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Healthcare | U.S. Biotechnology

26 February 2014

Trevena Inc.

Silver Bullet on Biased Ligands

Initiate at Overweight and $14 price target: Trevena is focused on the development of therapies that target G protein coupled receptors (GPCRs). Over 30% of currently marketed therapies target GPCRs but either inhibit or activate both the G protein and beta-arrestin pathways, which lead to subpar efficacy or considerable adverse events. Trevena's Advanced Biased Ligand Explorer (ABLE) platform is able to identify "biased" ligands that should result in more targeted products with improved therapeutic effects.

Product differentiation in key large markets: Trevena has a total of four products in its pipeline, of which two are in phase 2 trials. The company is targeting large markets such as heart failure and pain, where we believe product differentiation from existing standard of care will be key to the success of products given the number of genericized products. If Trevena is able to demonstrate an incremental benefit from current therapies, the market opportunity is significant given the size of these markets.

- TRV130 is being developed for post-operative pain. Early phase 1b data showed a more rapid onset of pain relief, higher number of responders, and reduced respiratory depression and nausea/vomiting compared to morphine. The first phase 2 trial will start in 2Q14 and the second in 2H14 with results from both in 2015.
- TRV027 is being developed for acute heart failure. Phase 2a results showed dose-dependent decreases in blood pressure and pulmonary capillary wedge pressure with preserved cardiac performance. The phase 2b trial was initiated in January 2014, and results are expected by the end of 2015.

Diversified portfolio: Unlike most early stage development companies, Trevena has several products in its pipeline, helping diversify development risks and offering investors multiple opportunities for upside. We include only TRV130 and TRV027 in our valuation given the lack of clinical data from earlier pipeline products. Our price target is based on TRV130 ($6/share) and TRV027 ($4/share) and cash of ~$4/share. Success of the earlier pipeline products would provide additional upside to our valuation.

TRVN: Quarterly and Annual EPS (USD)

	2012	2013			2014			Change y/y	
FY Dec	Actual	Old	New	Cons	Old	New	Cons	2013	2014
Q1	N/A	N/A	N/A	N/A	N/A	-0.35E	N/A	N/A	N/A
Q2	N/A	N/A	-1.72A	N/A	N/A	-0.37E	N/A	N/A	78%
Q3	N/A	N/A	-0.64A	N/A	N/A	-0.39E	N/A	N/A	39%
Q4	N/A	N/A	-0.69A	N/A	N/A	-0.40E	N/A	N/A	42%
Year	N/A	N/A	-2.44E	N/A	N/A	-1.52E	N/A	N/A	38%
P/E	N/A		N/A			N/A			

Source: Barclays Research.
Consensus numbers are from Thomson Reuters

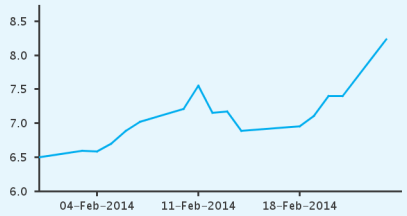
Stock Rating	OVERWEIGHT from N/A
Industry View	NEUTRAL Unchanged
Price Target	USD 14.00 from N/A

Price (25-Feb-2014)	USD 7.77
Potential Upside/Downside	+80%
Tickers	TRVN

Market Cap (USD mn)	200
Shares Outstanding (mn)	25.73
Free Float (%)	85.60
52 Wk Avg Daily Volume (mn)	0.2
Dividend Yield (%)	N/A
Return on Equity TTM (%)	N/A
Current BVPS (USD)	-3.36

Source: Thomson Reuters

Price Performance	Exchange-Nasdaq
52 Week range	USD 8.98-6.35



Link to Barclays Live for interactive charting

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U.S. Biotechnology — **Industry View: NEUTRAL**

Trevena Inc. (TRVN)

Stock Rating: OVERWEIGHT

Income statement ($k)	2012A	2013E	2014E	2015E	CAGR
Revenue	N/A	135	0	65,000	N/A
EBITDA (adj)	-14,823	-22,858	-39,181	30,493	N/A
EBIT (adj)	N/A	-23,405	-39,700	30,000	N/A
Pre-tax income (adj)	N/A	-26,051	-41,316	28,157	N/A
Net income (adj)	N/A	-26,051	-41,316	28,157	N/A
EPS (adj) ($)	N/A	-2.44	-1.52	1.02	N/A
Diluted shares (k)	N/A	10,667	27,192	27,740	N/A
DPS	N/A	N/A	N/A	N/A	N/A

Margin and return data					Average
EBITDA (adj) margin (%)	N/A	N/A	N/A	N/A	N/A
EBIT (adj) margin (%)	N/A	N/A	N/A	N/A	N/A
Pre-tax (adj) margin (%)	N/A	N/A	N/A	N/A	N/A
Net (adj) margin (%)	N/A	N/A	N/A	N/A	N/A
ROIC (%)	-323.3	-50.1	-60.3	31.6	-100.5
ROA (%)	-193.0	-46.4	-56.4	30.3	-66.4
ROE (%)	40,714.4	-55.8	-62.7	29.7	10,156.4

Balance sheet and cash flow ($k)					CAGR
Tangible fixed assets	910	441	122	128	-47.9%
Intangible fixed assets	N/A	N/A	N/A	N/A	N/A
Cash and equivalents	6,841	47,984	69,599	98,093	142.9%
Total assets	8,088	50,449	70,396	98,855	130.4%
Short and long-term debt	4,868	0	0	0	-100.0%
Other long-term liabilities	N/A	N/A	N/A	N/A	N/A
Total liabilities	4,195	275	275	275	-59.7%
Net debt/(funds)	-1,972	-47,984	-69,599	-98,093	N/A
Shareholders' equity	-39	46,716	65,889	94,846	N/A
Change in working capital	-12,080	43,345	65,915	94,865	N/A
Cash flow from operations	-14,805	-13,687	-38,674	28,194	N/A
Capital expenditure	-21	-78	-200	-500	N/A
Free cash flow	-14,784	-13,609	-38,474	28,694	N/A

