Trevena, Inc.

TRVN : NASDAQ : US$7.77

BUY

Target: US$17.00

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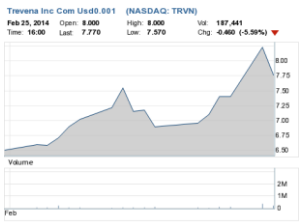
COMPANY STATISTICS:

Forecast Return:	119%
Shares Out (M):	25.8
Market Cap (M):	US$200.5
52-week Range:	US$6.00 - 8.98

EARNINGS SUMMARY:

FYE Dec		2013E	2014E	2015E
Revenue:		0.1	0.0	65.0
EPS:		(1.18)	(2.82)	1.49
Revenue:	Q1	0.0A	0.0	-
	Q2	0.0A	0.0	-
	Q3	0.0A	0.0	-
	Q4	0.0	0.0	-
Total		0.1	0.0	65.0
EPS:	Q1	(0.30)A	(0.59)	-
	Q2	(0.30)A	(0.67)	-
	Q3	(0.30)A	(0.74)	-
	Q4	(0.28)	(0.82)	-
Total		(1.18)	(2.82)	1.49

SHARE PRICE PERFORMANCE:



Source: Interactive Data Corporation

COMPANY DESCRIPTION:

TRVN is a clinical stage biotechnology company focused on new chemical entities that selectively target G protein coupled receptors. TRVN has advanced two product candidates into the clinic: TRV130 for postoperative pain and TRV027 in acute heart failure. TRVN is also quickly moving its lead preclinical products for various CNS diseases into the clinic.

All amounts in US$ unless otherwise noted.

Life Sciences -- Biotechnology

BIASED RECEPTOR SIGNAL PLATFORM BIASED TOWARD UPSIDE: INITIATING WITH BUY, $17 PRICE TARGET

Investment recommendation

Initiating coverage with BUY, $17 target on potential of TRV027 in AHF and TRV130 in first-line post-op pain. TRVN's lead product is a Ph2b next-generation inotrope for AHF that has positive Phase 2a data and new Ph2b data due mid-2015. Phase 2-ready TRV130 has generated Ph1b data suggesting superior efficacy and safety data to IV PCA morphine standard of care. We expect Phase 2 data in 2015 to be positive. Our $17.00 target is based on a pNPV analysis.

Investment highlights

- **G-protein biased ligand platform: novel approaches to modulate signaling of known receptors**. TRVN's proprietary ABLE platform identifies drugs that signal preferentially through one of the two intracellular pathways of known G-protein coupled receptors (GPCRs). One of these paths is often responsible for a drug's benefits, the other for side effects. Biased signaling can refine and optimize a drug's profile.
- **TRV027: a next-generation inotrope that could improve heart function, address a major unmet need in acute heart failure (AHF)**. TRVN's lead drug TRV027 may improve heart muscle contractility and function, unlike current standard-of-care drugs, which only reduce fluid load and blood pressure. Phase 1b data showed good efficacy in important surrogate and biomarkers of AHF including wedge pressure, mean arterial pressure and cardiac index, along with very good safety in these fragile patients. We expect the Phase 2b trial to have positive composite index efficacy data in mid-2015 and model $640M in peak US sales.
- **TRV130: a biased signaling mu-opioid agonist with potential for better pain relief and safety in the post-operative setting**. TRV130 is a biased signaling ligand to the mu-opioid receptor that is in development for first-line post-operative pain. TRV130 Phase 1b data suggests the drug could actually provide stronger pain relief than IV PCA morphine with less nausea, vomiting and respiratory depression at the optimal dose. Ph2 trials are to start soon and we model $790M in peak sales.

Figure 1: TRVN upcoming catalysts

Expected date	Drug/Program	Item	Impact
Q1/14	Parkinson's disease	Clinical candidate selection	+
Q2/14	TRV130 in postoperative pain	Ph2 trial initiation	+
Q2/14	TRV734 in acute/chronic pain	Ph1 trial initiation	+
Q4/14	TRV734 in acute/chronic pain	Ph1 data	++
Q1/15	TRV130 in postoperative pain	Ph2 data	+++

Source: Company reports and Canaccord Genuity estimates

Figure 2: TRVN pipeline

Drug/ Program	Indication	Licensing/ Partnership	Preclinical	Phase 1	Phase 2	Phase 3	Post-Marketing
TRV130	Postoperative pain	Wholly owned					
TRV027	Acute heart failure	Forrest Labs					
TRV734	Acute/chronic pain	Wholly owned					
Delta opioid biased ligand	Parkinson's, depression, pain	Wholly owned					

Source: Company filings

INVESTMENT THESIS

We think Trevena's G-protein biased signaling technology platform has the potential to generate multiple potential blockbuster drug candidates such as TRV027 for acute heart failure and TRV130 for acute post-operative pain. We view Trevena's ABLE drug discovery platform as incredibly unique and versatile, and see it as using a new approach to drug candidate profile optimization. Trevena's candidates can take advantage of current understanding of G protein function and may have the optimized therapeutic profile for a current drug class.

TRV027 may become a key therapy in a new emerging drug class of acute heart failure (AHF) therapies: a new generation of inotropes that improve contractility without stressing cardiac tissue. TRV027 is a beta-arrestin signal-biased agonist of the Angiotensin 2 Type 1 receptor (AT1R). AT1R signaling is blocked by current drugs as its G protein pathway signaling caused fluid retention and blood pressure elevation, making the heart work harder to pump blood and worsening the condition. ATR1 beta-arrestin signaling improves cardiac contractility, however, a desirable effect that would benefit AHF. TRV0127 appears to benefit cardiac contractility in just such a manner without increasing fluid retention and blood pressure. There is no HF drug that safely increases cardiac output today. Standard of care is diuretics, including furosemide (Natrecor), to reduce fluid load until patients stabilize and vasodilators to reduce blood pressure. First-generation inotropes are rarely used according to doctors we have spoken to as they stress heart tissue and damage the heart in the longer term.

Phase 2a data has shown TRV027 able to improve key biomarkers of heart function as well as vascular and renal health. Stable AHF Phase 2a data showed statistically significant dose-dependent decreases in mean arterial pressure in a subset of patients proven to have RAS activation (which represents ~50% of heart failure patients). Patients on '027 also showed numeric decreases in pulmonary capillary wedge pressure (PCWP), a biomarker closely related to dyspnea, the FDA's registrational endpoint for AHF. Finally, 027 showed stable cardiac index, which is marker of cardiac muscle function and contractility, while treatment with AT1 signal antagonists such as Angiotensin receptor blockers (ARBs) has been associated with decreases in cardiac index. Meanwhile, safety in this medically fragile Phase 2 population was positive, with only transient mild low blood pressure. There was no increase in heart rate seen, a marker for stress on heart tissue.

We view TRVN's Phase 2b trial is well designed with a good chance of success, which could trigger an opt-in by Forest/Actavis: we model $640M peak US sales potential . We think Phase 2b design using a composite endpoint (including standard CV outcomes, dyspnea and length of stay) will very meaningfully inform understanding of TRV027's activity and a potential Phase 3 pivotal design. We think, based on the strength of Ph2a response seen with 14 hours' infusion, a larger trial with longer follow-up will show clinically meaningful benefit supporting Ph3 development. We think Forest/Actavis would opt in on positive data such as this, triggering an assumption of clinical costs by Forest and a $65M option payment. TRVN would then be eligible for further milestones (up to $430M) and 10-20% royalties on sales.

TRV130 could become a key treatment option for front-line post-operative pain relief, which remains suboptimal to this day despite multiple treatments. 50-75% of post-

operative patients (depending on procedure type) still suffer from moderate to severe pain despite first-line morphine therapy and adjunct and rescue treatment options. Clinicians are concerned about traditional opiate side effects including respiratory depression, nausea and vomiting, which can all worsen patient outcomes and satisfaction, and also increase care costs and hospital stay. As such, optimized front-line treatment options would be welcomed by clinicians. TRV130 is a G-protein signaling pathway biased ligand of the mu-opioid receptor, which is hypothesized to increase G protein mediated pain relief and not trigger beta-arrestin mediate respiratory depression, nausea and vomiting.

Phase 1b data suggests a differentiated, superior therapeutic profile from current mu-opioid therapies: better efficacy, less respiratory depression. Data generated in healthy volunteers using a evoked cold-temperature pain study suggested that TRV130 could actually have more potent and quicker pain relief than morphine, generating statistically significant increase in latency of intolerable pain as well as pupil constriction (an accepted biological marker of opiate analgesia), and is associated with lower rates of nausea at optimum doses and lower rates of respiratory depression. Overall, we see Phase 1b data as showing strong efficacy with very good safety compared to current front-line post-op therapy.

We think the planned Phase 2 program has a high chance of success and will support advancement into Phase 3: we model $790M in US peak sales. We believe the strength of the Ph1b data, both efficacy and safety, supports very good chances of success in a planned Phase 2 post-operative pain relief trial. We think if the trial is set up like most Phase 2 post-operative pain trials, we think it has a very good chance of success and would support Phase 3 development. TRVN intends to commercialize TRV130 itself with a model hospital-based sales force of 75-100 sales reps and a strategy similar to one planned by AcelRx for its drug sublingual sufentanil tab Zalviso, which has an action date of late July 2014. We model $790M in peak US sales for TRV130 for first-line post-operative pain, and note the start of a Phase 1 program for TRV734, the oral version of the drug, which could be developed for acute or chronic pain. '734 could have an even larger market opportunity, but would have significantly stricter commercial constraints given greater abuse potential in the outpatient setting. We believe TRVN intends to partner this drug after generating proof-of-concept data.

INVESTMENT RISKS

Clinical risk – TRVN's planned Phase 2 trials may not be successful. *TRV027*: We note that the Phase 1b trial did not reach statistical significance in key efficacy measures due to an unexpected benefit experienced by the placebo group. There is no guarantee Ph2b or Phase 3 data could not be similarly confounded. Further, the current Phase 2b trial uses a substantially different endpoint than that of the Phase 1b, generating standard clinical risks associated with clinical trial design. *TRV130*: We note that all pain trials have a high risk of unusual placebo response which can frequently confound statistics despite strong efficacy of the investigational drug.

Clinical risk – Additional trials may show TRV027 and TRV130 to have an unacceptable safety and/or tolerability profiles. In the first healthy volunteer study, one patient who received a low dose of '027 has a severe episode of syncope. This was thought to be procedurally related, and this side effect was never seen again in all further development.

Drops in blood pressure have been seen in clinical development, necessitation drug discontinuation in one patient. While moderate drops in pressure are beneficial in heart failure, large drops can be problematic. *TRV130:* Data suggesting better safety for '130 versus current opioid drugs is preliminary but a large part of the promise of '130. Should the drug's nausea, vomiting and respiratory depression profile prove to be no different than that of current drugs, its commercial potential would be greatly curtailed.

Regulatory risk – TRV130 may not be approved by the FDA and/or EMA despite Phase 3 success, or scheduling/REMS restriction may greatly impair the drug's chance of success. TRV130 will very likely be scheduled as a controlled substance by the US DEA as it functions through the mu-opioid receptor. It will likely be designated schedule II like morphine, which complicates distribution and use of the therapy, limiting commercial potential. TRV must be able to address this in its commercial efforts.

Competitive risk –*TRV027*: '027 may compete with first-generation inotropes for use in AHF. However unpopular and dangerous these drugs are in select patients, they are still cheap and effective in the very short term. Further, Novartis' serelaxin, which works through a similar, overlapping mechanism, is under FDA review for treatment of heart failure. We think serelaxin's efficacy data is weak thus far, and likely will not support FDA approval (it was recently rejected by the EMA). However, if approved, it would have a head start on '027 for the market even with only weak efficacy data. We believe Amgen/Cytokinetics' Phase 2b omecamtiv, also in development for AHF, has a complementary mechanism to '027. ***TRV130***: '130 will be up against established and newer competitors. IV PCA morphine for front line is a cheap standard of care that has been used in the hospital setting for decades, leading to high levels of clinician familiarity and comfort. TRVN's marketing effort will have to generate proof of cost savings to compete. Further AcelRx is developing a new sufentanil tablet for hospital base post-operative use that we think will likely be approved in July 2014, and be associated with fewer administration errors that IV PCA morphine. While we think the product will be premium priced, it may have appealing cost-saving features and will very likely have a number of years head-start in marketing.

Commercial risk –.Both TRV027 and TRV130 will likely mainly be used in the hospital setting: a very cost conscious environment. Hospitals operate on very slim margins comparatively and further of often reimbursed by payors on a procedural or per admission basis. As such, any premium-priced therapy added to procedures of in-patient standard of care contributes to a hospital's expenses but does not increase reimbursement. Therefore we believe it is critical for TRVN to general cost-savings-to-the-hospital data (usually around length of stay or recovery unit time) to generate healthy adoption by hospitals.

VALUATION

We have built our valuation of TRVN using a probability-weighted NPV model of peak sales.

Potential upside to valuation

We see the following as potential drivers of upside to our model:

- **Stronger-than-expected Phase 2 data from either TRV027 or TRV130.** Should TRV027 show statistically significant major benefit in CV outcomes in Phase 2, we think it would exceed current expectations (a benefit in the composite only). Further, we think there is upside to TRVN should TRV130 prove to have significantly stronger and more rapid pain relief than IV PCA morphine.
- **Better-than-expected pharmaco-economic data from either program.** Should either drug prove to shorten length of stay by 36 hours or greater, we believe this could drive uptake higher than we have modeled, representing upside to our peak sales estimates and additional value to the share price.
- **Earlier-than-expected partnership for TRV734 based on strength of TRV130 data.** TRV734 works through the very same mechanism as TRV130. Should TRV130 Phase 2 data be particularly strong, TRVN may be able to strike a rich partnership for '734 even before proof of concept specific to that drug is generated.
- **Rapid development and positive data for delta opioid drugs in central nervous system (CNS) disorders**. TRVN also has a preclinical program for delta-opioid targeted drugs that could treat Parkinson's, depression and other CNS disorders. However, no candidate from this program is ready to enter the clinic soon. Should preclinical development go faster than expected, a new clinical program could add upside to shares.

Potential downside to valuation

As with all companies in commercial and clinical development, there always exists the risk of failed or inconclusive clinical trials, slower-than-expected commercial launches, or lower-than-expected peak sales, which could lead to downward pressure on the stock. For more detailed risks, see our "Investment risks" section

Figure 3: TRVN valuation

Product Development

Drug name	Indication	Status	Launch	Years to Launch	Years to Launch plus 6	Success	Sales (US$m)	Probability weighted Peak Sales (US$m)	Royalty	Profitability	Probability weighted Peak Profit (US$m)	Discount Factor	NPV (US$)
TRV130	Acute postoperative pain	Phase 2a	2018	4	12	55%	791.3	435.2	100%	90%	391.68	14.55	15.69
TRV027	Acute heart failure	Phase 2b	2020	6	12	45%	643.5	289.6	18%	100%	52.12	14.55	2.09
										Total			**17.77**

Source: Company reports and Canaccord Genuity estimates

REVENUE MODEL AND FINANCIALS

Our financial model forecast is built on the assumption that TRV130 will launch in the US by the end of 2018 for use in first-line post-operative pain. Our TRV130 market model in postoperative pain assumes peak TRV130 market share of 20-30% in US inpatient and outpatient surgeries and 10-15% in US inpatient/outpatient non-surgical setting. We assume peak sales will be reached in 2026, eight years from launch.

We assume that TRVN will price a 2.5-day course of TRV130 in the inpatient setting around $200 and an eight-hour course of TRV130 in the outpatient setting around $20 in the US at launch. However, we think this is a very conservative estimate and we expect further market research to support higher pricing based on superior phamacoeconomics and safety profile. Overall, we forecast peak sales for TRV130 in 2026 of ~$790M. We have not modeled potential revenue streams (either sales or royalties) from EU or ROW, which could increase the peak sales figure significantly.

For TRV027, we have built our financial model around the assumption that the drug will launch in the US in the beginning of 2020. Our TRV027 market model in acute heart failure assumes peak market share of 30% in the US. We assume peak sales will be reached in 2026, six years from launch.

We assume the ongoing TRV027 Phase 2 trial will yield positive data in mid 2015 and Forest will exercise the opt-in rights to the program around this period. We assume that TRVN/ Forest will price a course of TRV027 around $2,500 in the US at launch. Overall, we forecast peak sales for TRV027 in 2026 of ~$640M. Assuming a blended tiered US royalty of 18%, TRVN could receive $130M in royalties from peak year sales. We have not modeled potential revenue streams from EU or ROW, which could increase the upside for TRVN shares further.

TRVN reported current assets of $48.0M on September 30, 2013 and received $60.0M net proceeds from recent initial public offering. We think TRVN has sufficient cash to operate at least until the end of 2015, at which point we think the company will likely still have 2-3 quarters of operating cash remaining and receive the $65M opt-in payment from Forest, at which point Forest will be responsible for the ongoing research and development costs as well as the cost of commercialization for TRV027. However, this amount may not be able to fund the Phase 3 trials for TRV130 through completion, and we think TRVN may consider an equity issue in 2016 to secure operating expenses as well as funds for further clinical development of TRV130 for first-line postoperative pain management.

Figure 4: TRVN revenue projections – TRV130

		2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
TRV130 (post-op pain) market model														
US population	1.0%	321.2	324.4	327.6	330.9	334.2	337.6	340.9	344.3	347.8	351.3	354.8	358.3	361.9
Hospital inpatient setting		14,890,702	15,190,005	15,495,324	15,806,780	16,124,497	16,448,599	16,779,216	17,116,478	17,460,519	17,811,476	18,169,486	18,534,693	18,907,240
Incidence	1.0%	*0.046364*	*0.046827*	*0.047295*	*0.047768*	*0.048246*	*0.048729*	*0.049216*	*0.049708*	*0.050205*	*0.050707*	*0.051214*	*0.051726*	*0.052244*
Surgical		11,168,027	11,392,504	11,621,493	11,855,085	12,093,372	12,336,449	12,584,412	12,837,359	13,095,390	13,358,607	13,627,115	13,901,020	14,180,430
% of hospital inpatient	0.0%	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
Non-surgical		2,792,007	2,848,126	2,905,373	2,963,771	3,023,343	3,084,112	3,146,103	3,209,340	3,273,847	3,339,652	3,406,779	3,475,255	3,545,108
% of hospital inpatient	0.0%	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
Hospital outpatient setting		18,161,870	18,893,794	19,655,214	20,447,319	21,271,346	22,128,581	23,020,363	23,948,083	24,913,191	25,917,193	26,961,655	28,048,210	29,178,553
Incidence	3.0%	*0.056549*	*0.058245*	*0.059992*	*0.061792*	*0.063646*	*0.065555*	*0.067522*	*0.069548*	*0.071634*	*0.073783*	*0.075997*	*0.078277*	*0.080625*
Surgical		8,172,842	8,502,207	8,844,846	9,201,293	9,572,106	9,957,861	10,359,163	10,776,637	11,210,936	11,662,737	12,132,745	12,621,695	13,130,349
% of hospital outpatient	0.0%	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*
Non-surgical		4,495,063	4,676,214	4,864,665	5,060,711	5,264,658	5,476,824	5,697,540	5,927,151	6,166,015	6,414,505	6,673,010	6,941,932	7,221,692
% of hospital outpatient	0.0%	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*
Total addressable patients		26,627,938	27,419,051	28,236,378	29,080,861	29,953,479	30,855,247	31,787,218	32,750,486	33,746,188	34,775,500	35,839,648	36,939,901	38,077,579
TRV130														
Inpatient segment														
% of inpatient - surgical						*1.0%*	*4.0%*	*7.0%*	*10.0%*	*12.0%*	*14.0%*	*16.0%*	*18.0%*	*20.0%*
Number of pts on Tx						120,934	493,458	880,909	1,283,736	1,571,447	1,870,205	2,180,338	2,502,184	2,836,086
% of inpatient - non-surgical						*1.0%*	*3.0%*	*4.0%*	*5.0%*	*6.0%*	*7.0%*	*8.0%*	*9.0%*	*10.0%*
Number of pts on Tx						30,233	92,523	125,844	160,467	196,431	233,776	272,542	312,773	354,511
Outpatient segment														
% of outpatient - surgical						*1.0%*	*5.0%*	*10.0%*	*14.0%*	*18.0%*	*22.0%*	*26.0%*	*28.0%*	*30.0%*
Number of pts on Tx						95,721	497,893	1,035,916	1,508,729	2,017,968	2,565,802	3,154,514	3,534,074	3,939,105
% of outpatient - non-surgical						*1.0%*	*3.0%*	*5.0%*	*7.0%*	*9.0%*	*11.0%*	*13.0%*	*14.0%*	*15.0%*
Number of pts on Tx						52,647	164,305	284,877	414,901	554,941	705,596	867,491	971,870	1,083,254
Number of pts on TRV130						299,535	1,248,179	2,327,546	3,367,833	4,340,787	5,375,378	6,474,886	7,320,901	8,212,955
Blended TRV130 penetration						*1%*	*4%*	*7%*	*10%*	*13%*	*15%*	*18%*	*20%*	*22%*
Gross price - inpatient	3.0%					200.00	206.00	212.18	218.55	225.10	231.85	238.81	245.97	253.35
Net revenue - inpatient	0.5%					25.57	102.09	180.66	266.94	336.57	412.57	495.42	585.60	683.66
Gross price - outpatient	3.0%					20.00	20.60	21.22	21.85	22.51	23.19	23.88	24.60	25.34
Net revenue - outpatient	0.5%					2.51	11.54	23.70	35.56	48.98	64.15	81.23	93.74	107.62
Total TRV130 Revenue						28.08	113.63	204.36	302.49	385.55	476.72	576.65	679.34	791.28

