-
Acquisitions of patents	-	-	-	-	-	-	-	-	-	-	-	-	-
Acquisitions of licenses	-	0.0	(0.0)	(0.0)	0.0	0.0	0.0	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Increase in patents, deposits and other assets	-	-	-	-	-	-	-	-	-	-	-	-	-
TOTAL CASH FROM INVESTING	$ (0.2)	$ 0.0	$ (0.0)	$ (0.0)	$ 0.0	$ 0.0	$ 0.0	$ (0.0)	$ (0.0)	$ (0.0)	$ (0.0)	$ (0.0)	$ (0.0)
Cash From Financing Activities													
Proceeds from long-term debt borrowings	12.6	-	-	-	-	-	-	-	-	-	-	-	-
Repayment of borrowings	-	-	-	-	-	-	-	-	-	-	-	-	-
Proceeds from issuance of series B convertible preferred stock	-	-	-	-	-	-	-	-	-	-	-	-	-
Proceeds from exercise of common stock options	0.2	-	-	-	-	-	-	-	-	-	-	-	-
Costs paid in connection with initial stock offering	-	-	-	-	-	-	-	-	-	-	-	-	-
Other	-	-	-	-	-	-	-	-	-	-	-	-	-
TOTAL CASH FROM FINANCING	$ 12.7	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Increase (decrease) in cash and cash equivalents	(5.9)	(10.3)	(30.8)	(18.8)	(29.3)	(32.8)	(3.7)	12.6	24.3	27.6	28.7	29.9	31.1
Cash and cash equivalents at beginning of year	11.3	74.9	102.1	29.9	38.1	43.9	29.3	41.5	107.6	210.5	320.4	435.0	554.4
Cash and cash equivalents at end of year	$ 5.4	$ 64.5	$ 71.3	$ 11.0	$ 8.8	$ 11.1	$ 25.6	$ 54.2	$ 132.0	$ 238.1	$ 349.1	$ 464.8	$ 585.5
	-												

Source: Company reports and BMO Capital Markets.

RECEPTOS INC (RCPT)



Last Daily Data Point: May 29, 2013

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