Valuation and leverage metrics					Average
P/E (adj) (x)	N/A	N/A	N/A	7.7	7.7
EV/EBITDA (adj) (x)	-2.1	0.7	0.9	-2.2	-0.6
Equity FCF yield (%)	N/A	N/A	N/A	N/A	N/A
EV/sales (x)	N/A	-115.2	N/A	-1.0	-58.1
P/BV (x)	N/A	N/A	N/A	N/A	N/A
Dividend yield (%)	N/A	N/A	N/A	N/A	N/A
Total debt/capital (%)	100.8	0.0	0.0	0.0	25.2

Selected operating metrics					Average
SG&A/sales (%)	N/A	N/A	N/A	N/A	N/A
R&D/sales (%)	N/A	N/A	N/A	N/A	N/A
R&D growth (%)	N/A	44.7	81.9	-14.3	37.4
SG&A growth (%)	N/A	37.7	9.3	6.4	17.8

Source: Company data, Barclays Research
Note: FY End Dec

Price (25-Feb-2014) USD 7.77
Price Target USD 14.00

Why Overweight? Trevena develops GPCR targeted therapies and it's Advanced Biased Ligand Explorer platform discovers biased ligands that will help TRVN develop more targeted and selective therapies with improved efficacy and safety. It has two products in ph 2 trials in large markets (AHF and pain), which if successfully developed offer significant market opportunities.

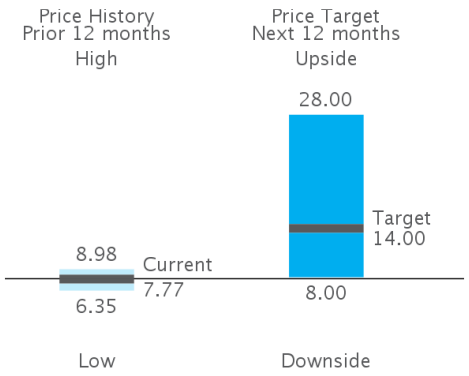
Upside case USD 28.00

Our upside scenario of $28 assumes an FDA approval for TRV130 as well as a positive outcome for the phase 2b for TRV027.

Downside case USD 8.00

Our downside scenario of $8 assumes the TRV027 acute heart failure program fails with TRV130 representing $6/share and some cash value.

Upside/Downside scenarios



Executive Summary

Trevena is focused on the development of therapies that target G protein coupled receptors (GPCRs)

Trevena is focused on the development of therapies that target G protein coupled receptors (GPCRs), which are cell surface receptors that activate two signalling pathways – G protein and β-arrestin. Trevena's Advanced Biased Ligand Explorer (ABLE) platform is able to identify "biased" ligands that are able to activate one pathway while inhibiting the other to develop more targeted and specific therapies with improved efficacy and safety profiles.

Trevena currently has four products in its pipeline, of which two are in phase 2 trials

Trevena currently has four products in its pipeline, of which two are in or entering phase 2 trials – TRV130 for the treatment of moderate to severe post-operative pain and TRV027 for the treatment of acute heart failure. If successfully developed, these products represent significant market opportunities for TRVN given the size of the markets.

- TRV130 is a small molecular G protein biased ligand that targets the μ-opioid receptor. TRV130 activates the G protein pathway thought to be associated with analgesia and inhibits β-arrestin signalling, which Trevena believes leads to adverse events often associated with opioids such as respiratory depression and constipation. The 3.0mg dose tested in the phase 1b trial demonstrated a more rapid onset of pain relief and a higher number of responders as well as reduced respiratory depression and nausea/vomiting when compared to 10mg of morphine. Trevena expects to start the first phase 2 efficacy and tolerability study for TRV130 in 2Q14 and the second in the second half of 2014 with results from both expected in 2015.

- TRV027 is a β-arrestin ligand that targets the angiotensin II type 1 receptor (AT1R). Trevena believes TRV027 is able to improve heart failure symptoms while reducing adverse events such as increases in blood pressure and fluid retention often associated with currently marketed products (diuretics, vasodilators, and inotropes). Phase 2a results showed dose-dependent decreases in blood pressure and pulmonary capillary wedge pressure. The phase 2b trial was initiated in January 2014 and results are expected by the end of 2015.

  Forest Laboratories has the option to license TRV027 following phase 2b results. If FRX decides to exercise the option, Trevena is eligible to receive up to $430 million in milestone payments and escalating royalties of 10%-20% on future sales. Actavis recently announced its plans to acquire Forest (expected to close in mid-2014). We still believe Actavis will exercise the option if phase 2b results are favourable.

Valuation

We are initiating coverage with an Overweight rating and a price target of $14.

We are initiating coverage of Trevena with an Overweight rating and a price target of $14. We arrive at our price target using a probability-adjusted NPV analysis. We estimate peak sales of roughly $416 million for TRV130 ($6/share) and peak royalties of ~$151 million for TRV027 ($4/share). Including ~$4/share of cash, we arrive at our price target of $14.

Major Catalysts

- 2Q14 – Start of phase 2 efficacy and tolerability trial for TRV130
- 2H14 – Start second phase 2 trial for TRV130
- 3Q14 – Results from phase 1 TRV734 trial
- 1Q15 – Complete phase 2 bunionectomy trial for TRV130
- End of 2015 – Complete second phase 2 trial for TRV130
- End of 2015 – Results expected for phase 2b trial for TRV027
- 2015 – Potentially start phase 3 trial for TRV130

Company and Technology Overview

Trevena is developing therapies that target G protein coupled receptors (GPCRs) for a variety of conditions. GPCRs are cell surface receptors that activate two signalling pathways – G protein and β-arrestin.