Source: Company reports and Canaccord Genuity estimates

Figure 5: TRVN revenue projections (cont'd) – TRV027

		2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
TRV027 (acute heart failure) market model														
US population	1.0%	321.2	324.4	327.6	330.9	334.2	337.6	340.9	344.3	347.8	351.3	354.8	358.3	361.9
Primary population		1,107,701	1,141,153	1,175,616	1,211,120	1,247,695	1,285,376	1,324,194	1,364,185	1,405,383	1,447,826	1,491,550	1,536,595	1,583,000
Incidence	2.0%	*0.003449*	*0.003518*	*0.003588*	*0.003660*	*0.003733*	*0.003808*	*0.003884*	*0.003962*	*0.004041*	*0.004122*	*0.004204*	*0.004288*	*0.004374*
Secondary population		1,091,491	1,118,942	1,147,083	1,175,932	1,205,507	1,235,825	1,266,906	1,298,769	1,331,433	1,364,919	1,399,246	1,434,437	1,470,514
Incidence	1.5%	*0.003398*	*0.003449*	*0.003501*	*0.003554*	*0.003607*	*0.003661*	*0.003716*	*0.003772*	*0.003828*	*0.003886*	*0.003944*	*0.004003*	*0.004063*
Hospitalization due to AHF		1,215,229	1,250,826	1,287,471	1,325,194	1,364,027	1,404,003	1,445,156	1,487,520	1,531,132	1,576,027	1,622,244	1,669,823	1,718,803
Incidence in primary population		*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*
Incidence in secondary population		*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
Increased RAS activation		607,614	625,413	643,736	662,597	682,014	702,002	722,578	743,760	765,566	788,014	811,122	834,911	859,401
incidence	0.0%	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Total addressable patients		607,614	625,413	643,736	662,597	682,014	702,002	722,578	743,760	765,566	788,014	811,122	834,911	859,401
TRV027 penetration rate								*3.0%*	*8.0%*	*15.0%*	*20.0%*	*24.0%*	*28.0%*	*30.0%*
Number of pts on TRV027								21,677	59,501	114,835	157,603	194,669	233,775	257,820
Gross price	3.0%							2,483.89	2,558.40	2,635.15	2,714.21	2,795.64	2,879.50	2,965.89
Growth to net	1.0%							2,090.19	2,152.90	2,217.48	2,284.01	2,352.53	2,423.10	2,495.80
TRV027 Revenue								45.31	128.10	254.64	359.97	457.96	566.46	643.47
FRX royalty to TRVN	18.0%							9.06	25.62	50.93	71.99	91.59	113.29	128.69

Source: Company reports and Canaccord Genuity estimates

RECOMMENDATION

We expect TRV027 to become a key therapeutic option for the management of acute heart failure in the inpatient setting. We think the drug's mechanism of action represents a much needed approach to the management of disease. Current inotropes damage heart tissue with even medium-term use, exacerbating disease. '027 appears to make the heart pump more efficiently, which actually reduces stress on the cardiac muscle. We believe the Phase 2a trial generated compelling signals of clinical benefit in a number of the most important markers of AHF function: wedge pressure, mean arterial pressure and blood pressure. There was no impact on renal markers, suggesting good renal safety, and the only side effect of note was on-target modest drop in blood pressure.

We believe the Phase 2 trial has a good chance of generating positive and, importantly, informative data, on '027's potential clinical benefit in acute heart failure. We also think the trial will show positive safety data. Together, we think the data package will encourage Forest/Actavis to exercise its option on the therapy, triggering a $65M payment to TRVN. Forest would then assume all Phase 3 development cost and responsibility. TRVN could receive up to an additional $430 in milestone payments, 10-20% royalties and an option to co-promote the drug in the US. We expect '027 to reach peak market share in 30% of acute heart failure hospitalizations, resulting in $640M peak sales and $130M revenues to TRVN.

We think TRV130 is an especially promising first-line post-operative analgesia drug candidate with real potential to provide superior pain relief with a better side effect profile. We think Phase 1b data supports positive Phase 2 and Phase 3 development and likely eventual approval. We think TRV130 may show better pain relief than the current standard of care IV PCA morphine. In our opinion, based on scientific rationale, there is also a good chance that TRV130 could have lower rates of respiratory depression, nausea and vomiting. This is potentially improved side-effect profile may drive cost savings that will promote rapid uptake. TRV intends to complete development and promote TRV130 itself, and promote it through a small specialized hospital focused sales force of 75-100 reps. If TRVN is able to make cost-savings arguments (based on lower cost of care and shorter hospital stays), we estimate TRVN peak sales in the US could be $790M.

COMPANY OVERVIEW

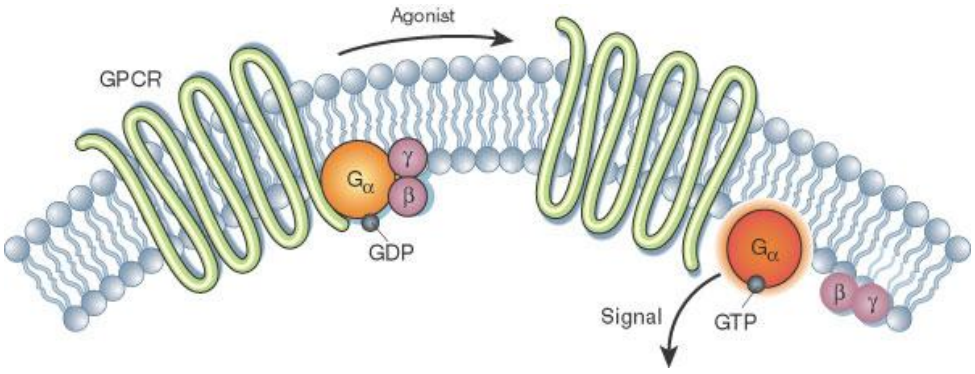
Novel biased ligands for GPCRs

TRVN is a clinical-stage biotechnology company focused on the development and commercialization of new chemical entities that selectively target G protein-coupled receptors. These novel biased GPCR ligands selectively activate one of two intracellular signaling pathways that connect to the receptor: either the G-protein pathway or the beta-arrestin pathway. while avoiding, or inactivating, other. This enhanced functional specificity is the basis for a new generation of GPCR drugs. TRVN has advanced two product candidates into the clinic: TRV130 for postoperative pain and TRV027 in acute heart failure. TRVN is also quickly moving its lead preclinical products for various CNS diseases into the clinic and, we think, will make an indication selection soon.

BIOLOGY OF OPIOID RECEPTORS

Opioid receptors are a part of the large family of seven transmembrane-spanning (7TM) G protein-coupled receptors (GPCRs). As a class, GPCRs govern the fundamental physiological function of mediating neurotransmitters and hormones. There are two principal signal transduction cascades involving the GPCRs: the cyclic adenosine monophosphate (cAMP) pathway and the phosphatidylinositol pathway. GPCRs undergo a conformational change as ligands bind to the receptors. The GPCR, in its new conformation, then acts as a guanine nucleotide factor by activating an associated G-protein by releasing a bound guanosine diphosphate (GDP) to allow the binding of a guanosine triphosphate (GTP). The alpha-subunit of the G-protein with the bound GTP will then dissociate from the beta and gamma subunits to relay the intracellular signal further.

Figure 6: GPCR structure



Source: Li, 2002

Pharmacology – receptor subtypes and opioid ligands

Opioid receptors are activated by endogenously produced opioid peptides and by exogenously administered opioid compounds such as morphine. To date, there are multiple subtypes of opioid receptor classified by their unique responses to the repertoire

of opioid ligands: MOR (mu for morphine), KOR (kappa for ketocyclazocine), DOR (delta for deferens) and NOR (for nociceptin/orphanin FQ).

The endogenous opioid peptides are derived largely from four precursors: pro-opiomelanocortin, proenkephalin, prodynorphin, and pronociceptin/orphanin FQ. With the exception of nociceptin/orphanin FQ, all peptides derived from the other precursors contain a pentapeptide sequence YGGFM/L (TyrGlyGlyPheMet/Leu). Nociceptin/orphanin FQ, on the other hand, contains a phenylalanine (F) instead of the N-terminal tyrosine, which is a necessary residue for high-affinity binding to the classic opioid receptors.

Figure 6: Selective opioid receptor ligands

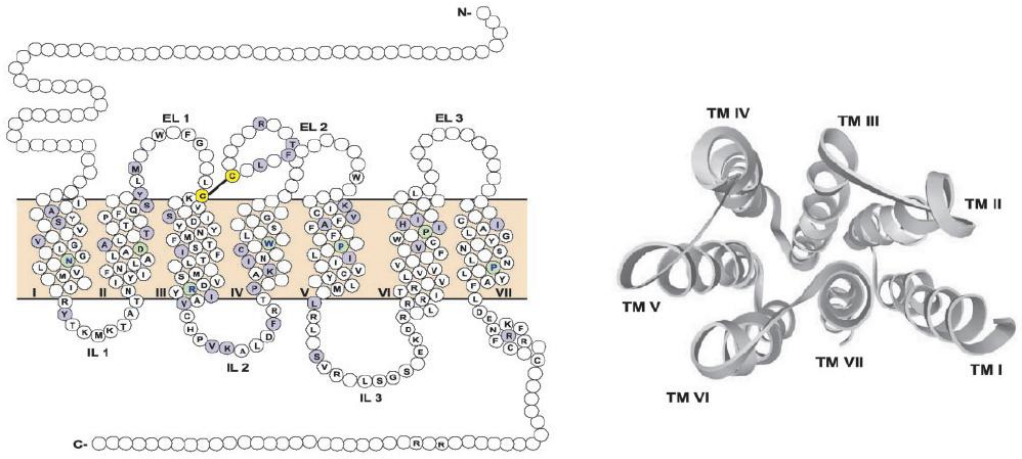
Receptor	Endogenous peptides	Peptide agonists	Peptide antagonists	Agonists	Antagonists
MOP-R	Endomorphin-1 Endomorphin-2 β-endorphin β-neoendorphin Dermorphin	DAMGO PL 017	CTOP Octreotide (SMS201,995)	Fentanyl Morphine Sufentanyl	β-FNA (affinity label) Naloxonazine (irreversible)
DOP-R	Leu^5-Enkephalin Met^5-Enkephalin Met^5-Enkephalin-Arg^6-Phe^7 Met^5-Enkephalin-$Arg^6Gly^7Leu^8$ Deltorphin Deltorphin I Deltorphin II	DADLE DPDPE DSLET	ICI 174,864 (inverse agonist) TIPP TIPP[ψ]	BW373U86 SIOM SNC 80 TAN-67	Benzylidenenaltrexone (BNTX) Naltriben (NTB) Naltrindole (NTI) NTI 5′ isothiocyanate (NTII)
KOP-R	Dynorphin A Dynorphin B	Dynorphin 1a		Bremazocine Ethylketocyclazocine (EKC) Ketocyclazocine CI-977 U-50,488 Spiradoline (U-62,066) U-69,593 ICI 199,441 ICI 197,067 BRL 52,537 BRL 52,656 6′-GNTI	DIPPA Nor-binaltorphimine (nor BNI) 5′-Guanidinonaltrindole (5′-GNTI)
NOP-R[a]	Nociceptin/orphanin FQ	$[Arg^{14}, Lys^{15}]$nociceptin [(pX)Phe^4]nociceptin (1-13) amide analogues $NC(1-13)NH_2$ Cyclo[Cys^{10}, Cys^{14}]$NC(1-14)NH_2$ ZP120	[N-Phe^1]$NC(1-13)NH_2$ UFP-101	Ro 64-6198	Benzimidazolinone (J-113397) JTC-801 TRK-820

Source: Whistler, 2004

Opioid receptors – structure

Opioid receptors is a member of the class A rhodopsin family of GPCRs with an extracellular N-terminal domain, 7TM helical domains connected by three extracellular and three intracellular domains, and an intracellular C-terminal tail that forms a fourth intracellular loop with its putative palmitoylation sites. According to the 2.8 angstrom resolution 3-D rhodopsin structure Palczewski et al elucidated in *Science* in 2000, it is widely accepted that the seven transmembrane helices of opioid receptors are arranged in a counter clockwise sequence that forms a tight helical bundle. The transmembrane helices and the extracellular domains of the receptor help dynamic binding of various opioid ligands. All four receptors have two cysteine residues that are conserved in the first and second extracellular loops that form a disulfide bridge and have multiple Asn-linked glycosyl modifications in the N-terminal domain.

Figure 7: Structure of opioid receptors



Source: Palczewski, 2000

Opioid receptors – ligand binding

All opioid receptors share a common binding pocket that situates in the inner interhelical conserved region among transmembrane helicies 3 through 7. And this cavity is partly covered by the extracellular loops. The highly diversified extracellular loops, along with residues from the extracellular ends of the transmembrane segments, significantly affect ligand selectivity.

Large ligands such as norbinaltorphimine fill almost all of the free space in the binding pocket and interface with both conserved and variable residues. On the other hand, small alkaloid agonists, namely morphine, interact predominantly with residues at the bottom of the pocket that are often conserved.

Ligand binding and selectivity are conferred through the recognition of two distinct structures inherent to the ligand. During binding, message tyramine moiety of the cyclic peptides lies at the bottom of the binding pocket and interacts with residues common to all types of opioid receptors. The ligands are oriented toward the extracellular surface of the transmembrane domain in the extracellular loop. These extracellular loops allow for the passage of certain ligands while excluding others.

In addition to distinct transmembrane residues, agonist ligand selectivity for KORs has been attributed to the second extracellular loop. Key residues in KORs determine peptide versus synthetic ligand binding and the process involves the negatively charged second extracellular loop. The loop in turn forms an amphiphilic helix that interacts with six positively charged residues in the endogenous peptide agonist ligand dynorphin A. On the other hand, binding of KOR selective agonists of the acylacetamide class utilizes residues Asp 138 in TM3 and Ile294, Leu295, and Ala298 as anchors for receptor binding.

G-protein-effector activation

Opioid receptors are predominantly coupled to G-proteins, and upon receptor activation, both subunits (alpha and beta-gamma) interact with multiple cellular effector cascades. The cascades then go on to inhibit adenylyl cyclases and volgate-gated calcium channels and stimulate G-protein-activated inwardly rectifying potassium channels and phospholipase C beta.

Activation of GPCRs/7TM receptors involves ligand-induced transmembrane motions that result in exposure of the intracellular loops that makes them more readily accessible to G-proteins. Intracellular loop 3 is the key determinant of coupling specificity among the different G-protein alpha subunits, whereas intracellular loop 2 is linked to the efficiency of G-protein activation.

An opioid agonist normally binds to one of the hydrophobic clusters in extracellular loop 3 or in N-terminal regions, which destabilizes the interactions between TM6 and TM7 on extracellular side of the receptor. The ligand then enters the binding pocket and disrupts hydrophobic and hydrophilic interactions within TM helices 3, 6, and 7. Movements of these helices ultimately result in a break of cytoplasmic ionic locks and the exposure of intracellular receptor domains to G proteins and other effector proteins.

Opioid receptors – function

Opioid receptor activation by endogenous and exogenous ligands results in a multitude of effects, which include analgesia, respiratory depression, euphoria, hormone release, inhibition of gastrointestinal transit, and effects on anxiety. In general, morphine remains the analgesics of choice for the treatment of chronic pain. However the major limitation to its long-term use is the development of physiological tolerance. In addition to tolerance, physiological dependence can ensue in certain patients.

Animal models of opioid receptor function

Tolerance to opioids is measured as a change in analgesic responses. The two most common behavioral assays in animals are the hot plate and the tail flick tests, where a heat source is applied to either the tail or hind paw of an animal. Dependence is measured in morphine-tolerant animals by either withdrawing the opioid agonist or administrating an opioid antagonist. The typical behaviors reflecting withdrawal/dependence symptoms in animals are elevated level locomotion, jumping, and weight loss. In addition, opioid-induced addiction is hypothesized to result from modulation of neural brain circuits associated with stress and anxiety, positive reinforcement, as well as learning and memory. In animals, positive reinforcement is measured by a method that monitors an animal's ability to develop a preference for a certain environment when paired with a drug. Anxiety is induced by exposing animals to a stressful situation, namely a forced swim test.

Morphine and opioid receptor trafficking

Morphine-activated MORs are unique because they do not require G-protein coupled receptor kinase phosphorylation nor do they efficiently recruit beta-arrestin. In addition, morphine fails to promote endocytosis of the wild-type MOR in cultured cells and native neurons, whereas endogenous peptide ligands, such as endorphins, encephalin, and several other opioid drugs readily promote receptor endocytosis. As such morphine-

activated MORs generally elude an important, highly conserved regulatory mechanism designed to rapidly modulate receptor-mediated signaling.

Tolerance

Though opioids like morphine are the analgesic of choice for many settings, their long-term use is often linked to the development of physiological tolerance. The development of opioid tolerance in humans varies depending on the route of administration and on the disease state for which the opioids are prescribed. Tolerance is usually not a concern for patients on short-term postoperative epidural or intrathecal opioids. Rather, tolerance often manifests after chronic exposure to epidural or intrathecal opioid use. On the other hand, patients with terminal malignancies experience an escalation in pain as their disease progresses, and this makes it difficult to distinguish between the development of opioid tolerance and an increase in opioids consumption for their pain. The development of tolerance involves multiple molecular and cellular mechanisms: receptor downregulation, receptor desensitization, and uncoupling from cAMP pathway.

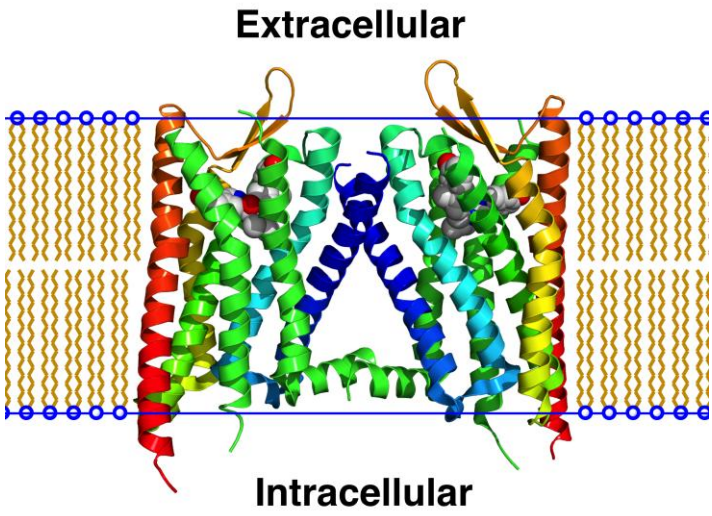
Dependence and withdrawal

In addition to the side effects of tolerance, respiratory depression, constipation, long-term use of opioids also lead to physiological dependence in some patients, who rely on continued administration of escalating opioid doses to prevent withdrawal. The physiological drug-dependent state often emerges after the analgesic is stopped.

Tolerance and dependence are complex physiological phenomena, but they may share a common mechanism as the severity of withdrawal signs and the extent of the development of tolerance are correlated in vivo and in vitro. For example, cAMP uncoupling has been suggested to play an important role in the development of tolerance and dependence.

One region of the brain that has been studied extensively as a model for opioid dependence and withdrawal is the locus coeruleus (LC). Following the chronic administration of morphine, the LC neurons show tolerance to morphine as well as cellular correlates of dependence and withdrawal. Some of the cellular changes include increases in the levels of G-protein subunits and adenylyl cyclases. Interestingly, upregulation of the cAMP pathway has been consistently observed in the LC, nucleus accumbens, amygdala, doral raphe nucleus, and ventral tegmental area. These considerations suggest that the pathway may be a cellular hallmark of the development of not only tolerance, but also dependence.

Figure 8: Crystallographic structure of human KOR1



Source: Wacker, 2012.

Opioid receptors – pain pathway

Opioid receptors are abundantly expressed on nerves principally responsible for pain transmission and modulation in the brain, spinal cord, and the periphery. Opioid receptors are present on C-fibers of primary sensory afferent and they inhibit the release of pain transmitters by blocking the activation and sensitization of these fibers. Moreover, opioid receptors in dorsal root ganglia are transported to the peripheral sensory nerve endings during the inflammatory process, while endogenous opioid peptides accumulate within immune cells in the inflamed tissue. Upon release, the opioid peptides interact with the neuronal opioid receptors to achieve local analgesia.

Beta-arrestin

Beta-arrestins (either subtype 1 and 2) are very broadly expressed proteins with highest levels of expression in the brain and spleen. These proteins are versatile adaptor proteins that complex intra-cellular with most GPCRs after ligad binding and subsequent receptor phosphorylation by G-protein-coupled receptor kinases. They are key in homologous desensitization and GPCR sequestration, which leads to downregulation and termination of G protein activation.

Beta-arrestin GPCR binding not only decouples receptors from heterotrimeric intracellular G proteins, but marks them for clathrin-coating and subsequent endocytosis. Recent studies also show beta-arrestin could also function as a GPCR signal transducer itself as the beta-arrestins bind directly to proteins such as Src, ERK1/2, or JNK3 MAP kinases that are involved in signal transduction. By recruiting different proteins directly to the GPCR, beta-arrestins can confer distinct enzymatic functions upon the receptors.

Beta-arrestin terminates GPCR signaling

Three distinct main receptor processes are responsible for dampening of GPCR signaling: receptor desensitization, sequestration, and downregulation.

- Desensitization begins seconds after agonists exposure and is mediated by receptor phosphorylation. Second-messenger-dependent protein kinases (e.g. cAMP-dependent protein kinases PKA and PKC) phosphorylate C-terminal domain or cytoplasmic loop threonine and serine residues on the GPCRs. Beta-arrestins deficiencies lead to sustained receptor-G-protein coupling efficiency. Homologous desensitization is mediated by receptor phosphorylation by GRKs and subsequent binding of beta-arrestin.
- Receptor sequestration (internalization of GPCRs) occurs over several minutes after agonist exposure. Agonist-induced GPCR endocytosis is mediated by GRK phosphorylation and beta-arrestin binding. Beta-arrestins have two motifs enable adaptor function, connecting GPCRs to clathrin-dependent endocytic pathway components. Studies have shown both beta-arrestin and corresponding receptors undergo rapid, beta-arrestin-induced ubiquitination after agonist binding. Receptor ubiquitination is also mediated by a beta-arrestin-linked ubiquitin ligase. Therefore, beta-arrestin ubiquitination may be required for receptor internalization but not necessarily its internalization.
- GPCR downregulation (sustained loss of cell surface receptors) takes place over a period of hours to days. Even though control of cell surface receptor density occurs mainly by regulation of transcription rates, agonist-occupied receptor removal from the cell surface and recycling is also key. Beta-arrestin-dependent endocytosis appears to play a role in the process.

Beta-arrestin-biased ligand

Until recently, ligand-mediated desensitization, internalization, and signaling of 7TMR were thought to be directly related to G-protein activity. However, new research suggests G-protein and beta-arrestin signaling efficacy can vary. They can be specifically modulated under the evolving paradigm of ligand bias. The discovery of non-desensitizing agonists further prove G-protein activation is not always enough to stimulate 7TMR phosphorylation and beta-arrestin recruitment. Given 7TMR function functional diversity, beta-arrestin bias could allow 'designer' agonists to have significant clinical advantages for well-elucidated target receptors. The ability to identify ligands that activate only therapeutic-benefit associated pathways is currently being used by Trevena to develop a novel class of biased-ligand agonists.

PAIN: A COMPLEX SENSORY EXPERIENCE

Pain is a complex sensory experience and is modulated significantly by the central nervous system. In fact, pain is the most common reason for medical appointments. Every year there are 40M pain-related visits in the US and the associated cost is estimated to be close the tune of $100M. There are two major classes of pain analgesics: opioids, such as codeine, fentanyl, and morphine, and non-opioid inhibitors of cyclooxygenase (COX), namely aspirin and ibuprofen. Both opioid and non-opioid analgesics are efficacious and widely used. Sales from these pain management products in the US exceeded $18B in 2012.

Opioid analgesics used in clinical settings like morphine act primarily through the MOR and has been considered the gold standard for the treatment of severe pain. However, AEs

associated with opioid receptor agonists like tolerance, respiratory depression, and constipation reduce their usefulness.

Physiology of pain

Acute pain and chronic pain are initiated by activation of a nociceptor, the sensory receptors in the periphery that respond to noxious stimuli that give rise to pain. Nociceptors are ubiquitous throughout the human body and they are the end organs that transduce noxious stimulus energy into electrical signals that are passed on to a second order neuron via axon in the spinal cord. Peripheral terminal of nociceptors are typically without a defining structure as nociceptors are often described as free nerve endings with no encapsulated end organ.

Pain is mediated by nociceptors that respond directly to some stimuli and other via the release of chemical signals from surrounding tissues such as histamine or acetylcholine. Based on the type of stimulus that evokes a response, nociceptors are classified into three distinct types: mechanical, thermal, and polymodal.

Mechanoreceptors respond to painful tactile stimuli and they are myelinated fast-conducting A-delta afferents that relay sharp pain sensations. Thermal receptors, on the other hand, can respond to noxious heat or a lack thereof. Thermal nociception is mediated by both vanillioid type 1 receptors and vanillioid receptor-like protein-1. Type 1 vanillioid receptors respond to noxious heat that exceeds 45 centigrade and they are sensitive to capsaicin. Contrarily, vanillioid receptor-like protein-1 is insensitive to capsaicin and response to a heat threshold in excess of 52 centigrade. The majority of nociceptors are polymodal nociceptors, and they respond to a wide range of mechanical, thermal and chemical stimuli.

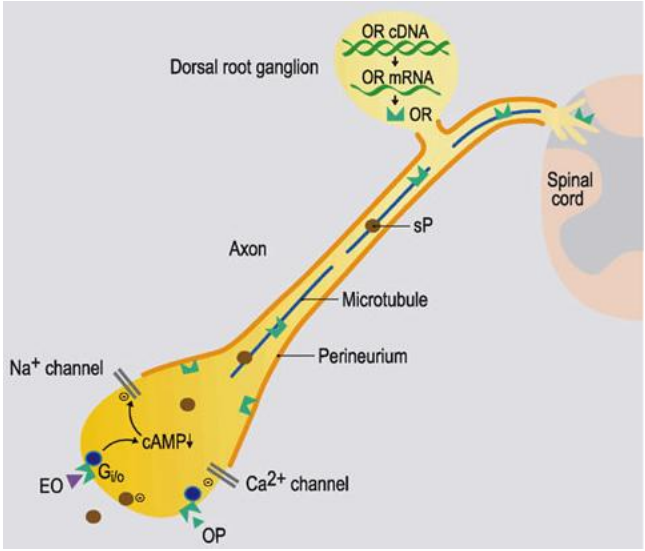
KORs are located both in the CNS and in the periphery. Centrally located KORs are involved in spinal-mediated thermal nociception, whereas peripherally located KORs are principally responsible for antinociceptive effects. In rodent visceral pain model, upregulation of endogenous KOR peptide dynorphin occurs following pain and mice lacking preprodynorphin experience increased tail flick and hot place responses while KOR deficient mice show elevated writhing response after peritoneal acetic acid injection.

Nociception pathways

Fast A-delta fibers and unmyelinated C fibers are involved in nociceptive transmission. Fast A-delta generates a sharp, well-defined pain sensation, while the unmyelinated C fibers relay slow burning sensation in damaged tissue and inflamed skin. It is important to note that all nociceptive afferents terminate in the dorsal horn of the spinal cord and the termination of various afferent fibers in distinct laminae shows rigid functional and anatomical control.

KORs are predominantly expressed on the cell linings of small nociceptive afferents in the dorsal root ganglion and spinal cord. In fact, high KOR expression is observed in the dorsal horn and substantia gelatinosa while lower expression is found in zona intermedia and ventral horn.

Figure 9: Opioid receptor transport and signaling in primary afferent neurons



Source: Nature, 2003

High levels of KORs are found in brain regions responsible for transmitting nociceptive signals such as the nucleus of the solitary tract and hypothalamic nuclei. KORs are also found in pain circuitries through the body. Anatomical distribution of KORs alongside MORs suggests close physiological interaction in nuclei-relaying nociceptive stimuli. The KOR positive neurons are located in the trigeminal and dorsal root ganglia, while peripheral KORs and peptides are found in nerve terminals of sensory neuron in the skin, muscles, and joints.

Preclinical behavioral models of pain

There is a plethora of established pre-clinical models for pain study and characteristic behaviors measured following external stimuli. Multiple behavioral models are necessary to evaluate and interpret the complexity of pain.

Thermal stimuli – This model of pain relies on ramped thermal stimuli to activate thermoreceptors. However the subject tends to quickly remove itself from the stimulus before nociceptor stimulation. The tail flick test is a common thermal model for pain and has been used to study the analgesic effects of opioids. However, KOR agonists tend to be less effective in thermal antinociceptive assays compared with other modes of stimuli.

Inflammatory model and hyperalgesia – This model is developed by injecting inflammatory agents into the paws of mice and involves longer stimuli duration. The animal model of inflammatory hyperalgesia closely resembles the clinical conditions for pain in human. There are two phases of this pain model. The inflammatory pain takes place after 0.5% to 1.5% of formalin is injected into the rodent paw, and the neuropathic pain sets in after the potency of the stimuli wears off with time. Pain effects are limited to the injected limbs in this model and the endpoints are often measured by paw withdrawal latency, flinching, or the duration of licking the affected paw. KOR agonists have shown to attenuate antinociceptive behaviors and decrease stimuli-induced edema by Obara et al. Injection of carrageenan, phorbol ester, or yeast elicit similar effects.

Neuropathic pain

Nerve ligation often results in thermal hyperalgesia, which is commonly measured by lower paw withdrawal latency in response to heat stimulus or focused light beam. In this model, cold and mechanical stimuli cause spontaneous pain and allodynia. KOR agonists produced a prolonged, reversible antinociceptive effect in a rodent model of peripheral mononeuropathy conducted by Keita el al. The pain was produced by moderate constriction of the sciatic nerve and the investigators measured vocalization thresholds to paw pressure as a nociceptive test.

It is widely accepted that the endogenous KORs are activated by nerve ligation as many studies found Prodynorphin derived opioids are released into the blood stream post-ligation to increase KOP receptor activation and produce antinociceptive effects.

Models for visceral pain

Distension and stretching of visceral muscle often trigger the activation of sensory innervations in the viscera. All visceral nociceptive fibers are relayed in both sympathetic and parasympathetic circuitries. As a result, pain signals transmitted through these C fibers have no spatial localization. Peripheral primary afferent neurons are principally responsible for nociception activation, transduction of sensory input. Recent studies by Gebhart et al suggest their expanded role in integrating nociceptive inputs and modulating peripheral sensitization.

Visceral nociceptor afferents are colocalized with sommatocutaneous afferents in the dorsal root ganglion and in the dorsal horn, and this is thought to contribute to somatic referred pain that often comes with visceral nociception. KOR agonists have been demonstrated to be antinociceptive in both cutaneous and mechanical visceral nociceptive models and their efficacy are directly proportional to KOR density in the periphery.

Figure 10: Summary of KOR agonists and antagonists in different animal models of pain

Pain Model	KOPr agonist/ antagonist	Findings	Reference
Models of visceral pain	Agonist		
Colorectal distension	C1977 U69,593 U50, 488H EMD61,7F3	Antinociceptive. dose-dependent attenuation of pressor and visceromotor responses. Order of potency as listed.	Burton and Gebhart 1998
Colonic inflammation induced by trinitrobenzene sulfonic acid	ICI204,488 EMD61,753 ICI204,488	Antinociceptive. dose-dependent inhibition of pelvic nerve afferent fibers with significantly greater potency in the inflamed colon.	Su et al. 1997; Sengupta et al. 1999
Thermal stimuli			
Heat-induced nociception	Ethlyketazocine Pentazocine	Inactive at doses producing sedation effects Inactive tail immersion, antinociceptive hot plate, also produced motor incoordination	Tyers 1980
Hot plate and tail immersion 50°C and 55°C	Nalorphine Mr2034	Inactive Inactive; tail immersion, antinociceptive in hot plate tests.	
	Mr1353	Antinociceptive in hot plate and tail immersion.	
Inflammatory models of pain and hyperalgesia	agonist		
Writhing and paw pressure tests. Acetic acid	SK-9709	Antinociceptive	Hiramatsu et al. 2001
Formalin test and writhing test	EMD60400	Antinociceptive in non-inflammatory and inflammatory pain	Barber et al. 1994
	ICI 197067	Antinociceptive in non-inflammatory and inflammatory pain	Machelska et al. 1999
Formalin	ICI 204448	Antinociceptive in non-inflammatory and inflammatory pain	
Complete Freund's adjuvant (CFA)	U50,488H	Antinociceptive	
	Dynorphin	Antinociceptive	Obara et al. 2009
	CI-977	Antinociceptive, decreased flinching response	Zhou et al. 1998
Mycobacterium butyricum (ankle joint)	U50,488H	Anti-inflammatory, antinociceptive	Bileviciute-Ljungar et al. 2006;
	Antagonist		
Formalin test	Dynorphin anti-sera nor-binaltorphimine (nor-BNI)	Increased flinching Increased flinching	Ossipov et al. 1996 Ossipov et al. 1996
CFA	Nor-BNI	Inflamed paw had increased response to mechanical and thermal sensitivity. Mechanical sensitivity in non-inflamed paw	Schepers et al. 2008
Neuropathic pain	Agonist		
Chronic nerve constriction of sciatic nerve	Asimadoline	Antinociceptive	Walker et al. 1999
	EMD60400	Antinociceptive	
	ICI 197067	Antinociceptive	
	ICI 204448	Antinociceptive	Keïta et al. 1995;
	U69593	Antinociceptive	Andreev et al. 1994
	Dynorphin	Pronociceptive and antinociceptive	Xu et al. 2004
	ICI 199441	Antinociceptive	Obara et al. 2009
Sham spinal surgery	U50,488H	Increased hypersensitivity	Herrero and Headley 1991
Spinalization	U50,488H	Antinociceptive	
	antagonist		
Spinal nerve ligation (SNL)	Dynorphin anti-sera	Reversed neuropathic pain following day 10 of SNL	Wang et al. 2001

Source: Prisinzano, 2010

KOR agonists have demonstrated antinociceptive activity in a number of pain models and their effects occur both centrally and peripherally. The pharmacological profile of KOR agonists in visceral pain models suggests that peripherally acting KOR agonists have tremendous clinical benefits for a variety of peripheral pain states. Further clinical investigation of peripherally restricted KOP agonists will no doubt elucidate the conditions in which KOR agonists will be most useful.

Pain management - the market opportunity

Pain is categorized as either acute or chronic, and is graded by severity as mild, moderate or severe. Acute pain is usually caused by an injury resulting in nerve, tissue or bone damage. It is expected to decrease in severity with tissue healing. Postoperative pain is an acute injury that constitutes a specific part of acute pain market. Chronic pain lasts significantly longer (from weeks to years), and can result from either an acute injury or an ongoing disease, such as diabetes-related neuropathic pain.

A 2011 Institute of Medicine report estimates ~100 million U.S. adults have chronic pain. Millions of others at any given time have acute pain from events like surgery, childbirth, injury and acute/episodic illness. Decision Resources estimated the total pain therapies sales in the seven major pharmaceutical markets (US, France, Germany, Italy, Spain, UK and Japan) were north of $37 billion in 2011.

Pain severity is critical determining the appropriate therapy for pain relief. Mild or mild-to-moderate pain can be treated with OTC products, like oral aspirin, acetaminophen and ibuprofen. Moderate-to-severe pain is usually treated with traditional mu-opioid analgesics. Mu opioids are considered quite effective, but they have a poor side-effect/ abuse profile, which greatly limits their use. However, opioid analgesics may be the only effective method of treating moderate to severe pain. As a consequence, opioids are among the largest US prescription drug classes. According to IMS, opioid analgesics represented 71% of the 341 million prescriptions written in 2012 with over $8.3 billion in sales.

Postoperative pain market

Postoperative pain is a substantial part of the overall acute pain market. HHS estimates Over 46M inpatient and 53M outpatient surgeries are performed every year in the US. In the in-patient setting, moderate-to-severe pain is treated with injectable analgesics. The US IV analgesics market consists primarily of mu-opioid agonists. These include fentanyl, morphine hydromorphone and non-opioid analgesics like Toradol or IV ketorolac generics, Caldolor (IV ibuprofen), and Ofirmev (IV acetaminophen). Decision Resources believes postoperative pain market reached $5.9 billion in 2010, roughly one-fifth of the total pain therapeutics market).

The standard of care for treating acute postoperative pain is multimodal analgesia. Multimodal treatment paradigm is based on the administration of two or more drugs that act through different mechanisms for providing analgesia in a way that minimizes AEs. When patients are ready to be discharged, a transition is made to a prescription oral pain medication, thereby allowing patients to administer relatively strong analgesics on their own. The transition from a potent IV painkiller to an oral analgesic is often described as IV-to-oral “step-down” therapy.

Strong mu-opioid analgesics are the mainstay pain treatment during the immediate postoperative period. However, they come with a wide array of serious side effects, including postoperative opioid-induced respiratory depression, postoperative opioid-related nausea and vomiting, and opioid-induced bowel dysfunction, which contributes to the severity of postoperative ileus. Opioid-induced respiratory depression can occur unexpectedly in three out of 10 patients and this has a clear negative impact on the length of stay and total treatment costs. On the other hand, post-op opioid-related nausea and vomiting occurs in one-third of all surgical patients, and it is one of the most important factors in determining length of stay after surgery. The resulting annual cost to the US

healthcare system has been projected to be around $1 billion by the CDC. It is evident that mu-opioid-related AEs not only drastically increase the cost of care, but lead to sub-optimal recovery.

Non-opioid analgesics formulated for injection or infusion, such as IV acetaminophen and NSAIDs, namely IV ibuprofen, are viable alternatives to mu opioids in helping patients relieve acute pain. However, their use is limited in a postoperative care setting due to their moderate efficacy. Like opioids, IV acetaminophen and NSAIDs have dose-dependent AEs that limit their use at higher doses. Acetaminophen has liver toxicity that can be fatal, and NSAIDs are associated with bleeding risks, serious GI AEs, kidney damage, and serious CV thrombotic events such as stroke and heart attack.

POST-OP PAIN DRUGS: A CLEAR UNMET NEED

Even with the large size of the pain market, there has been little to no recent innovation in new analgesics. Almost all recent new approvals are reformulations of existing drugs with alternate delivery methods. Mu opioids are still the most prescribed drugs for pain management despite inherent safety drawbacks. Clinicians are acutely aware of the drawbacks of mu-opioid agonist and tend to prescribe suboptimal doses that result in suboptimal pain relief. As a result, we think there remain large unmet needs in post-operative pain management for patients with moderate to severe pain. Clinicians we have spoken to would like better options to balance pain management with risks of causing severe AEs. Healthcare organizations and hospitals bear the costs and consequences of undertreated pain and AEs.

According to the Centers for Disease Control and Prevention, 46 million inpatient surgical procedures were performed in 2010 and almost all patients experience postoperative acute pain of varying intensity and duration that depend on the type, length, and tissue damaged in surgery. Unsurprisingly, pain is the most severe in the first days immediately following the operation. Many epidemiological studies estimate that ~50% of patients self-report inadequate pain relief with current treatments. Currently postoperative pain management is based on a multimodal approach:

Continuous wound infiltration – Prior to suturing up the incision site, a local anesthetic, usually sodium channel blockers such as ropivacaine, bupivacaine, or other ‘caines, is injected directly into and around the incision site. This treatment option provides immediate, robust postoperative base for pain relief while allowing additional pain treatments to be layered on top as needed. Importantly, this is a non-systemic method of action and limits potential side effects while allowing combinatorial therapeutic approach. ‘Caines, in particular bupivacaine, are universally used by surgeons and anesthesiologists because of their familiarity and a robust, decade-long safety and tolerability database. However, these sodium channel blockers have short half-life and short duration of analgesia, which is the greatest limitation of this approach. Case in point: bupivacaine, the longest acting ‘caine, only lasts up to 3.5 hours in adults. It is not feasible to repeat injection into the wound site for a recovering patient after surgery. Therefore, the majority of patients are put on additional systemic treatment of longer-duration pain management agents such as opioids and non-steroidal anti-inflammatories (NSAIDs). Approximately 23M continuous wound infiltrations are performed in the US every year.

Figure 11: Agents used in continuous wound infiltration procedures

Local anesthetic	Usage (number of procedures)
Ropivacaine	0.6M
Bupivacaine	7M
Lidocaine	15M

Drug	Half-life (hours)	Usage
Bupivacaine	3.5	Infiltration, nerve block, and epidural administration
Prilocaine	2.5	IV local anesthesia; combined with lidocaine for dermal
Ropivacaine	2	Infiltration, nerve block, epidural, intrathecal administration
Lidocaine	1.5 – 2	Minor surgery, dental procedures; topical outpatient use

Source: CDC reports and Canaccord Genuity research

We note the conventional immediate-release formulation of bupivacaine was approved by the FDA many years ago under the name Marcaine. The drug has since then been genericized and is commercially available through a number of manufacturers in the U.S: Hospira distributes both the branded and generic versions and APP Pharma (now a subsidiary of Fresenius SE) distributes the branded generic Sensorcaine.

Opioids – Commonly used opioids for postoperative pain include morphine, hydromorphone, oxycodone and fentanylm and they are considered the standard of care for acute pain management. 300M IV units of opioids are consumed in the US every year, and over 650M IV units are consumed annually worldwide. The potency and multiple modes of administration for opioids make them a popular choice among hospitalists as they offer consistent efficacy.

We note that since morphine is cleared through the kidneys, potential accumulation of the drug poses additional toxicity risks for renal-impaired patients. For instance, the morphine metabolite morphine-6-glucuronide (M6G) is a stronger analgesic than morphine itself and it crosses the blood-brain-barrier much more slowly. As such, it is possible that in patients with impaired renal functions, CNS effects such as sedation and dizziness will not only be more severe than in patients with normal renal functions, but can also be persist after morphine dosing has been completed.

As discussed in previous sections, excessive sedation, constipation, nausea, vomiting, and respiratory depression, are all common AEs associated with opioid use. Further, for certain patients subgroups such as the elderly, obsess, renal, or liver impaired patients, use of opioid would be ill-advised. The opioid related AEs (ORAEs) have clear negative implications for patient recovery, complication risk, concomitant medications, length of stay in high acuity hospital beds, and the overall cost of care. Therefore, opioid sparing is practically a universal objective.