Over 30% of current therapies on the market target GPCRs

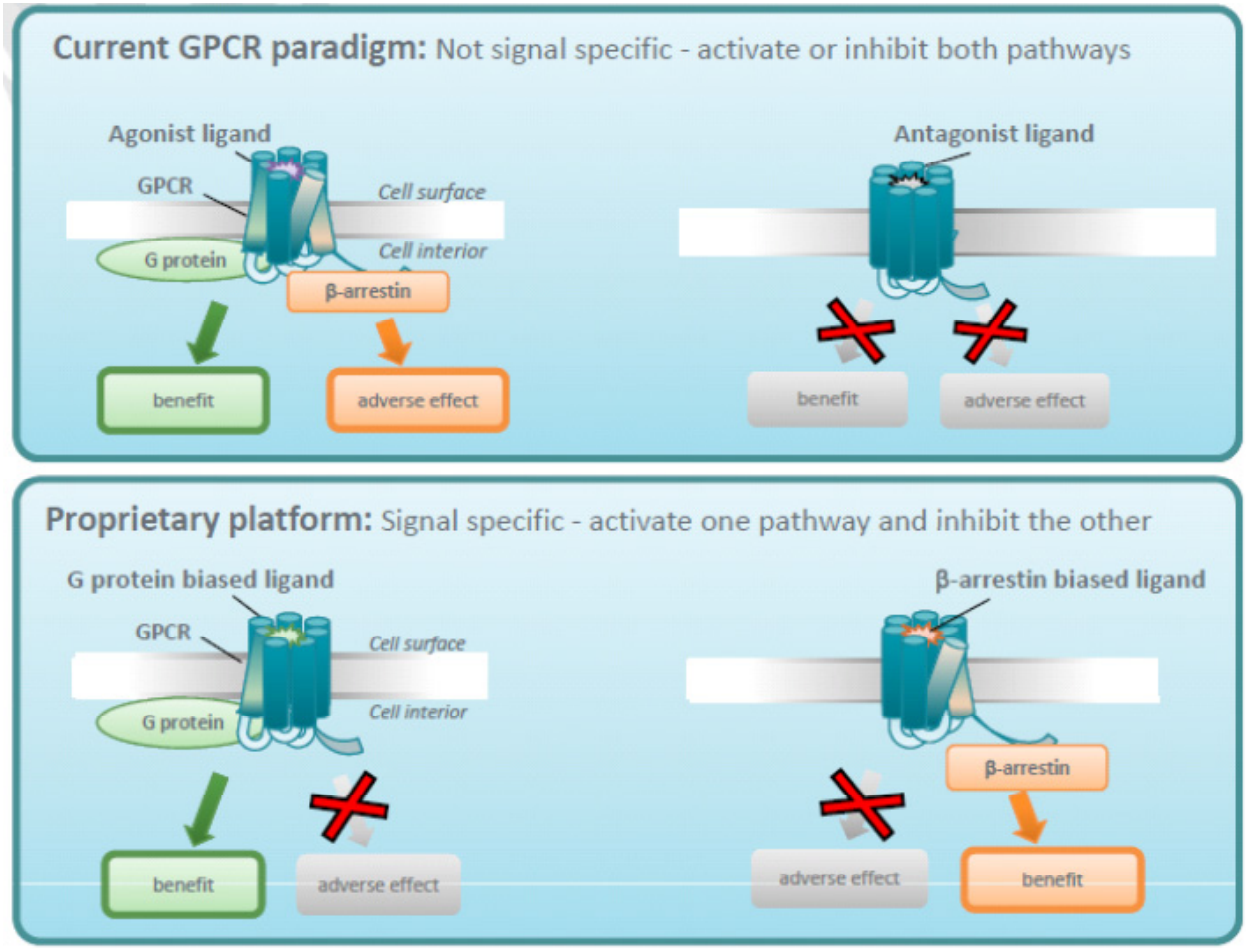
Over 30% of current therapies on the market target GPCRs, including GlaxoSmithKline's Zantac, Eli Lilly's Zyprexa, and Schering Plough/Merck's Clarinex. However, these approved products either turn off or on the receptor thus inhibiting or activating both pathways. Of the two pathways activated by GPCRs, Trevena believes one is usually associated with efficacy and the other with adverse events. Since current GPCR targeted therapies are not specific, this often results in either subpar efficacy or considerable side effects.

Trevena's Advanced Biased Ligand Explorer (ABLE) product platform is able to identify "biased" ligands that selectively activate one pathway while inhibiting the other.

Trevena's Advanced Biased Ligand Explorer (ABLE) product platform is able to identify "biased" ligands that selectively activate one pathway while inhibiting the other, which allows the company to develop more targeted and specific therapies with improved therapeutic profiles. Trevena is the first to test biased ligands in humans. The company's scientific cofounder Dr. Robert Lefkotwiz was the first to discover signalling through both G proteins and β-arrestin and later demonstrated that the two pathways can be modulated independently with biased liagnds. He was awarded a Nobel Prize in Chemistry in 2012 partly a result of his work to explain and clarify the multiple pathways signalled by GPCRs.