Non-steroidal anti-inflammatories (NSAIDs) – These agents are less potent opioid alternative, but they are not with complications. NSAIDs inhibit cyclooxygenase-1 and 2 and play a key role in inflammation through COX's involvement in the formation of prostaglandins. Ketorolac, diclofenac, ofirmev, and ibuprofen inhibit both COX-1 and 2 and they do not have the same risk of constipation or respiratory depression. However, besides being less potent analgesics, NSAIDs cause diarrhea, ulceration, and renal dysfunction.

NSAIDs are useful in postoperative pain management as they are antipyretic activity, but they can cause fluid retention in renal impaired patients and exacerbate hypertension.

Ketorolac is the most commonly used NSAIDs in the post-operative setting and it can be administered via IV, which means it can be used in wound infiltration and in patients who are unable to hold down oral solids. This class of drug is considered to be safer than opioids, and has played a role in reducing opioid consumptions.

Figure 12: Drug classes used for postoperative pain management

	Sodium channel blockers	Opioids	NSAIDs	Acetaminophen
Description	Binds to and blocks sodium channels on nerve cells to prevent depolarization	Binds to opioid receptors that mediate pain; most used in acute post-op pain	Reduces inflammation by inhibiting pro-inflammatory COX	Universal antipyretic and centrally acting analgesic
Common names	Bupivacaine Lidocaine Ropivacaine	Fentanyl Morphine Oxycodone	Ketorolac Ibuprofen Aspirin	Ofirmev Mapap Panadol
Usage	Administered directly to the wound; nerve block and epidural	Administered through IV PCA; management of break through pain	Often combined with opioids; maintain baseline control	In combination with NASIDs and opioids; maintain baseline control
Advantages	Limited systemic exposure	Most efficacious agent for post-op pain	No risk of respiratory depression	Orally administered; antipyretic
Shortcomings	<3.5hrs of efficacy	Numerous SAEs	GI/bleeding risk	Least potent

Source: CDC reports, company filings, and Canaccord Genuity research

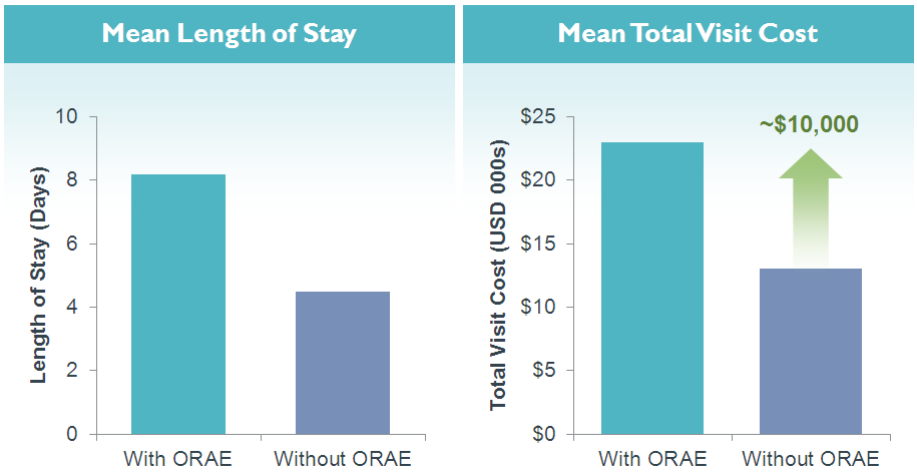
Current long-acting approaches

Oral administration of opioids such as Vicodin or Xolox in the immediate postoperative setting is limited by their slower onset of action and less efficacy than IV administration. The most common postoperative IV opioid administration modality is patient-controlled analgesia (PCA) pumps.

More than 15M PCA pumps are used in the U.S every year. Despite their popularity, current PCA pumps still leave plenty of room for improvement. Regardless of the route of administration, the active analgesic is still an opioid (morphine) with all the same risks, complications, and costs. In addition, all patients are tethered to an IV post, which delays ambulation and recovery. Any opioid-related AEs will slow down the discharge process further and increase hospital related costs. Even though PCA is by definition "controlled by patients," these devices require considerable amount of time from hospital staffs to set up and monitor: nurses need to program the devices, set up IV access, educate patients, and frequently monitor the pump usage. Despite laborious efforts from staffs, mis-programming of devices and interruptions of usage due to technical issues are still common.

Cost for three days' therapy on opioid IV PCA can easily exceed $500, excluding any impact of potential opioid-related adverse events. A CDC report in 2006 found 48% of morphine PCA patients reported opioid-related AEs (and 8% had respiratory depression). In a recent study by Gan et al, ORAEs are found to increase the length of stay in hospital by 2.7 days, and they resulted in $10,000 higher total hospital cost per patient per visit.

Figure 13: ORAEs significantly increase length of hospital stay and costs



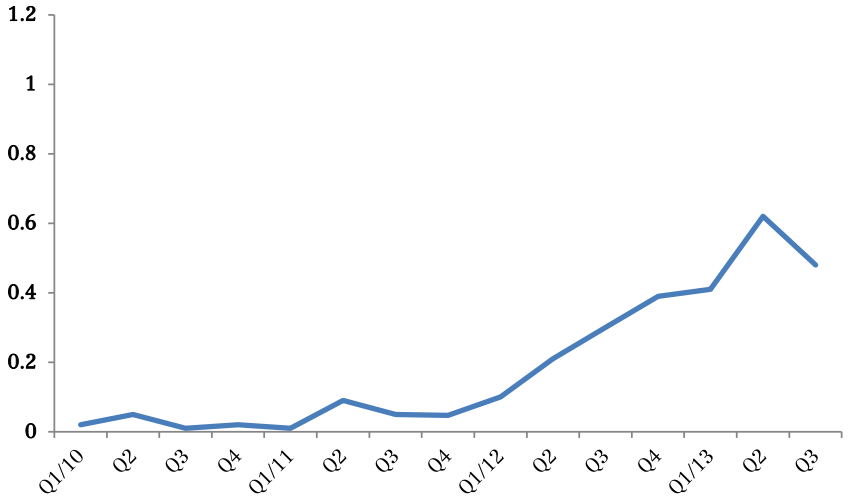
Source: Gan, 2012

Recent commercial launches in postoperative pain

Caldolor - an IV formulation of ibuprofen designed primarily for use in the hospital setting was launched in September 2009. Caldolor is approved as an injectable product in the US for postoperative pain management. Caldolor have been shown in multiple clinical trials to be safe and effective in reducing both pain and fever in 1,400 hospitalized patients.

Phase 3 trial data showed patients given 400 or 800mg of Caldolor every six hours reported lower post-surgical pain intensity in the first 24 hours (SPID 24) while also reducing morphine use. Clinical trials including critically ill and non-critically ill patients with fever showed temperature reduction in active versus placebo. No serious adverse events were deemed drug related.

Figure 14: Caldolor sales ($M)

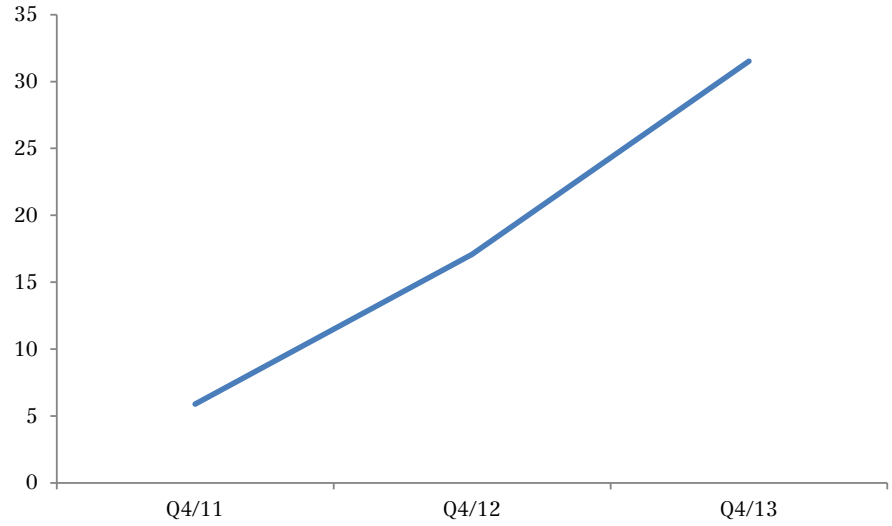


Source: Bloomberg and Canaccord Genuity research

Ofirmev - an IV formulation of acetaminophen targeted at patients suffering from acute postoperative pain. Cadence Pharmaceuticals' Ofirmev was launched in January 2011.

In a Phase 3 101-patient study in hip or knee replacement surgery, 1000 mg of Ofirmev every six hours was statistically superior to placebo for reduction of pain intensity over 24 hours (SPID24, $p<0.01$) with significantly less morphine consumption (33% over 24 hours, $p<0.01$). In a second 244-patient study in abdominal laparoscopy, Ofirmev 1000 mg every six hours, or 650 mg every four hours, showed a significant reduction in SPID24 versus placebo ($p<0.02$). In an adult volunteer study with induced fever, a single dose of Ofirmev 1000 mg showed a statistically significant reduction in temperature through six hours in versus placebo ($p<0.01$), with an 15 minute onset of pain relief. Ofirmev was well tolerated across multiple safety trials assessing a range patient and surgery types.

Figure 15: Ofirmev sales ($M)

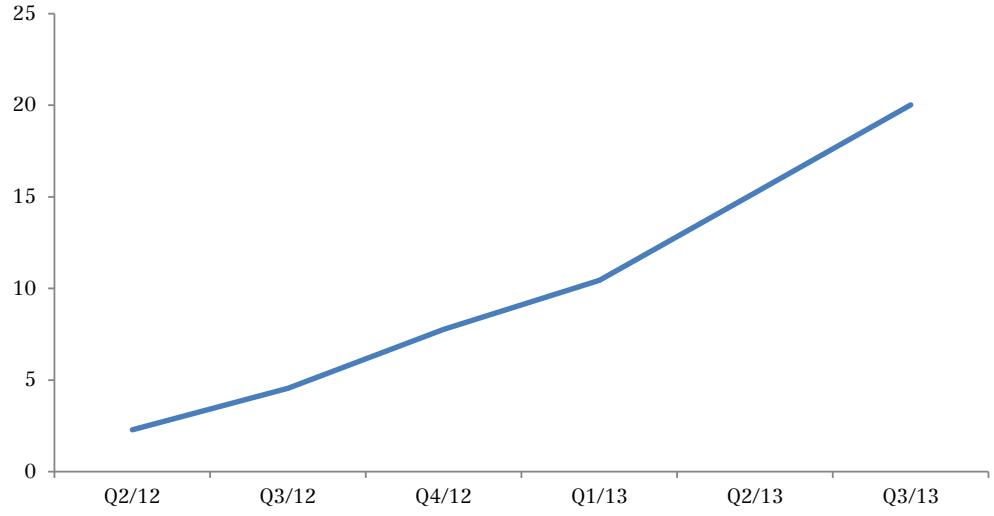


Source: Bloomberg and Canaccord Genuity research

Exparel – a multivesicular liposomal encapsulated, timed-release bupivacaine for pain management in in the postoperative setting that launched in April 2012. A single intraoperative injection of Exparel administered at the close of surgery gives postsurgical pain control with reduced opioid requirements for up to 72 hours. This makes the drug a good candidate for effective pain management in the first few days after surgery, when pain is most severe.

The safety of Exparel has been evaluated in over 1,300 subjects across 21 clinical trials. Locally administered Exparel, from 66 mg to 532 mg, at the surgical incision site was evaluated in 10 randomized, double-blind clinical studies with 823 patients undergoing various surgical procedures. In its Phase 4 study, Exparel showed a 64mg mean reduction in opioid consumption (P<0.0001). In addition, the patients on Exparel reduced their hospital stay by 24 hours (p=0.0019), which resulted in a $1,782 reduction in healthcare cost. Most importantly, only 8% of the patients in the treatment group experience ORAEs, versus 41% in the IV opioid-based PCA group (p=0.0019).

Figure 16: Exparel sales ($M)



Source: Bloomberg and Canaccord Genuity research

QRx Pharma

QRx Pharma has a dual opioid portfolio that includes an immediate-release oral capsule for acute pain, a controlled-release oral tablet for chronic pain, and an IV formulation for moderate to severe pain in the postoperative setting. QRx Pharma's lead dual opioid Moxduo has received two complete response letters thus fa. QRx Pharma is going in front of the agency for the third time to try to get the immediate release combo through the FDA. The data from the opioid combo trials provided the same analgesia with a reduction in side effects such as respiratory depression and overall lowered opioid loading. However, QRx Pharma's IR product has no tamper-proofing. It remains unclear how, in the current environment, the FDA or AdComm will go with recommending another opioid product on the market with no tamper-resistance.

TRV130 IN ACUTE POSTOPERATIVE PAIN

TRVN is developing the biased GPCR ligand TRV130 in IV formulation as a first-line treatment for acute moderate-to-severe pain in the postoperative setting. TRV130 is a small molecule G protein ligand that targets the mu-opioid receptor, a GPCR expressed in both CNS and intestines. TRV selectively activates the mu-opioid G protein pathway that triggers analgesia, while repressing the beta-arrestin effects that include constipation and respiratory depression. If TRV130 continue to show a lack of common AEs associated with mu-opioid receptors in subsequent studies, it could be a much more popular treatment for postoperative pain as speedy discharge and manageable ORAEs should be well received by the hospitalists.

Prescription pain management is an $8.3B market in the US

According to IMS Health, revenues of pain management drugs in the US exceeded $18.2 billion in 2012. Opioid analgesics represented 71% of the 341 million prescriptions written in 2012 and accounted for more than $8.3 billion in sales. Opioid analgesics decrease the

sensation of pain by stimulating mu, delta and/or kappa opioid receptors. All of these receptors are involved in the modulation of pain signals. The most widely used opioid analgesics such as morphine, fentanyl and hydromorphone act primarily through the activation of mu-opioid receptors in the CNS. However, because of the wide expression of mu-opioid receptors throughout the brain, morphine and other mu-opioid agonists also trigger a characteristic pattern of adverse "central" side effects that include nausea, vomiting, pruritus, and respiratory depression. Mu opioids have also been demonstrated to induce euphoria, which may lead to misuse, abuse and potential addictions.

TRV130: a new "old" analgesic with no baggage

Improved analgesia – TRV130 showed superior analgesia compared to a high dose of morphine in a Phase 1b trial with healthy subject. Moreover, it produced less respiratory depression, less nausea and less vomiting compared to morphine. TRV130's therapeutic profile with well-accepted tolerability and clean safety gives us confidence that it may have an improved profile compared to current SOC unbiased μ-opioid agonists,

Less time to peak effect – In preclinical studies, TRV130 achieved maximal efficacy five minutes after dosing, compared to morphine's 30 minutes. Full pharmacodynamic response in the form of pupil constriction, a well-validated proxy for opioid-induced analgesia, was reported 10 minutes after dosing in a Phase 1 trial. In addition, full analgesic effect was reported 10 minutes after dosing in the Phase 1b trial. If TRV130 continues to show this short response time, we think TRV130 could also be a strong contender in the peri-operative pain market where fentanyl is the most prescribed therapeutic, thus broadening TRV130's market potential.

A novel, clever way to target an established pain mechanism – TRV130 is a G protein biased ligand that acts on an extensively validated μ-opioid receptor mechanism. Even though unbiased μ-opioid analgesics like morphine, fentanyl and hydromorphone are the mainstays of therapy for postoperative pain, their strong analgesic efficacy comes with severe AEs. TRV130 essentially act on the same, potent analgesic molecular pathway but does not trigger any of the undesirable effects.

TRV130 has a strong safety track record

Reduced risk of respiratory depression – In a Phase 1b trial in healthy subjects using an evoked-pain model, TRV130 showed less respiratory depression compared to a high dose of morphine at doses delivering superior analgesia. In a preclinical proof-of-concept study, TRV130 showed less respiratory depression at equivalent analgesic doses compared to morphine. If the company can continue to demonstrate this safety advantage in clinical trials and TRV130 is ultimately approved, we believe it may be used as a first-line treatment of postoperative pain, particularly in patients with increased risk of respiratory depression.

Reduced postoperative nausea and vomiting (PONV) – TRV130-treated healthy volunteers had less nausea and vomiting at a dose eliciting greater analgesia compared to a high dose of morphine in a Phase 1 trial. We think this is in line with another Phase 1 study in which TRV130 showed no nausea or vomiting at doses eliciting equivalent or greater pupil constriction, compared to 20% to 30% PONV incidence with morphine or fentanyl. We believe the KOLs will see PONV reduction as a meaningful advantage unique to TRV130.

Reduced constipation – In several preclinical studies, TRV130-treated subjects reported significantly less constipation compared to morphine at doses delivering equivalent analgesia. We think TRV130 could show these potential benefits in the clinical setting, and it would translate into meaningful cost savings to the healthcare system.

Compelling clinical data for TRV130

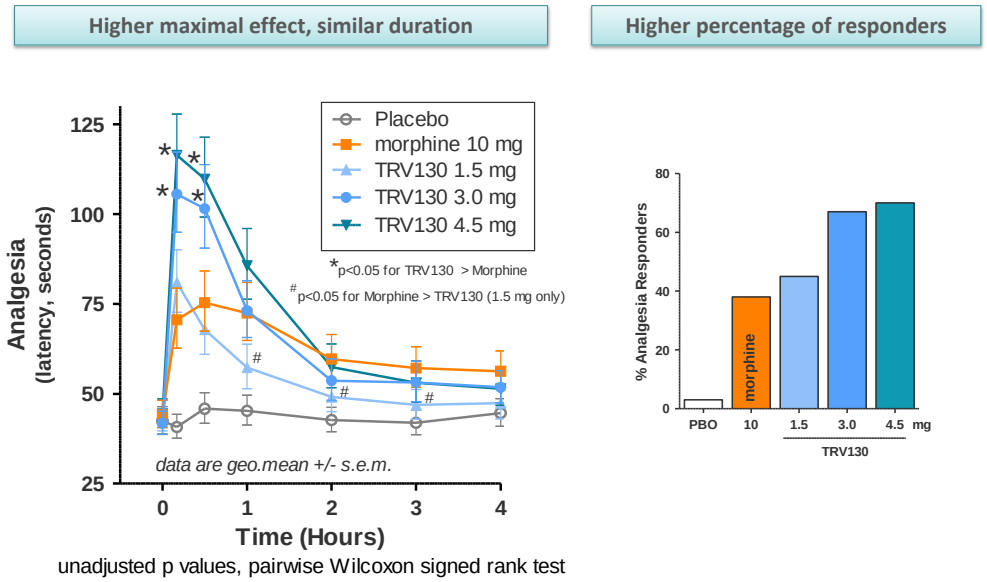
Since an active IND was granted in 2012, TRVN has dosed TRV130 in 121 healthy subjects across four clinical trials.

Phase 1b POC exploratory trial

TRV130's safety and analgesic effects were compared to a 10mg dose of morphine in this double-blind, five-period crossover design with 30 healthy male subjects. Each person was randomized to receive a two-minute infusion of three dose levels of TRV130 (1.5mg, 3.0mg and 4.5mg), 10mg morphine, and placebo in random order. TRV130's analgesic effects were evaluated by a cold pain test. Time to hand removal from a temperature-controlled cold water bath was measured. In addition, nausea was record on the visual analog scale and respiratory depression was reported through ventilatory response to hypercapnia.

At 3.0mg and 4.5mg, TRV130 showed statistically significant superior efficacy than a 10mg morphine dose ($p<0.05$) at the 10 and 30 minute after dosing. The durability of the analgesic effect was similar to morphine. In addition, the time to peak effect was much shorter than morphine and there were a higher number of responders, defined as a subject who experienced a doubling of latency, at the 3.0 mg and 4.5mg dose levels compared to morphine.

Figure 17: Ph1b study – TRV130 showed superior analgesia to morphine

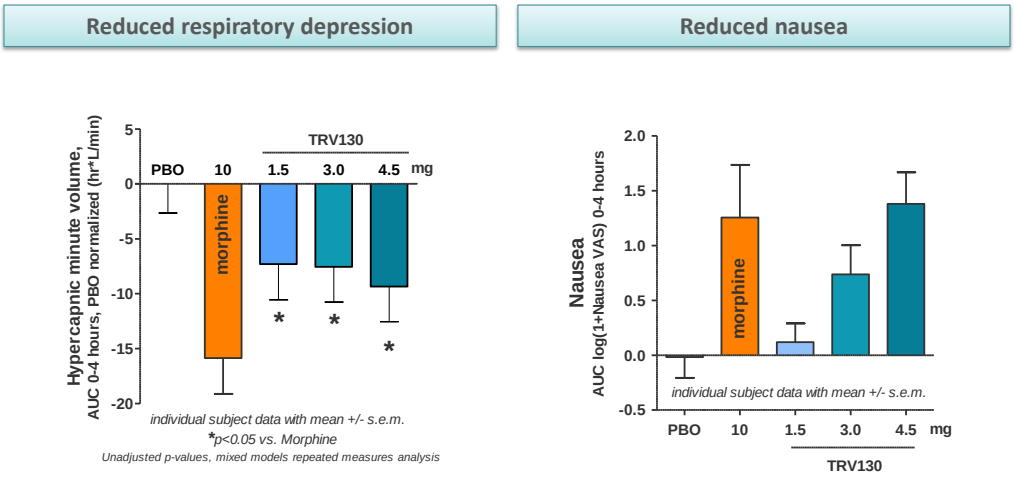


Source: Company presentation

Overall, TRV130 was well tolerated. Subjects receiving TRV130 reported less nausea and vomiting at 1.5mg and 3.0mg doses compared to a 10mg dose of morphine. TRV130 also had less respiratory depression, measured as minute volume (MV), compared to morphine.