FIGURE 1

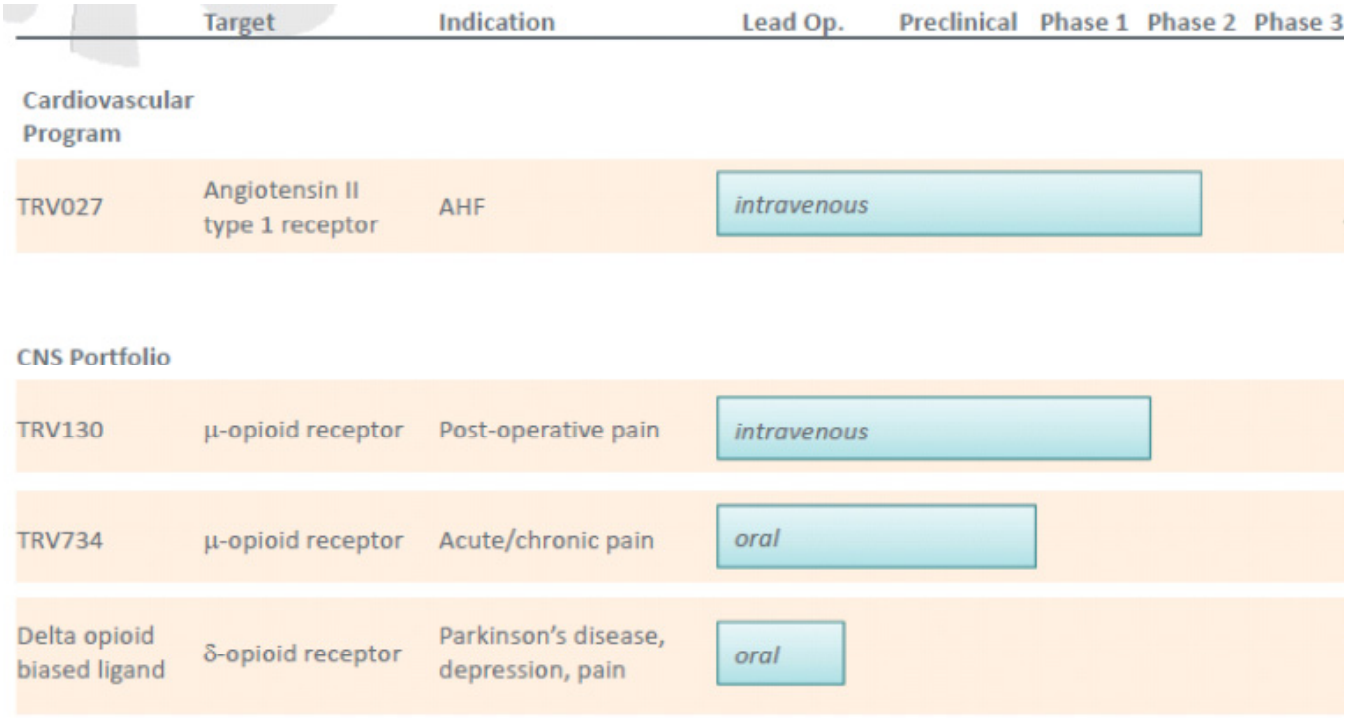
Currently Marketed GPCR Targeted Therapies vs. Trevena's Biased Ligand Technology



Source: Company data

Trevena currently has four products in its pipeline, of which one is in cardiovascular and three in the central nervous system (CNS) space, primarily for the treatment of pain, as well as early stage products to treat Parkinson's disease and depression.

FIGURE 2
Trevena's Product Pipeline



Source: Company data

The two products furthest along in development are TRV027 for the treatment of acute heart failure and TRV130 for the treatment of post-operative pain.

- TRV027 for acute heart failure. TRV027 is a peptide β-arrestin biased ligand that targets the angiotensin II type 1 receptor (AT1R), a GPCR on cardiovascular cells. TRV027 inhibits G protein signalling which causes increases in blood pressure and fluid retention but activates β-arrestin g signalling associated with cardiac contractibility.
- TRV130 for moderate to severe post-operative pain. TRV130 is a small molecule G protein biased ligand that targets the μ-opioid receptor. TRV130 activates the G protein pathway which is thought to be associated with analgesia and inhibits β-arrestin signalling, which Trevena believes leads to adverse events often associated with opioids such as respiratory depression and constipation.

TRV027 – Specific Targeting of AT1R in Acute Heart Failure

According to the National Hospital Discharge Survey (NHDS), there were over 1 million hospital discharges in 2010 of which heart failure was the primary diagnosis.

Acute heart failure is a result of gradual or rapid changes in symptoms of patients suffering from chronic heart failure resulting in the need for urgent care and hospitalization. Patients may present with decreased cardiac performance, severe dyspnea (shortness of breath), swelling, and potentially damage to other organs such as the kidneys. According to the National Hospital Discharge Survey (NHDS), there were over 5 million in hospital discharges in 2010 where heart failure was listed as a diagnosis and over 1 million of which heart failure was the primary diagnosis. In Europe, a total of 1.6 million hospitalizations in 2010 indicated heart failure as the primary diagnosis. The majority of patients who experience an episode of acute heart failure will see a worsening of chronic heart failure and approximately 50% are still symptomatic when discharged from the hospital, primarily due to limitations of current treatment options. The rate of readmission is high at 25% after 30 days and the one-year mortality rate is also high at approximately 30%.

The rate of readmission for acute heart failure patients is high at 25% after 30 days and the one-year mortality rate is also high at approximately 30%.

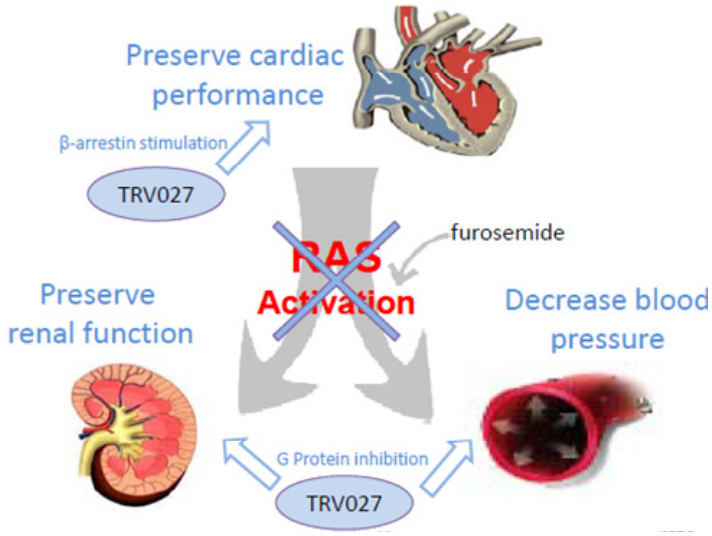
Angiotensin II activates the angiotensin II type 1 receptor (AT1R), a GPCR on cardiovascular cells and sustained activation of AT1R has been shown to lead to cardiac dysfunction, hypertension and myocardial hypertrophy. Angiotensin II is also a mediator of the renin angiotensin system (RAS), an important regulator of blood pressure and fluid balance in the body and RAS is often activated in patients with acute heart failure. Angiotensin II stimulates cardiac contractibility through β-arrestin signalling but also causes increases in blood pressure and fluid retention through G protein signalling (activation of RAS), which can lead to a worsening of heart failure and cause dyspnea (shortness of breath) and edema (swelling/fluid retention).