MV is a product of respiratory rate and tidal volume, which measures the amount of air exhaled in a single breath. Therefore, it has been used as a measurement to captures the body's ability to expel carbon dioxide. All TRV130 doses resulted in statistically significant reduction in respiratory depression compared to a 10mg morphine dose ($p<0.05$). The 3.0mg dose of TRV130 had superior efficacy, less nausea and vomiting, and less respiratory depression. As such, we think TRV130 is well positioned to be a better analgesic with its improved safety and tolerability compared to existing unbiased mu-opioid agonists.

Figure 18: SPID24 following postoperative treatment in CLIN2002



Source: Company filings

Three-part Phase 1 trial in healthy subjects

Based on the pharmacodynamics data collected from all three trials, TRV130 is deemed appropriate to be administered by continuous IV bolus infusion. Moreover, we think TRV130 can be conveniently administered through patient-controlled analgesic device, which could help drive uptake in the postoperative setting.

TRV130 was well tolerated in the studies. In Part A, TRV130 was administered as a one-hour infusion, and no nausea or vomiting was reported until doses up to 4 mg/hr, which then led to a reduction in pupil diameter. When the dose was increased to 7 mg/hr, four TRV130 treated subjects reported nausea and four reported vomiting. TRV130 administered over one hour produced strong pupil constriction at doses starting at 1.2 mg/hr. Mean pupil diameter decreased as much as 3.5 mm at a 7 mg/hr dose. At the well-tolerated 4mg/hr dose, TRV130 produced a mean reduction in pupil diameter of approximately 2.5 mm, higher than effective morphine or fentanyl doses. At these effective doses of both morphine and fentanyl, 25% of subjects reported nausea and vomiting. Therefore, the 4 mg/hr dose may be as effective as morphine and fentanyl without the opioid-induced nausea and vomiting.

We note that one subject in Part A on 0.25 mg/hr TRV130 experienced a severe episode of vasovagal syncope and it was classified as serious adverse events. The subject subsequently recovered with no medical intervention and experienced no known adverse consequences thereafter. TRVN removed several potential triggers of vasovagal syncope

from the protocol with dose escalation proceeded up to 7 mg/hr. No additional vasovagal syncope events were reported in the study.

In these studies, TRV130 showed a dose-dependent increase in exposure and its primary metabolism through liver enzymes CYP2D6 and CYP3A4. Low-levels of CYP2D6 activity is observed in ~13% of the population. In Part B of the trial, TRV130 was evaluated in a group of poor metabolizers to assess whether dose adjustments will be necessary. The maximum TRV130 plasma concentration in this population was on the upper end of normal metabolizers'. The poor metabolizers exhibit similar TRV130 tolerability to non-poor metabolizers. There was a 50% reduction in clearance in the poor metabolizers and a lower dosing frequency may be required to achieve effective pain relief.

Reducing infusion time when administering TRV130 as a bolus in Part C did not significantly change exposure, which suggests TRV130's viability as an intermittent bolus infusion without compromising drug exposure. In Part C, TRV130 was given to six subjects receiving on successive days a 1.5 mg dose with an infusion time of 30 minutes, 15 minutes, five minutes and one minute. TRV130 was well tolerated with pupil constriction of approximately 1 mm. This data was used to design another intravenous bolus trial described below to assess higher bolus doses.

IV bolus Phase 1 trial

TRV130 was well tolerated up to 3.5 mg in a follow-up trial with bolus doses of 2.0, 3.0 or 3.5 mg administered over two minutes. One subject experienced mild nausea when 3.5 mg TRV130 was given. No nausea was reported with the lower doses. When 3.5 mg of TRV130 was administered, pupil diameter decreased by approximately 2 mm from baseline, which is in line with high-dose morphine or fentanyl.

Drug-drug interaction Phase 1 study

A single dose of TRV130 was administered to healthy subjects in conjunction with ketoconazole, a CYP3A4 inhibitor. The results showed that TRV130 was safe and well-tolerated in the presence of ketoconazole with no meaningful change in TRV130 exposure.

Preclinical studies

Morphine, hydromorphone and fentanyl activate both the G protein and the beta-arrestin pathways, while all three drugs offer significant analgesia at the risk of respiratory depression and constipation. Beta-arrestin knock-out mice were treated with morphine to assess whether the efficacy seen with morphine could be separated from the respiratory and GI effects of the drug. Morphine showed superior analgesia and less respiratory depression and constipation compared to wild-type mice. This supports the hypothesis that a G protein biased ligand at the mu-opioid receptor could deliver better analgesic efficacy with fewer side effects.

In preclinical models, TRV130's G protein biased signaling profile showed analgesic efficacy comparable to morphine but reached peak effect more quickly than morphine. Time to peak effect occurred within five minutes for TRV130 compared to 30 minutes for morphine. TRV130 had a significantly improved therapeutic index of analgesia to respiratory depression, measured as blood carbon dioxide, and analgesia to constipation.

Phase 2 development plans

Following the recent Phase 1b clinical trial using the cold pain model, TRVN is conducting an additional Phase 1 trial in healthy subjects to further elucidate TRV130's PK/PD, safety, and tolerability. This is a multiple ascending dose trial to evaluate the safety and tolerability of multiple doses of TRV130 and to characterize the multiple dose pharmacokinetics.

TRVN will initiate a Phase 2 program of TRV130 in Q1/14 to show analgesic efficacy and confirm TRV130's safety and tolerability profile compared to existing opioid pain medications. We think the Phase 2a/b trial read out by end of Q1/15 and that additional supportive clinical work to be completed by EOY 2015. In addition, TRVN intends to complete other clinical trials that would support Phase 3 development.

The Phase 2a/b trial will use a bunionectomy model to demonstrate drug efficacy in hard tissue pain. We believe the trial will be at least 90% powered to show superior analgesia versus morphine. In addition, we think TRVN will take this opportunity to identify the optimal TRV130 dose in future trials. We think the additional tolerability trial will most likely confirm TRV130's benign safety profile and support differentiation from mainstay MOR based pain therapy in the acute postoperative period. We expect the data to support Phase 3 development of TRV130.

Figure 19: TRV130 – Ph2 development plan

Phase 2a/b bunionectomy trial	Phase 2 tolerability trial
• Data available 1Q 2015 – Phase 3 ready • Demonstrate superior analgesia and therapeutic index versus morphine • Approach: – Sample size of 400 subjects to power for superior analgesia vs. morphine – Adaptive dose selection to identify the optimal TRV130 dose vs. morphine • Study start 2Q 2014	• Data available 4Q 2015 – not critical path to Phase 3 • Study powered to show superior tolerability (GI tolerability and respiratory depression) – Support differentiation – Inform Phase 3 design • As-needed-dosing • Study start 4Q 2014

Source: Company filings

Commercial strategy

TRVN intends to first position TRV130 as the treatment of moderate to severe, acute postoperative pain where IV administration is preferred. However, we see TRV130's potential in perioperative use, non-surgical hospitalized patients such as burn victims, and end-of-life palliative care. We think emergency service trauma care and military applications would also be appropriate, if supportive results are generated in future trials. Alternative dosage forms such as oral or transdermal administration may further expand TRV130's commercial promise.

TRVN plans on developing and commercializing IV TRV130 alone and it will build out an infrastructure for acute care in the US while fully retain rights in the US. For ex-US geographies, TRVN may seek pharmaceutical partners to commercialize TRV130. However, we think the decision will be made after Phase 2 data readout.

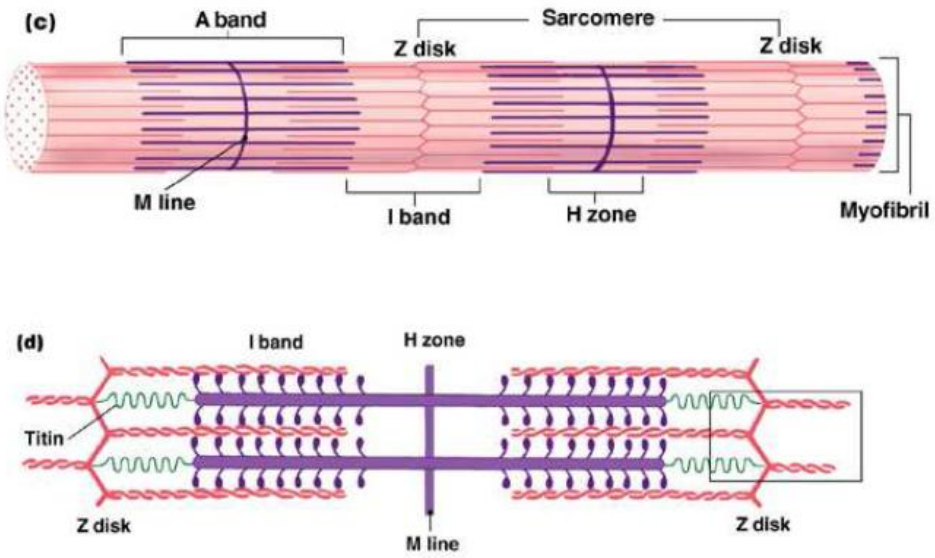
TRV734: emerging CNS portfolio

TRV734 is an orally available, small molecule mu-opioid G protein biased ligand agonist. TRVN is planning on developing TRV734 as a treatment of moderate to severe acute and chronic pain. In preclinical studies, TRV734 has a similar profile to TRV130 in vivo and in vitro. TRV734 achieved oxycodone-like analgesia with less constipation. TRVN intends to initiate several Phase 1 studies to assess the safety, tolerability, and PK/PD of TRV734. The first of the Phase 1 trials is expected to complete by Q3/14. TRVN is open to commercializing TRV734 with a partner who has deep expertise in chronic pain management, while retaining US rights in hospital and specialist markets.

TRV027 AND CARDIAC MUSCLE BIOLOGY

Muscle cells have three basic functions – contractility, growth and secretion of endocrine factors. The basic unit of contraction in a muscle is a sarcomere (Figure 20). A discrete muscle may be composed of millions of these sarcomeres that are connected to (or enervated by) special nerve cells (called motor neurons). Signals from these motor neurons trigger muscle contraction. The unit achieves contractility by sliding filaments (actin and myosin) by each other (this process is described in further detail in the next section). Contraction also produces heat, which contributes to body temperature. In fact, quick, limited repetitive muscle contractions, or shivering, can be used by the body to help regulate body temperature when it falls too low. Muscle growth is achieved through repetitive use. When muscles are strained, the sarcomeres tear and are rebuilt stronger during a resting phase. Muscle cells are also metabolically active and secrete numerous cellular molecules that are important for organ system and metabolism regulation.

Figure 20: Sarcomere physiology and structure



Source: Pearson Education

The contraction and relaxation process

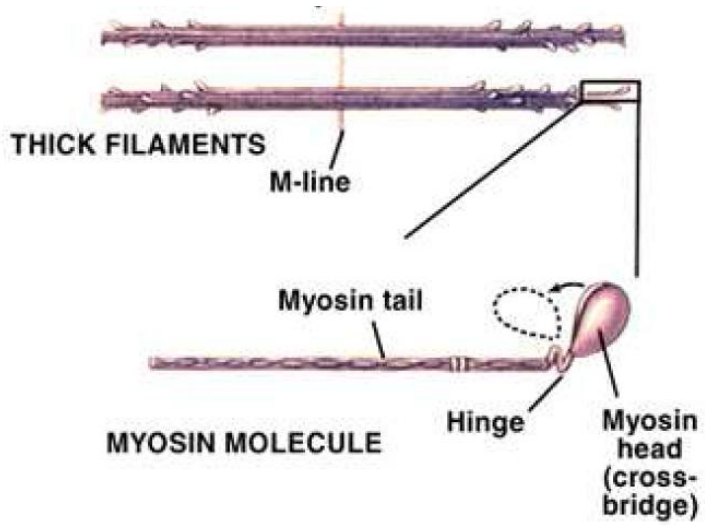
Myofibrils are sets of protein filaments that run along the length of the structure. Myofibrils are sets of protein filaments that run along the length of the structure. Each myofibril is made up of numerous sarcomeres. The thick myosin and thin actin filaments which constitute the myofibrils mediate the mechanics of muscle contraction. Thick filaments are made of a protein fiber called myosin. A thick filament is a shaft of myosin molecules arranged in a cylinder. Thin actin filaments look like two strands of pearl-like connected acting protein molecules twisted around each other.

During contraction, specific sites on the myosin thick filaments (the head structure at the ends, also called the crossbridge) attach to other specific sites on the actin thin filaments and form a reversible bond. The thick filaments pull the thin filaments past them, making the sarcomere shorter. In a muscle fiber, the signal for contraction is synchronized over the entire fiber so that all of the myofibrils that make up the sarcomere shorten simultaneously.

There are two molecules that reside in the grooves of each thin actin filament that enable the actin fiber to slide along and then attach to myosin. The first of these molecules is a long, rod-like protein called tropomyosin. The second is a shorter, bead-like protein complex called troponin. Troponin and tropomyosin are the molecular switches that control the actin-myosin crossbridge formation during a muscle contraction.

Initially, the crossbridge is extended (Figure 21) with an attached adenosine diphosphate (ADP) and inorganic phosphate (Pi). As soon as the myosin head attaches to the actin, it bends inward at the hinge, sliding the actin filament past the myosin, contracting the sarcomere (much like triggering a spring-loaded trap) and creating force. This bending of the crossbridge and sliding of the filaments is a process is called the power stroke. During the power stroke, myosin releases the ADP and Pi. Once ADP and Pi are released, a molecule of adenosine triphosphate (ATP) binds to the myosin. When the ATP binds, the myosin releases the actin molecule. The ATP molecule is then de-phosphorylated, or gets split into two parts (ADP and Pi) by the myosin. This split releases energy which resets the myosin head to its original extended position. The powerstroke and reset process is repeated for as long as the muscle is receiving a nerve signal triggering contraction. The filaments slide further and further along each other and the sarcomere gets shorter and shorter. The actions of all the myofibrils in a sarcomere are not synchronized. At any given moment, some myosins are attaching to the actin filament, others are bending crossbridges and finally others are in the release step, while others are in the ATP driven reset step. This entire process is referred to as crossbridge cycling, as the actin-myosin crossbridge bonds are constantly being formed, bent and finally broken.

Figure 21: Sarcomere contraction

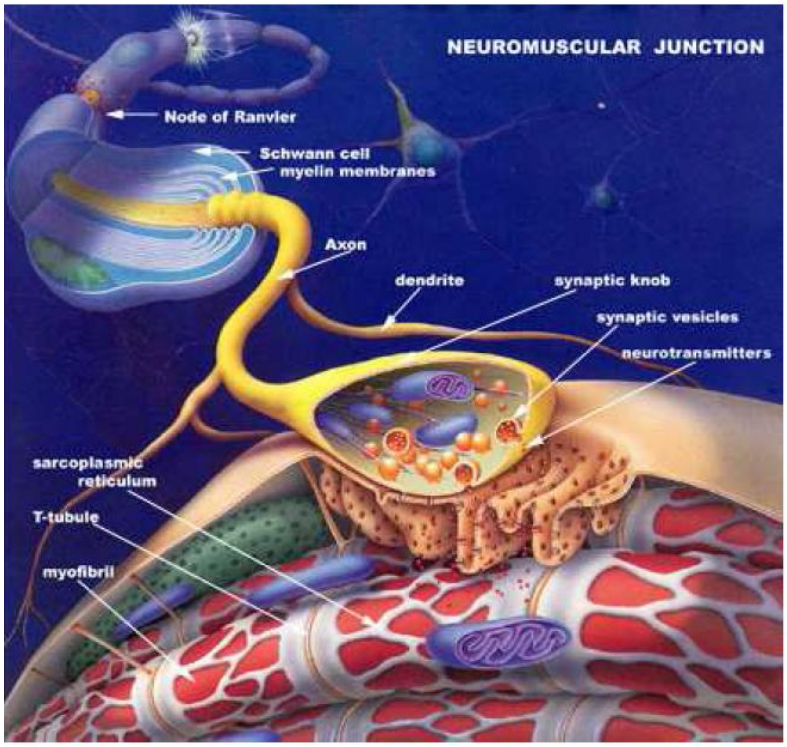


Source: Canaccord Genuity Research

Triggering and reversing contraction. The trigger signal for initiating the crossbridge cycle and muscle contraction is an electrical impulse, or action potential, from the attached motor neuron. The signal triggers a series of events which are slightly different between skeletal, smooth and cardiac muscle. An electrical signal travels down to the end of the motor neuron, causing it to release a chemical messenger molecule or neurotransmitter into a small gap between the end of the nerve cell and membrane of muscle cell, called the synapse. The neurotransmitter crosses the synaptic gap and binds to a receptor on the muscle-cell membrane. This causes ion channels in the muscle membrane to open which generates an action potential on the muscle cell membrane. The action potential rapidly spreads along the surface muscle cell and enters the cell through a region called the transfer-tubule or T-tubule (Figure 20).

This muscle action potential then opens channels in the muscle's calcium ion stores, contained in an intracellular structure called the sarcoplasmic reticulum. Calcium ions then flood into the muscle cytoplasm, where they come into contact with actin and myosin filaments, as well as troponin and tropomyosin.

Figure 22: Neuromuscular junction

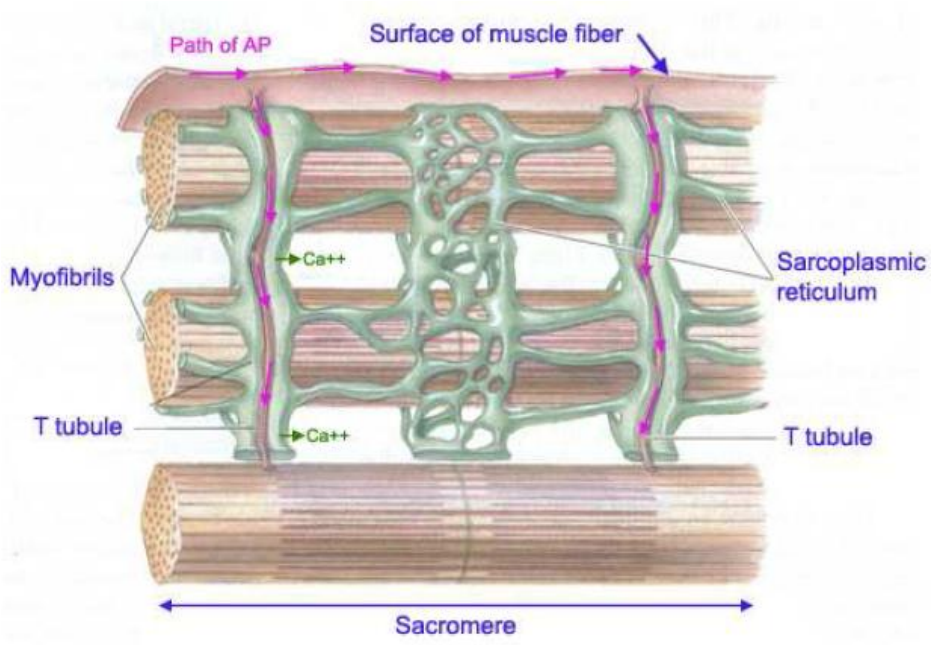


Source: *Biology*, Campbell's 7th *edition*

The newly released calcium ions bind to troponin-tropomyosin molecules in the grooves of the actin filaments. Normally, the rod-like tropomyosin molecule covers the sites on actin where myosin crossbridges attach. However, when calcium ions bind to troponin, the protein changes shape and pushes tropomyosin out of its groove, exposing the actin-myosin binding sites. This allows for crossbridge cycling.

After the action potential has passed, the calcium gates close. Calcium pumps located on the sarcoplasmic reticulum transport the free calcium ions out of the cytoplasm, sequestering them back in the sarcoplasmic reticulum. Calcium ions come off the troponin, which then returns to its normal shape and allows tropomyosin to cover the actin-myosin binding sites on the actin filament. No binding sites are now available now and therefore no crossbridges can form: the muscle relaxes. As and more calcium is sequestered, cytoplasmic levels of calcium falls and the muscle stops contracting. In skeletal muscle, calcium ions work at the level of actin (actin-regulated contraction). They move the troponin-tropomyosin complex off the binding sites, allowing actin and myosin to interact.

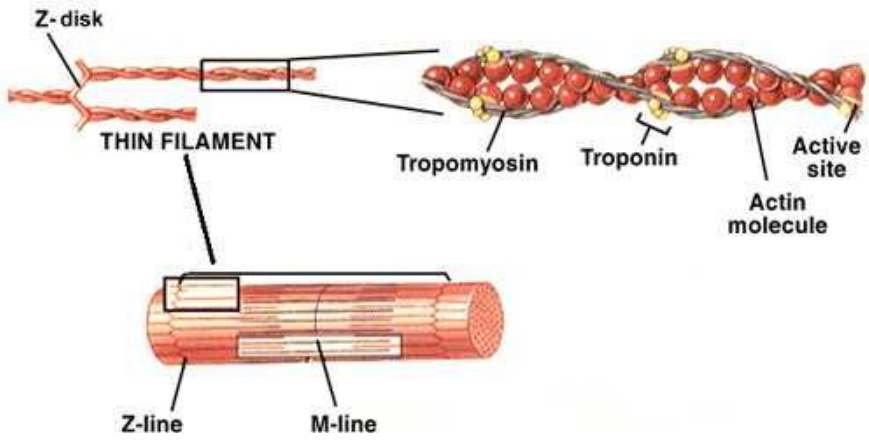
Figure 23: The role of action potentials and calcium ions in muscle contraction



Source: A.D.A.M. Education

All muscle contraction requires energy and muscles use energy in the form of ATP. The energy from ATP is used to reset the myosin crossbridge head and release the actin filament. Muscles have a mixture of two basic types of fibers: fast twitch and slow twitch. Fast-twitch fibers are capable of generating greater force and contracting faster. They also have higher functional capacity in a low-oxygen environments. Slow-twitch fibers in comparison generate force relatively slowly but can maintain contractions longer. They are also significantly more efficient at generating usable energy (in the form of ATP) through aerobic (oxygen-based) metabolism. ATP generation occurs in an intracellular body known as mitochondria. Mitochondria are known as the powerhouses of the cell which take in nutrients and oxygen, break them down, and create energy for the cell.

Figure 24: Proteins regulating muscle fiber construction and contraction



Source: A.D.A.M. Education

Cardiac muscle

Cardiac muscle tissue forms the bulk of the wall of the heart. Cardiac muscle is striated to the eye. The muscle fibers appear to contain alternating light and dark bands (striations) that are perpendicular to the long axes of the fibers. Unlike skeletal muscle tissue, its contraction is usually not under conscious control (involuntary).

Cardiac muscle cells (also known as cardiac myocytes) are unique to the heart. They are involuntary and heavily dependent on oxygen. These cells are easily damaged and quickly die when deprived of oxygen (such as during heart attacks). Cardiac myocytes connect to each other at irregular angles and in a branched manner as opposed to the linear and longitudinal connections of skeletal muscle.

One of the major differences between cardiac muscle and the other two types of muscle is the cardiac muscles' dependence on extracellular calcium ions in order to contract. This has given rise to a class of hypertension drugs known as calcium channel blockers, which inhibit calcium ion uptake and thus reduce the force with which the heart contracts, resulting in decreased blood pressure.

Figure 25: Heart failure is the most serious disease affecting cardiac muscle

Heart failure	Cardiac muscle damage that reduces the heart's ability to pump blood. This results in an inadequate oxygen supply to body tissues, which can cause chronic fatigue, fluid buildup in the lungs, wasting and additional heart disease.

Source: Heart Failure Society of America

Smooth muscle

Smooth muscle makes up part of the walls of hollow body structures like blood vessels, the stomach, intestines, the iris of the eye and bladder. Vascular smooth muscle is localized in blood vessel's tunic media (middle) layer, which exists in large and small arteries and veins. Smooth muscle is present wherever there is involuntary movement in the body except the heart.

Smooth muscle is usually involuntary, non-striated and, like skeletal and cardiac muscle tissue, can undergo hypertrophy. There are also certain smooth muscle fibers, such as those in the uterus that can retain their ability to divide and grow by hyperplasia. Smooth muscle is structured differently and functions differently from cardiac and skeletal muscle. Individual smooth muscle cells are joined together by adherens junctions that allow action potentials, which trigger muscle contraction, to rapidly travel between cells.

Figure 26: Diseases affecting smooth muscle

Condition	Description
Chronic Obstructive Pulmonary Disease (COPD)	A chronically constricted airway that is a result of the combination of chronic inflammatory bronchitis and emphysema. COPD is progressive and causes significant difficulty in breathing, which can be fatal.
Hypertension (HT) or high blood pressure:	Higher-than-normal mean arterial blood pressure. The threshold for normal arterial pressure is 115 mmHg diastolic pressure (during the cardiac cycle, or heart beat, when the heart is emptying) and 75 mmHg systolic pressures (at the beginning of the cardiac cycle when the heart is filling). Pressure higher than this is considered dangerous. High blood pressure can lead to blood vessel disease, heart attack, stroke and kidney disease.
Pulmonary Arterial Hypertension (PAH)	PAH is localized high blood pressure in the pulmonary artery, pulmonary vein or other lung blood vessels. This often leads to shortness of breath, dizziness and fainting. PAH is a progressive and fatal disease and represents a significant unmet medical need.

Source: Canaccord Genuity research

Skeletal muscle

Skeletal muscle is striated; and contains characteristic alternating light and dark bands (striations) perpendicular to the long axes of the fibers. Skeletal muscles are voluntary.

Figure 27: Diseases affecting skeletal muscle

Condition	Description
Amyotrophic Lateral Sclerosis (ALS):	A progressive, fatal neurodegenerative disease that is caused by a degeneration of motor neurons responsible for voluntary muscle movement. The disorder causes muscle weakness and atrophy throughout the body, and eventual respiratory failure.
Myasthenia Gravis	An autoimmune neuromuscular disorder characterized by variable weakness of voluntary muscles, which often improves with rest and worsens with activity.
Sarcopenia	A degenerative loss of skeletal muscle generally associated with aging. Different from pure muscle atrophy in that muscle fibers are replaced with fat and there is an increase in fibrotic connective tissue in and around muscles.
Cachexia	Generally associated with patients who have cancer, AIDS, chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF), it is characterized by loss of weight, muscle atrophy, fatigue, weakness and significant loss of appetite. The mechanism by which cachexia is caused is not well understood. Treatment response for this condition is usually very poor.

Source: Canaccord Genuity research

All skeletal muscle fibers are not alike in structure or function. For example, skeletal muscle fibers vary in color depending on their content of myoglobin. Myoglobin is a protein that binds and stores oxygen within the muscle until needed by the mitochondria, making muscle function less dependent on blood flow. Skeletal muscle fibers contract with different speed and force, depending on their ability to split ATP.

Faster contracting fibers have can ATP and reset their crossbridges more rapidly than other fibers. Skeletal muscle fibers can differ in how they metabolically generate ATP, and therefore how quickly they become fatigued. In the case of hypoxia (lack of oxygen) smooth and skeletal are able to switch to a non-oxygen-based way (anaerobic) to generate ATP. However, an extended period of anaerobic respiration results in the buildup of a by-product of the process, lactic acid, which causes muscle fatigue.

There are three types of skeletal muscle fibers with different various structural and functional characteristics: Type I fibers, Type II B fibers and Type II A fibers.

Type I Fibers – These are called slow twitch or slow oxidative. They contain large amounts of myoglobin, many mitochondria and a rich blood supply. Type I fibers are red, split ATP slowly, have a slow contraction velocity, are very resistant to fatigue and have a high capacity to generate ATP by oxidative (or oxygen-based) metabolic processes. Many of these fibers are found in neck muscles involved in posture.

Type II A Fibers – These are called fast twitch or fast oxidative fibers. Like Type I fibers, they also have high quantities of myoglobin, mitochondria and a rich blood supply. Type II A fibers are red, have a very high capacity for generating ATP by oxidative metabolic processes, split ATP at a very rapid rate, have a fast contraction velocity and are resistant to fatigue. Such fibers are infrequently found in humans.

Type II B Fibers – These are also called fast twitch or fast glycolytic fibers. They contain little myoglobin, few mitochondria, a relatively small blood supply and large amounts glycogen (the raw material for non-oxygen based ATP generation). Type II B fibers are white, geared to make ATP by non-oxygen based metabolism, fatigue easily, split ATP at a fast rate and have a fast contraction velocity. These fibers are common in arm muscles.

Figure 28: Comparison of the three skeletal muscle types

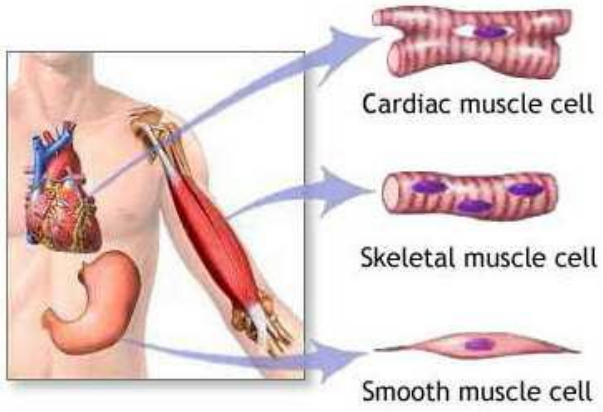


Table. Comparison of Muscle Types

	Muscle Type		
Characteristic	Skeletal	Cardiac	Smooth
Nuclei	Multinucleated; peripherally located	Single nucleus; centrally located	Single nucleus; centrally located
Banding	Actin and myosin form distinctive bands	Actin and myosin form distinctive bands	Actin and myosin; no distinctive bands
Z disks	Present	Present	Z disks not present; cytoplasmic dense bodies are present
T tubules	T tubules at A-I junction; triads present	T tubules at Z disk; diads present	No T tubules; no triads or diads; caveolae are present
Cellular junctions	No junctional complexes	Intercalated disks	Gap junctions
Neuromuscular junctions	Present	Not present; contraction is intrinsic	Not present; contraction is intrinsic, neural, or hormonal
Ca 2+-binding	Troponin	Troponin	Calmodulin
Regeneration	Limited; satellite cells	None	High

Source: A.D.A.M Education

HEART FAILURE

Heart failure, also called congestive heart failure, is a life-threatening and progressive condition in which a weakened heart can no longer pump enough blood to the rest of the body. The patient's body tissues are then chronically deprived of oxygen, especially during physical exertion. Heart failure can also lead to fluid accumulation in the extremities (lower legs, ankles and hands), abdomen and most importantly the lungs. Fluid retention in the lungs can lead to difficulty breathing. Patients often experience fatigue, weakness, faintness, palpitations and muscle wasting. They also have increased heart rates as a failing heart pumps blood at a faster rate in an attempt to compensate and meet body oxygen demands.

Figure 29: NYHA heart failure severity classification

	Definition	Disability	Prognosis
Class I	No limitation of physical exercise	No symptoms on ordinary activity	Poor
Class II	Slight limitation of physical activity	Symptoms on ordinary activity	Bad
Class III	Marked limitation of physical activity	Symptoms on less than ordinary activity	Awful
Class IV	Inability to carry out any physical activity without discomfort	Symptoms at rest	Terminal

Source: Heart Failure Society of America

Pathology of heart failure

Heart failure is most often caused by damage to heart muscle caused by acute or chronic oxygen deprivation. This lack of oxygen can be the result of a heart attack or milder impaired blood flow to the heart (almost always caused by coronary artery disease). Cardiomyopathy or thickening of the heart walls (also referred to as cardiac hypertrophy) is usually a response to the body's lack of oxygen. The body induces overgrowth of the heart muscle tissue in an attempt to increase pumping power. Heart failure can also be caused by heart valve disease, as malfunctioning heart valves can also interfere with normal blood flow and cardiac function. Finally, heart failure can also be caused severe congenital heart disease.

Heart failure can be chronic or acute, although chronic heart failure is significantly more common. The disease is classified by the severity of heart function impairment (Figure 29). 50% of the patients with the most advanced stage of heart failure die within a year. Chronic heart failure can due to systolic or diastolic dysfunction:

Systolic: This condition is when the pumping action of the heart is reduced or weakened. A common clinical measurement is the ejection fraction (EF) which is the amount of blood ejected out of the left ventricle during a heartbeat (stroke volume), divided by the

maximum volume in the left ventricle at the end of diastole/relaxation phase. A normal ejection fraction is greater than 50%. Systolic heart failure patients have ejection fraction of less than 50%.

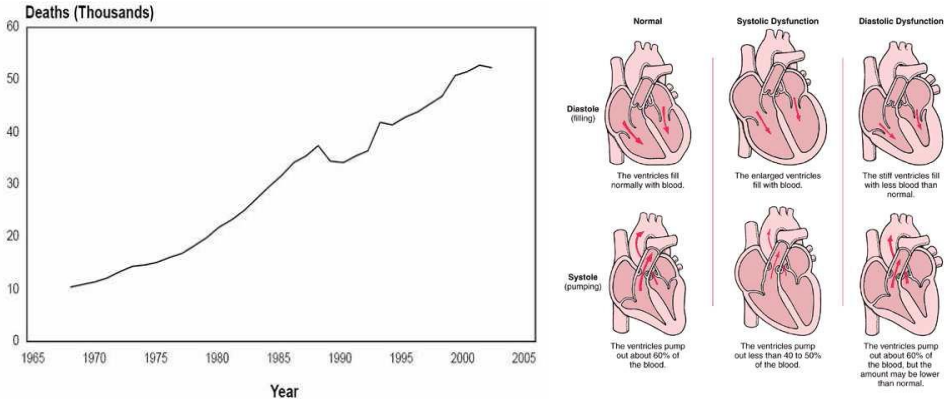
Diastolic: The condition is characterized by a heart than can contract normally (ejection fraction can be normal) but is stiff, or less flexible, especially during diastole when it is relaxing and filling with blood. This impedes the heart filling with blood and results in fluid backup into the lungs and heart failure symptoms. While ejection fraction may be normal, diastolic heart failure still results in less blood flow to the body. Diastolic heart failure is more common in patients older than 75 years, especially in women with high blood pressure.

Acute heart failure. Acute heart failure is a critical condition that is often a period of acute disease exacerbation commonly seen in patients who already have chronic heart failure. Acute heart failure patients typically present with severe shortness of breath, among other symptom, but not with chest pain that is characteristic of a heart attack. Acute heart failure patients who require hospitalization can have mortality rates as high as 10-20%.

Incidence/prevalence of heart failure

According to the Heart Failure Society of American, over 5.7 million people in the United States have heart failure. The HFSA also estimates that 670,000 people are diagnosed with some stage of heart failure every year. The AHA also estimates that there are 300,000 deaths in the US from the condition each year. The World Health Organization estimates that there are approximately 23 million people worldwide with congestive heart failure (CHF), although some estimates range up to 65-70 million patients and 2 million new cases of CHF diagnosed each year. Annually, according to the HFSA, the condition accounts for 12-15 million office visits, 6.5 million hospital days, and a total medical cost of over $29 billion.

Figure 30: Deaths from congestive heart failure, US 1968-2002



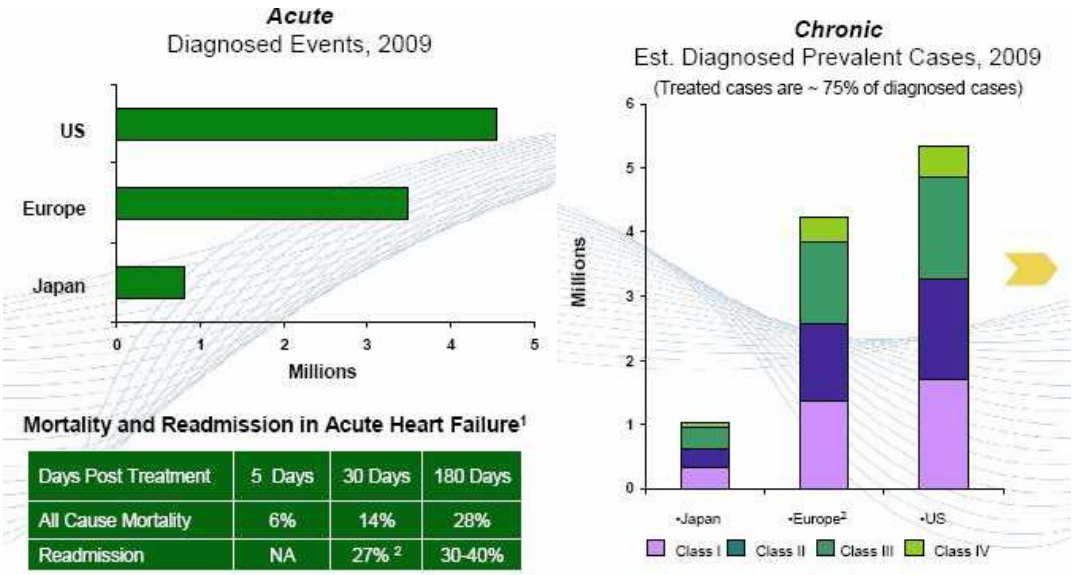
Source: Vital Statistics of the US, NCHS

The demographic at highest risk for heart failure are people age 65 and older and the condition is the leading cause of hospitalization for this age group. African Americans also have a higher risk for developing heart failure than other races, and also tend to have worse disease and prognosis. Overweight and obese patients are also at higher risk for

heart failure as excess weight often results in high blood pressure, which results in a greater strain on the heart.

While the incidence rates of other heart diseases such as heart attacks and strokes have actually declined during the past few decades, the incidence of heart failure is on the rise. It is, in fact, the most rapidly growing cardiovascular disorder in the United States. The prevalence of heart failure doubles for each decade of life after 50. As the average age of the general population increases, as well as the worldwide incidence of overweight and obesity, experts believe that the incidence and prevalence of heart failure will continue to grow.

Figure 31: Prevalence of and chronic heart failure



Source: HFSA

Market size

IMS estimates sales of heart failure drugs were $1.33 billion in 2004. They are expected to reach $4.13 billion by 2011. The exact market size for heart failure drugs is hard to quantify as most of the drugs commonly used to treat heart failure address blood pressure, and so are widely used in high blood pressure patients without heart failure. The economic burden of congestive heart failure is enormous, with an estimated cost to the US health care system in 2005 of $37.2 billion.

Market drivers

Most clinical and cardiovascular market experts believe the incidence and prevalence of heart failure is growing as a result of the aging population. In addition, growing prevalence of diabetes and obesity are considered major contributing factors as well. Moreover, growth in the heart disease population is also driven by the improved survival rate of people after heart attacks.

Long-term clinical data reinforcing compliance: Clinical trials have established that combination therapy with ACE inhibitors, beta blockers, and diuretics is the most effective

current treatment for the relief of heart failure symptoms and the prevention of disease progression.

Current drugs

Heart failure patients receive several chronic oral drugs, most of which are designed to benefit other target of cardiac health. These drugs can generally be classified into four distinct groups: diuretics, ACE inhibitors, beta-blockers and inotropic agents. ACE inhibitors and beta blockers have already been shown to reduce these rates significantly

Angiotensin-converting enzyme (ACE) inhibitors. ACEs have been proven to improve heart failure symptoms and patient survival. They are vasodilators that widen or dilate blood vessels to lower blood pressure, improve blood flow and decrease the workload on the heart. Examples include enalapril (Vasotec), lisinopril (Prinivil, Zestril) and captopril (Capoten). ACE inhibitors also mediate the effects of hormones that promote salt and water retention. However, these drugs can cause an irritating cough in some patients that is severe enough to warrant discontinuation.

Angiotensin II (A-II) receptor blockers (ARBs). These drugs, which include losartan (Cozaar) and valsartan (Diovan), have many of the same clinical benefits on blood pressure as ACE inhibitors, as they work through the same hormonal pathways. However, ARBs do not cause the persistent cough that can be associated with ACE inhibitors in some patients. ARBs may be an alternative for people who can't tolerate ACE inhibitors.

Digoxin (Lanoxin). High doses of digoxin, also called digitalis, increases the cardiac contraction strength of heart muscle and slows the heart rate. The drug's exact mechanism is not yet well understood, but it is currently thought to work by inhibiting the sodium and chloride ion pump in cardiac cells. This inhibition leads to higher cardiac muscle cell calcium levels, which may result in stronger contraction and better heart function. Data shows that digoxin also reduces heart failure symptoms and improves patient survival, but some experts believe that meaningful benefit in heart muscle contractility only occurs at very high doses rarely used in the clinical setting.

Beta blockers. These drugs slow heart rate and reduce blood pressure. Examples include carvedilol (Coreg), metoprolol (Lopressor) and bisoprolol (Zebeta). They can also reduce the risk of abnormal heart rhythms. Beta blockers may reduce signs and symptoms of heart failure and improve heart function.

Diuretics. Often called water pills, diuretics eliminate excess body fluid by increased urination. Commonly prescribed diuretics for heart failure include bumetanide (Bumex) and furosemide (Lasix). Diuretics also decrease fluid in the lungs, which is characteristic of certain types of heart failure. Diuretics induce potassium and magnesium loss, and therefore need to be given together with supplement and sometime require regularly blood monitoring.

Calcium channel blockers. Calcium channel blockers are used to treat diastolic heart failure. These drugs slow the heart rate by blocking the number of electrical signals that induce heart muscle contractions and heartbeats. Calcium channel blockers may help hearts with diastolic heart failure fill with blood more easily by slowing heart rate and lowering blood pressure. Slowing the heart rate gives the organ more time to fill with blood between each heartbeat. Calcium channel blockers may also help the heart muscle to relax, which can help it fill with blood. Lower blood pressure may help treat diastolic heart

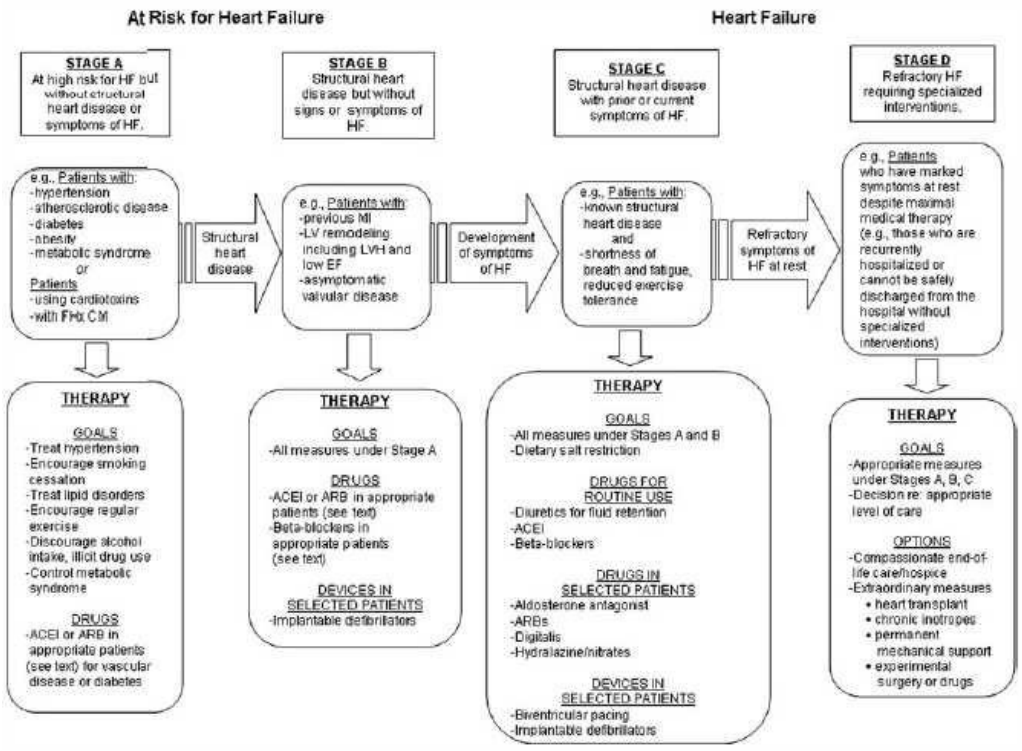
failure because the heart does not have to work as hard to pump blood. Importantly, these drugs can actually worsen systolic heart failure due to their ability to slow heart rates.