Blocking AT1R or the effects of angiotensin II has been shown to improve morbidity and mortality in chronic heart failure patients and has been targeted by angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs), which have been used as first-line therapies to treat chronic heart failure for over 35 years. However, by blocking AT1R, they also reduce cardiac performance in the short-term (likely due to blocking the β-arrestin pathway) and therefore are not appropriate for treating acute heart failure. Patients with acute heart failure admitted to the hospital are typically treated with diuretics, vasodilators, and inotropes. Each of these products target one of the three main organ systems associated with heart failure - the heart (cardiac contractibility), blood vessels, or kidneys. However, all are accompanied by considerable adverse events that limit their use and extended use can actually lead to a worsening of kidney and/or heart function.

Trevena is developing TRV027 as a first line treatment for acute heart failure for use with standard diuretic therapy

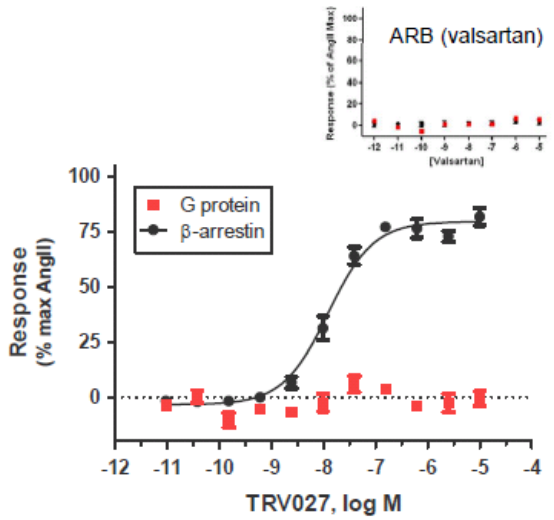
Trevena is developing TRV027 as a first line treatment for acute heart failure for use with standard diuretic therapy such as furosemide (used as first-line treatment in roughly 90% of acute heart failure patients). Trevena's TRV027 is a peptide β-arrestin biased ligand that targets AT1R – activates β-arrestin signalling and inhibits G protein signalling. The company believes TRV027, if approved, will be the first acute heart failure treatment to modulate RAS and could potentially relieve heart failure symptoms while also preserving the function of the heart and kidneys.

FIGURE 3
TRV027 Benefits the Heart, Kidneys, and Blood Vessels



Source: Company data

FIGURE 4
TRV027 Demonstrates Biased Signaling



Source: Company data

Clinical evidence

TRV027 was shown to be well tolerated up to the highest dose of 20μg/kg/min for four hours. There were no safety signals and no withdrawals as a result of adverse events.

Phase 1 trial – TRV027 shown to be well tolerated

In a phase 1 trial of 20 healthy volunteers, TRV027 was evaluated for safety and tolerability in doses ranging from 0.01 to 20μg/kg/min. TRV027 was shown to be well tolerated up to the highest dose of 20μg/kg/min for four hours. There were no safety signals and no withdrawals as a result of adverse events. Treatment-related adverse events were mild and were corrected by the end of the study. There were no differences seen in creatinine clearance (measure of renal function), systolic blood pressure, diastolic blood pressure, and mean arterial pressures of patients receiving TRV027 versus placebo. TRV027 has a short half-life and was shown to rapidly clear the patient's system after infusion is ceased- a safety measure as it would allow physicians to quickly adjust the dose and avoid sustained adverse events.

TRV027 has a short half-life and was shown to rapidly clear the patient's system after infusion is ceased.

A phase 1b trial of 17 patients with stable chronic heart failure showed that standard dosing without weight adjustments is appropriate and could be more easily used in a hospital setting where patients are not routinely weighed. TRV027 was well tolerated even in kidney impaired patients and the addition of TRV027 to furosemide does not impair furosemide's ability to reduce swelling. Trevena believes the addition of TRV027 may actually improve the use of furesomide as concerns on worsening renal function, which is associated with higher mortality and readmission rates, is a limiting factor in its use. If TRV027 is able to demonstrate a preservation of kidney function, it may allow increased use of furesomide to help fully resolve symptoms.

Phase 2a trial Demonstrates Meaningful Blood and Pulmonary Pressure Reductions

The phase 2a trial enrolled approximately 33 patients with stable chronic NYHA Class III/IV heart failure with an ejection fraction of ≤35% and baseline average pulmonary capillary wedge pressure (PCWP) of ≥20mmHg. This was a randomized, double-blind, placebo-controlled ascending dose study and patients were administered TRV027 with IV furesomide. The phase 2a study was completed in October 2012 and the results were presented at the American College of Cardiology meeting in March 2013.

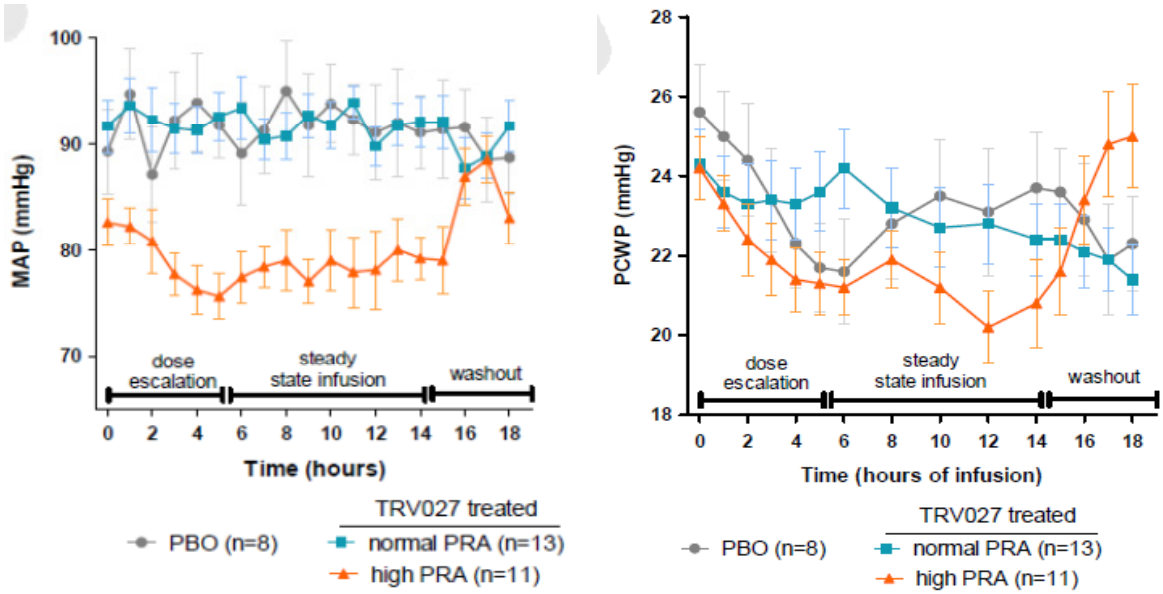
Approximately 24 patients were enrolled to receive TRV027 and were divided into three cohorts and 9 patients were randomized to placebo. Patients had their dose titrated up over 5 hours from either 0.1μg/kg/min up to 1μg/kg/min, or 0.3μg/kg/min up to 3μg/kg/min, or 1μg/kg/min up to 10μg/kg/min. Results were analyzed based on plasma rennin activity (PRA) elevations, which is a measure of RAS activity. Patients were divided into three groups –normal PRA subgroup (13 patients), high PRA subgroup (11 patients), and placebo (9 patients). The high PRA group was considered to be the sicker patients and arguably more closely aligned with acute heart failure patients admitted to hospitals.

The results showed a dose dependent decrease in MAP and PCWP in patients with high PRA.

The results showed a dose dependent decrease in mean arterial pressure (MAP) or blood pressure in patients with high PRA. These results were statistically significant ($p<0.05$) and the decrease in MAP was quickly reversed during the washout period, another signal that the TRV027 effectively reduced MAP. Patients in the high PRA group also saw a decrease in pulmonary capillary wedge pressure (PCWP – a decrease in PCWP helps improve dyspnea) during the titration and infusion phases and a reversal after treatment was stopped. The increase in PCWP after treatment ceased was statistically significant when compared to the normal PRA group ($p<0.01$), again demonstrating that TRV027 was effective in reducing pulmonary pressure. Approximately 73% of the high PRA patients were considered responders, which was defined as seeing a decrease in both MAP and PCWP during the treatment phase.

FIGURE 5

Changes in MAP and PCWP – TRV027 vs. Placebo



Source: Company data

There were no meaningful changes seen in heart rate, cardiac index, or creatinine levels in patients with normal or high PRA.

Safety results were similar to what was seen in the earlier phase 1 trials. There were no meaningful changes seen in heart rate, cardiac index, or creatinine levels in patients with normal or high PRA. One patient discontinued therapy after experiencing hypotension (low blood pressure). Trevena believes the risk of severe hypotension should be lower than vasodilators as the trial showed dose dependent decreases in blood pressure were capped at 3μg/kg/min. The short half life of TRV027 also reduces the risk of prolonged hypotension if it does occur. Patients who received placebo or were in the normal PRA group saw an increase in brain natriuretic peptide (BNP) levels (indication of cardiac stress). However, patients who were in the high PRA group did not see an increase, which Trevena argues may be connected to TRV027 protecting the patient from cardiac stress.

Phase 2b trial – Results Expected 4Q15

Trevena hopes to demonstrate that TRV027 is able to reduce the number of hospital readmissions and length of hospital stay, which will be beneficial on both a regulatory and reimbursement basis

Trevena initiated the phase 2b trial, BLAST-AHF, in January 2014. The trial is a randomized, double-blind, placebo-controlled study and will enrol approximately 500 patients with acute heart failure. The study will evaluate three doses – 1.0mg/hr, 5.0mg/hr, and 25mg/hr. The company is targeting to administer TRV027 within six hours of the patient being admitted to the hospital and patients will receive TRV027 infusion for 48-96 hours. The primary endpoint will be a composite of clinical outcomes, including dyspnea, mortality, worsening heart failure, hospital readmission rate, and length of hospital stays. Trevena hopes to demonstrate that TRV027 is able to reduce the number of hospital readmissions and length of hospital stay, which will be beneficial on both a regulatory and reimbursement basis, particularly as CMS increases its focus on reducing readmission rates associated with heart failure.

Full phase 2b results are expected by the end of 2015

An interim analysis will be conducted at 300 patients and based on the results management will decide whether to reduce the number of doses being evaluated. Interim results will not be released. Full phase 2b results are expected by the end of 2015. If the results are favourable, the phase 3 trial will likely start in the second half of 2016 and an FDA approval may be granted sometime in 2020.

Forest Labs Agreement Offers Trevena a Cash Stream

Forest made an initial equity investment of approximately $30 million and has the option to license global rights toTRV027 following the completion of the phase 2b trial.