Aldosterone antagonists. These drugs include spironolactone (Aldactone) and eplerenone (Inspra). They're primarily potassium-sparing diuretics, but they also improve heart function, may reverse post-heart attack scarring of the heart and may also improve survival. Spironolactone can raise the level of potassium in the blood to dangerous levels.

A majority of heart failure patients are treated with drug therapy, but for patients with advanced congestive heart failure, device-based therapy or transplantation are their only alternatives. A large number of patients with advanced CHF have received left ventricular assist devices, and a number of promising technologies, including biventricular pacing and defibrillators, ventricular remodeling, and ventricular assist devices represent exciting, growing markets.

The poly-pharmacy approach has led to an estimated 50% medication compliance rate among heart failure patients. Main reasons for non-compliance include high cost of medicine, intolerance of side effects, and high dosage frequency / low dosage rates (many doctors prescribe dosages much lower than those used in clinical trials due to fear of adverse reactions).

Figure 31: AHA/HFSA treatment guidelines for heart failure



Source: Heart Failure Society of America

Serelaxin

Serelaxin is a recombinant human relaxin-2, which is a naturally occurring peptide hormone that mediates the maternal physiological cardiovascular and renal adaptations

during pregnancy and has potential protective effects against organ damage. The Phase 3 RELAX-AHF (Relaxin in Acute Heart Failure) study examined the effects of serelaxin in patients with AHF and serelaxin demonstrated improvement in one of the two primary endpoints. Serelaxin improved visual analogue scale through day 5, which is a measure of dyspnea, but it did not affect the dyspnea relief assessed using the Likert scale at 6, 12, and 24 hours. Serelaxin also did not show reduction in cardiovascular death or heart failure readmissions through day 60 (or days alive) and out of the hospital through day 60. In addition, we note the pre-specified all-cause 180-day mortality was significantly reduced by serelaxin administration, and these results were similar to those of the Pre-RELAX-AHF Phase 2 trial.

Serelaxin Phase 3 results

1161 patients were randomly assigned to serelaxin (n=581) or placebo (n=580) in the Phase 3 RELAX-AHF study that examined the effects of serelaxin on dyspnea reduction and 60-day outcomes. Serelaxin significantly reduced dyspnea, as measured by change from baseline on a 100-point visual analogue scale over 5 days compared with placebo (p=0.007), but had no significant effect on the other primary endpoint (Likert scale; placebo, p=0·70).

In addition, serelaxin administration did not affect 60-day readmissions or death (p= p=0·89, p=0·37), largely because of the lack of an effect on readmissions. Serelaxin administration was associated with other beneficial effects on congestion, length of stay in the intensive care unit, and length of initial hospital stay as well as a reduction of 180-day all-cause mortality (p=0·019).

EU rejection and delayed FDA AdComm

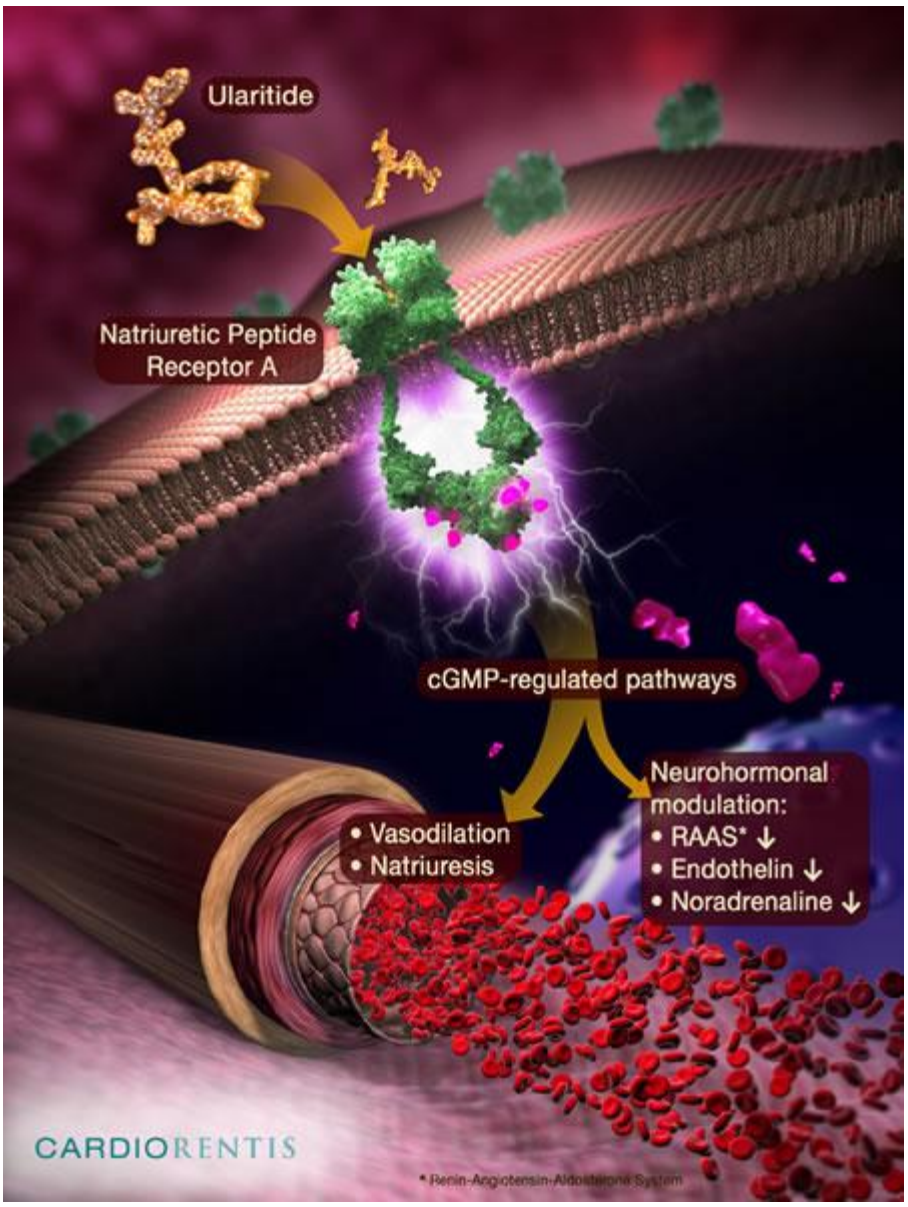
On February 11, 2014, the Committee for Medicinal Products for Human Use (CHMP) recommended that serelaxin not be approved as a treatment to relieve symptoms in patients with acute heart failure. In its opinion, CHMP highlighted results that showed serelaxin failed to provide short-term relief despite benefits over five days. The committee questioned the clinical relevance of that benefit and called for further studies. In its press release, Novartis said it planned to submit a revised filing with new analyses in mid-March and Novartis has a 15-day window after notification to request a re-examination of the CHMP's decision.

Also on February 11, 2014, FDA officially postponed the serelaxin AdComm scheduled for February 13, 2014. We think Novartis' serelaxin will receive an automatic 3-months extension and potential FDA decision will come in H2/14.

Cardiorentis' ularitide

Ularitide is an advanced natriuretic peptide in Phase 3 development as an IV infusion treatment for (AHF) by Cardiorentis. Ularitide is the chemically synthesized form of urodilatin. Urodilatin is a natriuretic peptide naturally occurring in humans produced in the kidneys and induces natriuresis and diuresis to regulate fluid balance and sodium haemostasis by binding to specific natriuretic peptide receptors (NPR-A, NPR-B and other natriuretic peptide receptors), thereby increasing intracellular cyclic guanosine monophosphate (cGMP) helping to relax smooth muscle tissues, leading to vasodilation and increased blood flow.

Figure 32: Mechanism of action of ularitide



Source: Cardiorentis.com

Figure 33: Ularitide Phase 3 trial design

	Efficacy and safety of ularitide for the treatment of acute decompensated heart failure
NCT ID	NCT01661634
Design	Randomized, placebo controlled, double blind
Enrollment	2152 (estimated)
Dosing	Ularitide, lyophilizate for i.v. infusion, 15 ng/kg BW/min, for 48 hours
Key inclusion criteria	• Males and females aged 18 to 85 years. • Unplanned hospitalization or emergency department visit for ADHF. Acute HF is defined as including all of the following: o Dyspnea at rest in a recumbent sitting position (30 to 45 degrees), which has worsened within the past week o Radiological evidence of HF on a chest X-ray o Brain natriuretic peptide (BNP) >500 pg/mL or N-terminal pro-brain natriuretic peptide (NT-pro BNP) >2000 pg/mL. • Ability to start infusion of the study drug within 12 h after initial clinical assessment performed by a physician at the emergency room/hospital. • Ability to reliably carry out self-assessment of symptoms. • Systolic blood pressure ≥116 mmHg and ≤180 mmHg at the time of randomization. • Persisting dyspnea at rest despite standard background therapy for ADHF (as determined by the Investigator) which must include IV furosemide (or equivalent diuretic) at ≥40 mg (or its equivalent) at any time after start of emergency services (ambulance, emergency department, or hospital). At the time of randomization, the patient must still be symptomatic. In addition, the patient should not have received an IV bolus of a diuretic for at least 2 h prior to randomization, and the infusion rates of ongoing IV infusions must not have been increased or decreased for at least 2 h prior to randomization. • Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local privacy regulations).
Key exclusion criteria	• Known active myocarditis, obstructive hypertrophic cardiomyopathy, congenital heart disease, restrictive cardiomyopathy, constrictive pericarditis, uncorrected clinically significant primary valvular disease. • Treatment with dobutamine at a dose >5 µg/kg/min or use of drugs for support of BP at the time of randomization. • Treatment with levosimendan, milrinone, or any other phosphodiesterase inhibitor within 7 days before randomization. • Treatment with nesiritide within 30 days before randomization. • Creatinine clearance <30 mL/min/1.73m² (as measured by the MDRD formula) at the time of screening. • Planned coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass grafting) within 5 days of randomization. • Clinical diagnosis of acute coronary syndrome meeting any 2 of the following 3 criteria: o Prolonged chest pain at rest, or an accelerated pattern of angina o Electrocardiogram changes indicative of ischemia or myocardial injury defined as: a new ST elevation at the J point of two anatomically contiguous leads with the cut-off points: ≥0.2 mV in men ≥40 years (>0.25 mV in men <40 years) or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads; or ST depression and T wave changes. New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or new T inversion ▪ 0.3 mV in two contiguous leads. o Serum troponin >3 times upper limit of normal. • Clinically suspected acute mechanical cause of ADHF (e.g., papillary muscular rupture). The diagnosis need not be confirmed by imaging or cardiac catheterization. • Anemia (hemoglobin <9 g/dL or a hematocrit <25%). • Known vasculitis, active infective endocarditis, or suspected infections including pneumonia, acute hepatitis, systemic inflammatory response syndrome, or sepsis. • Body temperature ≥38°C just prior to randomization. • Acute or chronic respiratory disorder (e.g. severe chronic obstructive pulmonary disease) or primary pulmonary hypertension sufficient to cause dyspnea at rest, which may interfere with the ability to interpret dyspnea assessments or hemodynamic measurements. • Terminal illness other than congestive heart failure with expected survival <180 days. • Any previous exposure to ularitide. • Known allergy to natriuretic peptides. • Participation in an investigational clinical drug trial within 30 days prior to randomization. • Current drug abuse or chronic alcoholism sufficient to impair participation and compliance to the study protocol. • Women who are breast-feeding. • Women of child-bearing potential (i.e. pre-menopausal women) without documentation of a negative urine/blood pregnancy assay within 12 h prior to randomization. • Any condition that, in the Investigator's opinion, makes the patient unsuitable for study participation. • Legal incapacity or limited legal capacity. • Patients requiring mechanical circulatory support. • Patients with severe hepatic impairment.
Primary endpoint	Two Co-primary Efficacy Endpoints: • Improvement in a hierarchical clinical composite comprised of elements associated with: patient global assessment using a 7-point scale of symptomatic improvement, lack of improvement, or worsening; persistent or worsening heart failure (HF) requiring an intervention (initiation or intensification of IV therapy, circulatory or

Source: Clinicaltrials.gov

TRV027 IN ACUTE HEART FAILURE (AHF)

TRVN is developing TRV027, a peptide beta-arrestin biased ligand that targets the AT1R, inhibiting G protein signaling and activating beta-arrestin signaling for the treatment of acute heart failure (AHF), to be used in combination with standard diuretic therapy. In a Phase 2a study, TRV027 reduced blood pressure and preserved renal and cardiac function. TRVN has started enrolling patients in its Phase 2b clinical trial to evaluate the safety and efficacy of TRV027 in AHF. Based on strong scientific rationale and clean safety profile, we think TRV027 has the potential to be a first-line in-hospital AHF treatment. Moreover, if TRV027 shows improvements in AHF symptom in future trials, shortened length of stay, and reduced readmission and mortality rates after discharge, it may be well-received by the physicians and could achieve rapid uptake.

Key differentiating attributes of TRV027

TRV027 may benefit blood vessels, heart and kidneys. TRV027 rapidly, reversibly lowered blood pressure and pulmonary capillary wedge pressure (PCWP, a key heart failure marker that often correlates with dyspnea improvement and often to referred to as wedge pressure). TRV027's beneficial blood pressure and PCWP lowering allows the heart to pump against less resistance and move blood around the body more effectively. This is turn can in turn preserve cardiac performance by stressing cardiac tissue. TRV027 may also preserve kidney function, as evidenced by a number of renal function markers. This suggests treatment with TRV027 could result in improvements in heart failure symptoms and outcomes (e.g. hospital readmission rates, length of stay, mortality).

Enhances diuretic effects on wedge pressure. Furosemide is a common diuretic used as first-line treatment in ~90% of AHF patients. The drug causes a patient's body to excrete excess fluid which in turn lowers blood pressure and stress on the heart. However, furosemide's renal safety concerns limit its use, resulting in suboptimal dosing. Due in part to this, around half of AHF patients remain symptomatic at hospital discharge. Combination therapy of TRV027 together with with furosemide may improve dyspnea by directly and additively reducing pressure on the heart and lung and without triggering RAS activation. In a dog model of heart failure, TRV027 demonstrated additional significant decreases in wedge pressure when combined with furosemide versus furosemide monotherapy. TRV027's synergy with furosemide may resolve dyspnea more quickly, reduce the length of stay and more fully eliminate AHF symptoms, thereby cutting down readmissions.

TRV027 targets RAS, a central mechanism to AHF, and its activity is specific to that pathway. No currently approved AHF therapy had been proven to currently improve long-term patient outcomes. In several studies, RAS blockade has been associated with decreased morbidity and mortality in chronic heart failure. TRV027 could be the first therapy in the acute settings that modulates RAS. This would allow the physician to improve blood circulation while protecting the heart and kidneys. Further, TRV027 lowered blood pressure only in subjects with elevated RAS activity. This fidelity to target pathophysiology is crucial for any drug that is used in emergency departments since the initial diagnosis may be uncertain

TRV027 has a favorable safety profile. In a Phase 1 trial, TRV027 administrated in healthy volunteers showed no significant AEs even at doses 20 times higher than the expected

therapeutic level. In the Phase 2a trial with fragile, severe chronic heart failure patients, TRV027 also showed no reported SAEs. This clean tolerability profile is consistent with preclinical toxicology findings of TRV027.

Dose-dependent blood pressure decrease. In a Phase 2a clinical trial, TRV027 showed a dose-dependent decrease in blood pressure up to doses of 1 µg/kg/min. Even though no further reduction in blood pressure was reported at doses up to 3 µg/kg/min, this effect could still offer a safety advantage over current vasodilators, which has severe drawbacks due to hypotension.

TRV027-induced blood pressure lowering is rapidly reversible. In clinical data collected to date, TRV027 had a very short half-life and its effects were rapidly reversible. This should allow the physician in the acute care setting to alter the dose promptly so prolonged hypotension can be avoided.

TRV027 action is specific to RAS activity.

Compelling clinical data

TRVN has completed three clinical trials of TRV027.

Phase 2a trial in subjects with advanced stable heart failure

This study looked at TRV027 efficacy and safety in 24 advanced stable heart failure subjects using a step-wise dose titration over five hours. The highest dose was limited to 10-fold higher than the starting dose. After titration, the highest dose was continued for nine hours in a steady-state infusion to evaluate the stability of TRV027's hemodynamic benefit. Reversibility of TRV027's effects was studied for four hours after treatment discontinuation. 14 different doses were studied across three dosing regimens: 0.1 µg/kg/min titrated up to 1 µg/kg/min; 0.3 µg/kg/min titrated up to 3 µg/kg/min; and 1 µg/kg/min titrated up to 10 µg/kg/min.

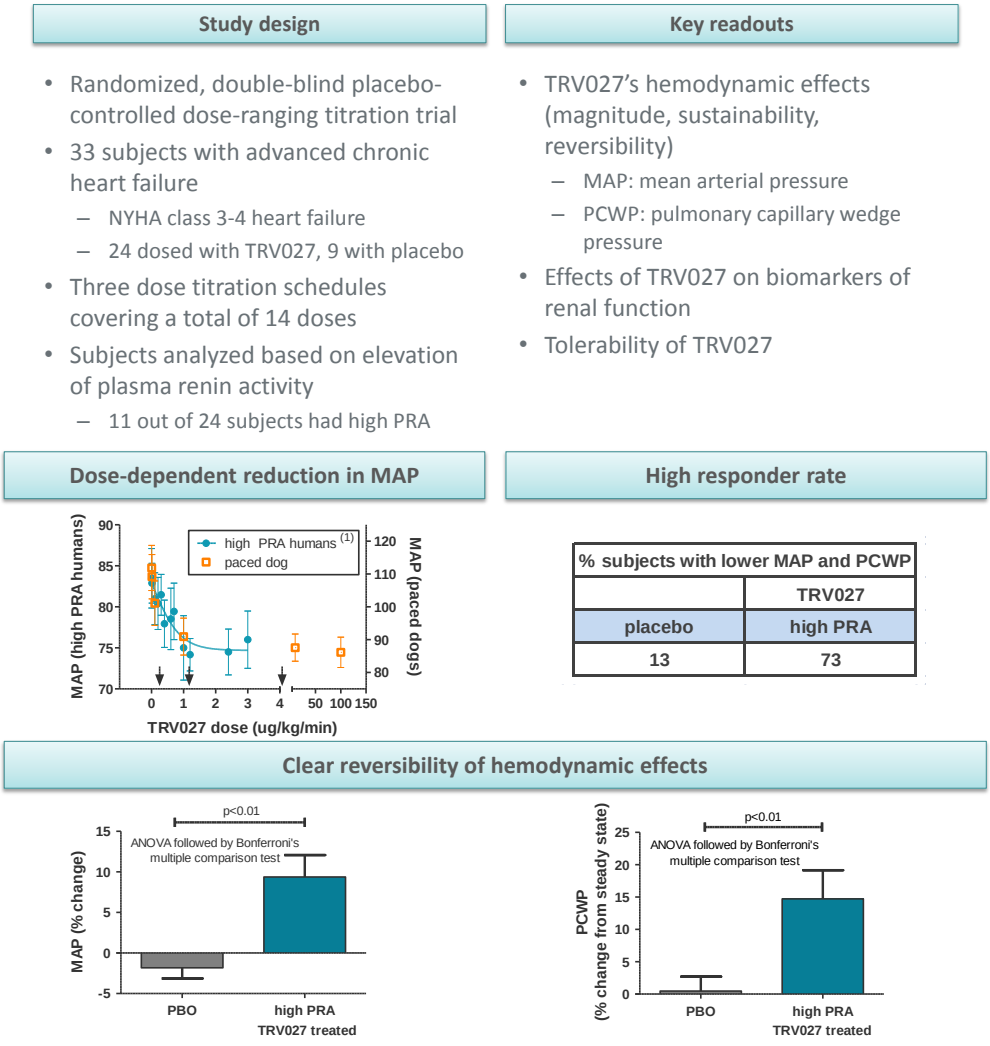
Based on previous clinical data, the hemodynamic effect of TRV027 was expected to correlate with a patient's elevated RAS activity (also referred to as patients with high plasma renin activity or PRA). TRV027 produced a dose-dependent decrease in mean arterial pressure (MAP), which was subsequently reversed in the washout period. This reversal of effect was statistically significant compared to both placebo and normal PRA subjects ($p<0.01$, $P<0.001$).

Wedge pressure started to decrease in high PRA subjects during dose titration, and this decrease was sustained throughout the infusion period, and reversed during the wash-out phase. The increase in PCWP after discontinuation of TRV027 infusion was clear in high PRA compared to normal PRA subjects ($P<0.01$). Of all high PRA subjects, 73% were responders to therapy (defined as decreases in both MAP and PCWP during continuous infusion) vs. 38% for normal PRA subjects and 13% for placebo subjects. No notable change in cardiac index or heart rate was observed following TRV027 administration.

One subject who experienced hypotension that required dose reduction and subsequent TRV027 discontinuation. Other than this incident, no other drug-related SAEs were reported. In addition, high-PRA subjects on TRV027 treatment showed less of an increase in brain natriuretic peptide (BNP), a marker of cardiac stress, versus placebo and low-PRA groups. This suggests TRV027's may have the ability to relieve cardiac stress. Despite the significant MAP reduction in TRV027 high-PRA subjects, there was no spike in heart rate

or cystatin-C and creatinine levels. These renal function biomarkers suggest kidney function was maintained while the blood pressure decreased. This result is consistent with preclinical findings.

Figure 34: TRV027 – Phase 2a trial summary



Source: Company filing and Canaccord Genuity research

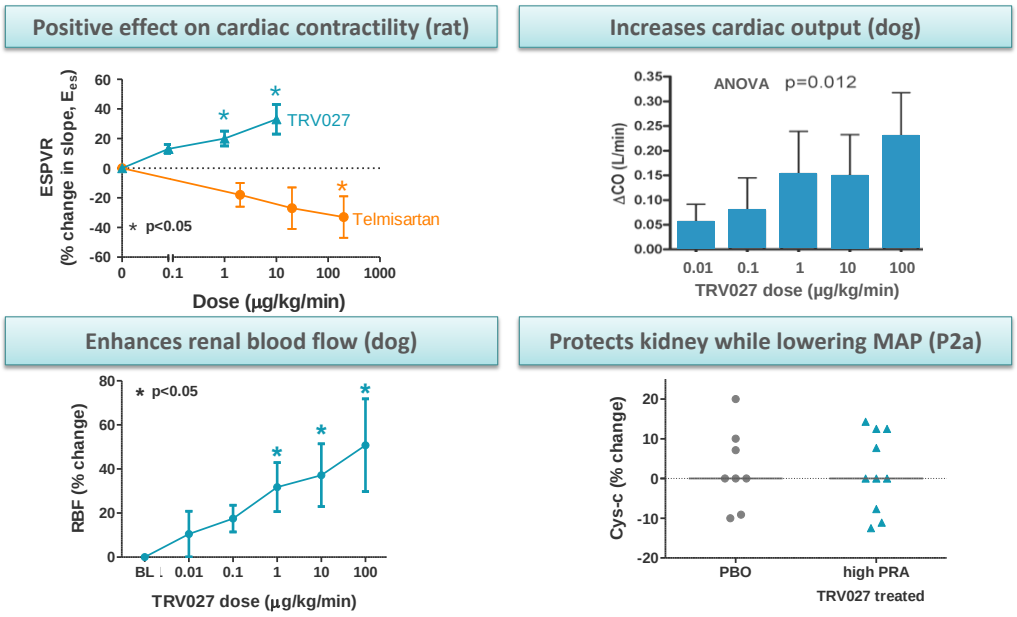
The sickest AHF patients most often have the highest PRA: these subjects tend to have higher BNP levels and a lower ejection fraction. Given TRV027's clinical data to date, AHF patients with high PRA levels should be responsive to TRV027.

Twenty-one of 24 TRV027 trial patients were on ACE inhibitors. These and other drugs were withheld on the day of dosing, but this was not sufficient to wash-out background ACEi levels. As such, TRV027 was effectively studied in combination with ACE in this trial.

Phase 1b trial in subjects with stable chronic heart failure

In the two-period Phase 1b trial, TRV027 was co-administered with furosemide in 17 heart failure subjects with concomitant renal dysfunction. The 17 subjects were split into three cohorts of six, six and five. TRV027 doses of 1.25 mg/hr, 6.25 mg/hr and 31.25 mg/hr were administered without weight correction. The resulting plasma concentrations were no different from TRV027 administered on a per-kg basis. We note a standard dosing approach without adjustment like this could be beneficial in the emergency treatment setting where patients are not routinely weighed. In addition, TRV027 was well tolerated and there were no drug-related AEs.

Figure 33: TRV027 – preclinical/Phase 1 data summary



Source: Company filings

Phase 1 clinical trial

TRV027 was evaluated in a single center, crossover trial with 20 healthy subjects receiving four-hour infusions at doses ranging from 0.01 to 20 µg/kg/min. TRV027 was well tolerated and there were no drug-related AEs even at doses 20 times the expected therapeutic dose.

TRV027 was rapidly cleared after dose discontinuation, which may make it easy to reverse any unexpected hypotensive effects. There was a dose-dependent linear increase in exposure and there was no urinary excretion of TRV027. The pharmacodynamic effects of TRV027 were induced by a brief sodium restriction paradigm that physiologically activates RAS. As a result, four of the 20 subjects experienced a measurable RAS elevation. Modest MAP decreases were observed in three of the four subjects with elevated RAS.

Preclinical studies

TRV027 decreased MAP and PCWP in a dog animal model of heart failure, and it also increased renal blood flow and moderately increased cardiac output. When studied in

combination with furosemide in a paced dog model, TRV027 showed additive effects on reducing PCWP, which is consistent with beneficial effects on dyspnea in the clinic. Combining the data in normal dogs, paced dogs and paced dogs treated with furosemide, there was meaningful blood pressure decreases only in animals with elevated RAS, which is consistent with the data seen in the clinical trials. Furthermore, the dose-dependent response observed in paced dogs was consistent with Phase 2a trial results.

Development strategy

On January 9, 2014, TRVN dosed the first patient in its Phase 2b BLASH-AHF trial. This is a randomized double-blind, placebo-controlled trial comparing TRV027 with SOC versus SOC monotherapy. Three doses of TRV027, 1.0 mg/hr, 5.0 mg/hr and 25 mg/hr are being evaluated on a composite score that include mortality, worsening heart failure, hospital readmission rate, dyspnea and length of hospital stay.

TRVN plans to have an interim analysis after 300 patients have been enrolled and, depending on the outcome of the interim analysis, enrollment into one or more of the active dose groups may be discontinued. An endpoint measuring dyspnea in Phase 3 trials could form the basis for FDA approval of TRV027. However, the FDA may be open to other well-defined benefit parameters, such as a hospitalization benefit or a patient and caregiver quality-of-life benefit. The composite endpoint tested in Phase 2b will facilitate the evaluation of potential alternative proposals to be discussed with the FDA during the end-of-Phase 2 meeting.

Figure 34: TRV027 Ph2b trial summary

	A study to explore the efficacy of TRV027 in patients hospitalized for acute decompensated heart failure
NCT ID	NCT01966601
Design	Randomized, placebo controlled, double blind
Enrollment	500
Dosing	Three doses of TRV027 via continuous IV infusion and placebo
Key inclusion criteria	• Men or women aged ≥21 years and ≤ 85 years 1a.Women of non-child-bearing potential • Able to provide written informed consent • Pre-existing diagnosis of heart failure • Systolic blood pressure ≥120 mmHg and ≤ 200 mmHg within 30 minutes of randomization • Ventricular rate ≤125 bpm. Patients with rate-controlled persistent or permanent atrial fibrillation (aFib) at screening are permitted. • Presence of ADHF defined by: o BNP > 400 pg/mL or NT-proBNP > 1600 pg/mL ▪ For patients with BMI >30 kg/m2: BNP > 200 pg/mL or NT-proBNP > 800 pg/mL ▪ For patients with rate-controlled persistent or permanent aFib: BNP > 600 pg/mL or NT-proBNP > 2400 pg/mL o AND at least two (2) of the following: ▪ Congestion on chest radiograph (CXR) ▪ Rales by chest auscultation ▪ Edema ≥ +1 on a 0-3 + scale, indicating indentation of skin with mild digital pressure that requires 10 or more seconds to resolve in any dependent area including extremities or sacral region. ▪ Elevated jugular venous pressure (≥8 cm H2O) • Receipt of a IV loop diuretic at a minimum dose 40 mg furosemide (or equivalent loop diuretic) for the treatment of dyspnea due to ADHF at least 1 hour prior to anticipated randomization and the initiation of study medication • Patient report of dyspnea at rest or upon minimal exertion during screening at least one hour after administration of IV loop diuretic
Key exclusion criteria	• Women who are pregnant or breast-feeding • Clinical presentation: o ACS in the 3 months prior to screening or planned during current admission. o Temperature >38.5oC o Clinically significant anemia o Current or planned ultrafiltration, paracentesis, hemofiltration or dialysis at time of screening o Any mechanical ventilation o CPAP/BiPAP discontinued less than 1 hour prior to randomization o History of primary pulmonary hypertension o History or current use of left ventricular assist devices (LVADs) or intra-aortic balloon pumps (IABPs) o Intravenous radiographic contrast agent within 72 hours prior to screening or presence of acute contrast induced nephropathy at the time of screening o Presence of clinically significant arrhythmia • Medications: o nitroprusside or nesiritide o Intravenous nitrates o use of inotropes o Use of ARBs within 7 days of prior to randomization o Use of any investigational medication within 30 days o clinically significant hypersensitivity or allergy to, or intolerance of, angiotensin receptor blockers • Medical history: o Major surgery within 8 weeks prior to screening o Stroke within 3 months prior to screening o eGFR (sMDRD) <20 mL/min/1.73m2 or >75 mL/min/1.73m2 between presentation and randomization o Post cardiac or renal transplant o Listed for renal transplant or cardiac transplant with anticipated transplant time to transplant < 6 months o History of severe left ventricular outlet obstruction (either valvular or sub-valvular), severe mitral valve stenosis or severe aortic regurgitation o Cardiac valvular abnormality that requires surgical correction o Complex congenital heart disease o Hypertrophic or restrictive cardiomyopathy o significant pulmonary or hepatic disease that could interfere with the evaluation of safety or efficacy of TRV027 o life expectancy of less than 6 months
Primary endpoint	The primary clinical endpoint is a of the following outcomes: (1) time from randomization to death through day 30, (2) time from randomization to heart failure re-hospitalization through day 30, (3) time from randomization to worsening heart failure through day 5, (4) change in dyspnea VAS score (calculated area under the curve) from

Source: Clinicaltrials.gov

Collaboration with Forest

In May 2013, TRVN entered into an option agreement and a license agreement with Forest, under which Forest was granted an exclusive option to license TRV027. If Forest exercises this option, the license agreement will become effective, and Forest will have an exclusive worldwide license to develop and commercialize TRV027 and specified related compounds. Forest will be responsible for subsequent development, regulatory approval and commercialization of TRV027 at Forest's expense. Forest may exercise its option at any time before TRVN delivers the Phase 2b clinical trial results to Forest and during a specified period of time thereafter. If Forest exercises the option, TRVN could potentially receive up to $430 million in the aggregate, including an upfront option exercise fee of $65 million and milestone payments depending upon the achievement of future development and commercial milestones. TRVN could also be eligible to receive tiered royalties between 10% and 20% on net sales of licensed products worldwide, with the royalty rates on net sales of licensed products in the US higher than the royalty rates on net sales of licensed products ex-US.

If Forest elects to exercise its option, the term of the royalty on sales of TRV027 for a given country would extend until the latest to occur of (i) 10 years from first commercial sale of TRV027 in that country, (ii) the expiration of the last to expire patent claiming TRV027 that is sufficient to block the entrance of a generic version of the product, or (iii) the expiration of any period of exclusivity granted by applicable law or any regulatory authority in such country that confers exclusive marketing rights on the product.

Forest has the right to grant sublicenses under the license agreement to affiliates and third parties. Any sublicensing does not relieve Forest of any of its obligations under the license agreement, including Forest's obligation to make milestone payments to TRVN with respect to TRV027 or pay royalties on sales of TRV027 by such sublicensee.

INTELLECTUAL PROPERTY

TRVN has filed for patent protection covering compositions of matter and methods of use for its drug candidates. TRVN owns one issued and two pending U.S. patents, the first of which is expected to expire no earlier than 2029, that cover the compound TRV027 and the methods of using these compounds. TRVN also relies on trade secrets and careful monitoring of proprietary information to protect aspects of its business that are not amenable to patent protection.

TRV130's patent portfolio consists of two pending U.S. patents claiming methods of making and using these compounds. If issued, these pending U.S. applications are should expire no earlier than 2032. A related PCT application was filed and national patent applications have been filed in a number of other countries.

TRVN's wholly owned TRV723 patent portfolio includes two pending U.S. patents claiming methods of making and using the compound. If issued, the pending U.S. applications should expire no earlier than 2032. A related PCT application was filed and national patent applications have been filed in a number of other countries. In addition, TRVN also has patent applications directed to compounds that modulate various opioid receptors, specifically the delta opioid receptors and other GPCRs, and peptides and peptide mimetics targeting the AT1R that are beta-arrestin effectors besides TRV027. With the exception of two patents, TRVN has filed 33 U.S. provisional patent applications, U.S. non-provisional patent applications, foreign applications and PCT applications covering compositions and methods of making and using compounds that target G protein coupled receptors.

Figure 34: Summary of key TRVN patents

Patent	Title	Expiration
8,486,885	β-arrestin effectors and compositions and methods of use thereof	2029

Source: Company reports and Canaccord Genuity estimates

MANAGEMENT TEAM

The Trevena management team has a strong history of corporate leadership, development and commercialization in the biotechnology industry.

Maxine Gowen, Ph.D., has served as the president and chief executive officer of Trevena and as a member of the Board of Directors since November 2007. Prior to joining Trevena, Dr. Gowen was senior vice president for the Center of Excellence for External Drug Discovery at GSK, where she held a variety of leadership positions during her tenure of 15 years. Before GSK, Dr. Gowen was a senior lecturer and head of the Bone Cell Biology Group, Department of Bone and Joint Medicine, at the University of Bath, U.K. From 2008 until 2012, Dr. Gowen served as a director of Human Genome Sciences, Inc. She received her Ph.D. from the University of Sheffield, U.K., an M.B.A. with academic honors from The Wharton School of the University of Pennsylvania, and a B.Sc. with honors in biochemistry from the University of Bristol, U.K.

Michael W. Lark, Ph.D., has served in a number of capacities with Trevena since February 2008, and currently serves as the chief scientific officer and senior vice president, research since March 2011. Prior to joining Trevena, he was vice president of biology at Centocor Inc., a division of Johnson & Johnson, from 2004 until 2008 and the senior director of cardiovascular and metabolic diseases at Centocor from 2002 to 2004. Prior to that, Dr. Lark was director of musculoskeletal diseases at GSK, from 1999 until 2002. Dr. Lark received his Ph.D. in molecular biology and microbiology from the Case Western Reserve University Medical School and his B.S. in microbiology from the Pennsylvania State University.

Roberto Cuca joined Trevena as senior vice president and chief financial officer in September 2013. Prior to joining Trevena, he held various leadership positions in the finance organization of Endo Health Solutions Inc., a pharmaceutical company, from March 2010 to August 2013, including, most recently, treasurer and senior vice president, finance. Prior to that, he was director, corporate and business development, at moksha8 Pharmaceuticals, Inc., an emerging markets-focused pharmaceutical company, from March 2008 until February 2010. From 2005 until 2008, he worked at JPMorgan Chase & Co. as an equity analyst covering U.S. pharmaceutical companies. Mr. Cuca received an M.B.A. from the Wharton School of The University of Pennsylvania, a J.D. from Cornell Law School, an A.B. from Princeton University and he is a CFA charterholder.

David Soergel, M.D., has served in multiple positions since joining Trevena in November 2009 and since September 2012 has served as the senior vice president, clinical development. Prior to joining Trevena, he served as senior director, clinical development for Concert Pharmaceuticals, Inc. from July 2008 to November 2009. Prior to Concert, Dr. Soergel served as director, discovery medicine, in the Cardiovascular Urogenital Center of Excellence in Drug Discovery at GSK, from 2005 until 2008. Dr. Soergel received an M.D. from Cornell University Medical College and a B.A. from The Johns Hopkins University. Dr. Soergel completed his clinical training in pediatric cardiology at Johns Hopkins Hospital and underwent additional training in heart failure and transplant at the Children's Hospital of Philadelphia.

Rosamond Deegan has served in multiple positions since joining the company in March 2008 and currently serves as senior vice president, business development and operations, a position she has held since December 2013. Prior to joining Trevena, she held a variety of positions during a tenure at GSK beginning in 2001 and ending in 2008, most recently serving the role of director, business development. Before GSK, Ms. Deegan was a Senior Consultant at KPMG in their healthcare management consulting practice from 1998 to 2000. Ms. Deegan received an M.B.A from INSEAD and an M.Phil and B.A. from Cambridge University.

Figure 35: Trevena key management members

Name	Title	Work History	Joined Trevena in:
Maxine Gowen, Ph.D.	President and Chief Executive Officer	GlaxoSmithKline University of Bath Human Genome Sciences, Inc.	2007
Michael W. Lark, Ph.D.	Chief Scientific Officer, SVP of Research	Centocor Inc. GlaxoSmithKline	2008
Roberto Cuca	Chief Financial Officer, SVP of Finance	Endo Health Solutions, Inc. moksha8 Pharmaceuticals, Inc. JPMorgan Chase & Co.	2013
David Soergel, M.D.	SVP of Clinical Development	Concert Pharmaceuticals GlaxoSmithKline	2009
Rosamond Deegan	SVP of Business Development and Operations	GlaxoSmithKline KPMG	2008

Source: Company reports and Canaccord Genuity estimates

Figure 36: TRVN P&L

	2011A	2012A	Q1/13A	Q2/13A	Q3/13A	Q4/13E	2013E	Q1/14E	Q2/14E	Q3/14E	Q4/14E	2014E	2015E	2016E
TRV130	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Product revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Grant revenue	2.4	0.8	0.0	0.0	0.0	-	0.1	-	-	-	-	-	65.0	15.0
Total revenues	**2.4**	**0.8**	**0.0**	**0.0**	**0.0**	**-**	**0.1**	**-**	**-**	**-**	**-**	**-**	**65.0**	**15.0**
Cost of goods sold		-	-	-	-	-	-	-	-	-	-			
Gross Profit	**2.4**	**0.8**	**0.0**	**0.0**	**0.0**	**-**	**0.1**	**-**	**-**	**-**	**-**	**-**	**65.0**	**15.0**
R&D expense	15.1	13.3	4.1	4.1	4.1	6.0	18.2	14.0	16.0	18.0	20.0	68.0	20.0	25.0
SG&A expense	3.1	3.1	0.9	0.9	0.9	1.2	4.0	1.3	1.3	1.4	1.5	5.4	6.0	6.6
Other operating expense							-	-	-	-	-	-	-	-
Total operating expense	**18.2**	**16.4**	**5.0**	**5.0**	**5.0**	**7.2**	**22.3**	**15.3**	**17.3**	**19.4**	**21.5**	**73.4**	**26.0**	**31.6**
Operating income	**(15.8)**	**(15.6)**	**(5.0)**	**(5.0)**	**(5.0)**	**(7.2)**	**(22.1)**	**(15.3)**	**(17.3)**	**(19.4)**	**(21.5)**	**(73.4)**	**39.0**	**(16.6)**
Net Interest/Investment income	0.0	-					0.0					0.0	0.0	0.0
(interest expense)	(0.1)	(0.2)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1
Other non-operating income (expense)	0.0	0.2					-					-	-	-
Interest and other, Net	(0.1)	(0.0)	-	-	-	-	-	-	-	-	-	-	-	-
Pre-tax income	**(15.8)**	**(15.6)**	**(5.0)**	**(5.0)**	**(5.0)**	**(7.2)**	**(22.1)**	**(15.3)**	**(17.3)**	**(19.4)**	**(21.4)**	**(73.4)**	**39.1**	**(16.5)**
Income tax expense (benefit)	-	-	-	-	-	-	-					-	-	-
Net income (loss)	**(15.8)**	**(15.6)**	**(5.0)**	**(5.0)**	**(5.0)**	**(7.2)**	**(22.1)**	**(15.3)**	**(17.3)**	**(19.4)**	**(21.4)**	**(73.4)**	**39.1**	**(16.5)**
Basic EPS	**(0.96)**	**(0.95)**	**(0.30)**	**(0.30)**	**(0.30)**	**(0.28)**	**(1.18)**	**(0.59)**	**(0.67)**	**(0.74)**	**(0.82)**	**(2.82)**	**1.49**	**(0.63)**
Diluted EPS	**(0.96)**	**(0.95)**	**(0.30)**	**(0.30)**	**(0.30)**	**(0.28)**	**(1.18)**	**(0.59)**	**(0.67)**	**(0.74)**	**(0.82)**	**(2.82)**	**1.49**	**(0.63)**
Basic shares outstanding	16.5	16.5	16.5	16.5	16.5	25.7	18.8	25.8	26.0	26.1	26.2	26.0	26.2	26.3
Diluted shares outstanding	16.5	16.5	16.5	16.5	16.5	25.7	18.8	25.8	26.0	26.1	26.2	26.0	26.2	26.3

Source: Company reports and Canaccord Genuity estimates

APPENDIX: IMPORTANT DISCLOSURES

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	990*	100.0%	

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