In May 2013, Trevena entered into an exclusive licensing agreement with Forest Laboratories for the development of TRV027 for acute heart failure. Forest made an initial equity investment of approximately $30 million and has the option to license global rights toTRV027 following the completion of the phase 2b trial. If Forest decides to license the product, Trevena is eligible to receive up to $430 million in total development and commercial milestones, which includes a $65 million payment once Forest decides to exercise the option. Trevena will also be able to receive royalties on global sales, escalating from 10%-20%. Forest will be responsible for all development, regulatory and commercialization costs following the phase 2b trial. If Forest does not opt to license TRV027 within the specified timeframe, Trevena would then be free to enter into a collaborative agreement with another partner.

On February 18, Actavis announced its plan to acquire Forest Labs for ~$25 billion in cash and equity. Pending approvals, the transaction is expected to close in mid-2014. While the acquisition does add another layer to the option agreement, we believe it aligns with Actavis' reasoning behind acquiring Forest – to expand its brand pipeline and diversify its therapeutic reach. If Actavis/Forest decides not to exercise the option, Trevena is confident that it will be able to find another partner, particularly with the available of phase 2b results.

We are assuming ACT will opt to license the product if phase 2 results are positive. We estimate global TRV027 peak sales of $757 million in 2030 before the expiration of the composition of matter patent in 2031 and that Trevena will receive 10%-20% royalties on sales, which results in peak royalties of $151 million.

Competitive Products

If approved, TRV027 would compete with the current standard of care in acute care hospitals, which includes diuretics, vasodilators, and inotropes. The cost of therapy of these genericized therapies range between $35-$200/day with branded products such as Natrecor at approximately $875/day. We are estimating a price of approximately $850/day for TRV027, which we believe is appropriate if not conservative as the product will launch in the 2020 timeframe.

There are other acute heart failure products under development, including serelaxin by Novartis, omecamtiv mecarbil being developed by Amgen in collaboration with Cytokinetics

and ulartide by Cardiorentis, although both serelaxin and omecamtiv mecarbil have had setbacks in development and regulatory efforts.

- serelaxin – Novartis is evaluating serelaxin for the treatment of acute heart failure. Serelaxin received a negative CHMP opinion in January 2014 and the company is submitting a revised filing package with new data analyses and an updated opinion is expected in 2Q14. The product is also under review by the FDA. Novartis is conducting a second phase III trial (over 6,000 patients) that started enrolment in September 2013 to support the results of its first phase 3 RELAX-AHF trial.
- omecamtiv mecarbil – Amgen and Cytokinetics are developing omecamtiv mecarbil for the treatment of both acute and chronic heart failure. The ATOMIC acute heart failure trial did not meet the primary endpoint of dyspnea response measured by the 7-point Likert scale through 48 hours (p=0.33) but showed favourable dose and concentration-related trends. The two companies are waiting for results from the COSMIC chronic heart failure trial before deciding how to proceed with the acute heart failure indication. In January, Amgen and Cytokinetics decided to increase the size of the COSMIC-HF trial and also amended the protocol to include a dose titration strategy.
- ularitide – Cardiorentis' ularitide is being evaluated in a phase 3 study, TRUE-AHF, for use in addition to conventional therapy in patients with acute heart failure.

Post-Operative Pain – Easing the Pain of Pain Products

According to IMS Health, there were approximately 30 million reimbursement claims for IV opioid use by US hospitals in 2010

According to IMS Health, there were approximately 30 million reimbursement claims for IV opioid use by US hospitals in 2010, of which approximately 14 million were inpatient claims and 16 million were outpatient. Roughly 75% of these inpatient claims and 50% of outpatient claims were surgery related. The National Hospital Discharge Survey (NHDS) estimates that over 30 million inpatient surgical procedures were performed in the US in 2010 and estimates a similar rate in Europe.

In a survey of 250 surgical patients in the U.S., 70% still experience pain right before hospital discharge and of these nearly half indicate they are experiencing severe pain.

The current standard of care for treating post-operative pain is intravenous or injectable opioids such as morphine, hydromorphone, and fentanyl to treat postoperative pain although adverse events associated with opioids, such as vomiting, constipation, and respiratory depression, has limited their use. Nearly half of the time, intravenous non-opioids such as non-steroidal anti-inflammatory drugs (NSAIDs) are added to help alleviate pain while avoiding added adverse events associated with opioids. In a survey of 250 surgical patients in the U.S., 70% still experience pain right before hospital discharge and of these nearly half indicate they are experiencing severe pain. The use of opioids has also delayed recovery and prolonged hospital stay in some instances. Trevena estimates that approximately $5 billion is spent each year in added hospital costs due to adverse events associated with the use of these opioids.

Trevena believes its TRV130 product will be able to offer an effective alternative to currently used IV opioids while reducing the rate of adverse events.

Trevena believes its TRV130 product will be able to offer an effective alternative to currently used IV opioids while reducing the rate of adverse events. TRV130 is a G protein biased ligand that targets the same μ-opioid receptor as morphine and fentanyl, a GPCR expressed on cells in the central nervous and intestinal systems. TRV130 activates the G protein pathway that provides the analgesia but inhibits β-arrestin signalling, which the company believes is associated with constipation and respiratory depression. Trevena will target TRV130 to treat moderate to severe acute postoperative pain when IV therapy is used.

Clinical Evidence – Phase 1

Phase 1b – 3.0mg dose demonstrates quicker onset of relief and improved safety

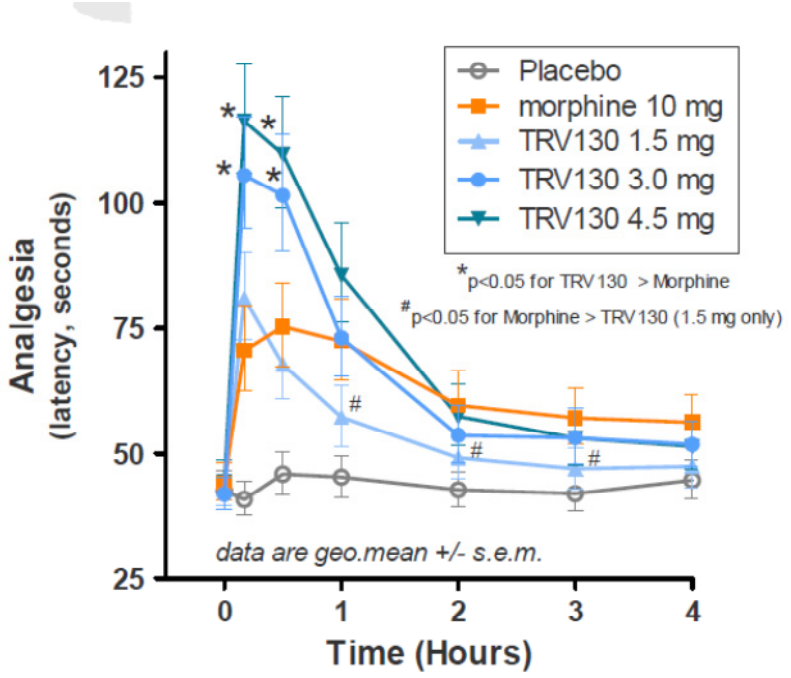
The phase 1b proof of concept study evaluated the efficacy and safety of TRV130 compared to 10mg of morphine. The trial enrolled 30 healthy individuals and had a 5-period crossover

design. Each individual received a 2-minute infusion of three doses of TRV130 (1.5mg, 3.0mg, and 4.5mg of TRV130), morphine or placebo in random order. A cold pain test was used to evaluate the analgesic effect – patients are measured on the time to hand removal from a cold water bath. Nausea was measured on a visual analog scale and respiratory depression through ventilator response to hypercapnia.

The two higher doses of TRV130 demonstrated superior efficacy when compared to 10mg of morphine at 10 and 30 minutes after dosing (p<0.05).

The two higher doses of TRV130, 3.0mg and 4.5mg, demonstrated superior efficacy when compared to 10mg of morphine at 10 and 30 minutes after dosing (p<0.05). TRV130 demonstrated a quicker onset of relief and time to peak effect. There were a higher number of responders (defined as doubling of time versus baseline) in the TRV130 group versus morphine. The length of pain relief was comparable to morphine.

FIGURE 6
Analgesic Effect of TRV130 versus Morphine



Source: Company data

Looking at safety, individuals who received TRV130 experienced less nausea and vomiting at the 1.5mg and 3.0mg doses versus morphine.

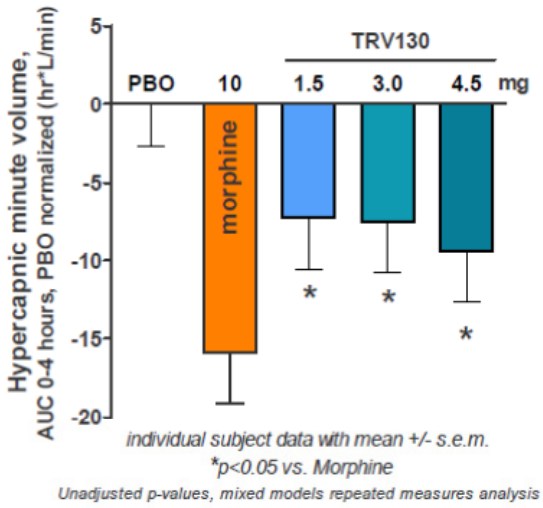
Looking at safety, individuals who received TRV130 experienced less nausea and vomiting at the 1.5mg and 3.0mg doses versus morphine but comparable to morphine at the high 4.5mg dose. Respiratory depression was measured as minute volume area (air exhaled in a single breath) under the curve over 4 hours. All three doses of TRV130 saw a statistically significant reduction in respiratory depression versus 10mg of morphine (p<0.05). Patients on TRV130 also experienced less nausea and vomiting and significantly less constipation compared to morphine.

All three doses of TRV130 saw a statistically significant reduction in respiratory depression versus 10mg of morphine (p<0.05).

Based on these results, 3.0mg of TRV130 may be an appropriate dose to evaluate further in phase 2/3 trials. The 3.0mg dose showed improved efficacy (quicker analgesic effect), was well tolerated, and reduced the level of nausea, vomiting, and respiratory depression versus 10mg morphine. The 1.5mg does not appear to offer adequate pain relief compared to morphine, while the 4.5mg does not offer an improved safety profile compared to morphine. Given the competitiveness of the post surgical pain market, we believe TRV130

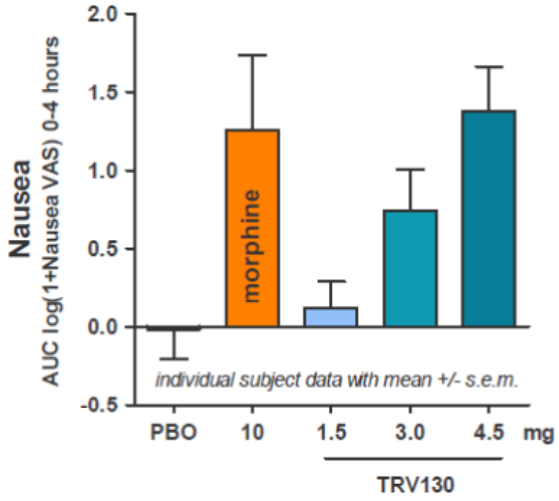
will need to demonstrate an improvement in pain relief (either quicker onset or increased analgesia) as well as a meaningful reduction in adverse events to be a competitive player in the market.

FIGURE 7
Respiratory Depression – TRV130 vs. Morphine



Source: Company data

FIGURE 8
Nausea – TRV130 vs. Morphine



Source: Company data

Trevena plans to initiate a phase 2 efficacy and tolerability trial in the second quarter this year to evaluate TRV130 in patients undergoing a bunionectomy (bunion removal) surgery.

Phase 2 Trials Expected to Start 2Q14

Trevena will develop TRV130 internally. The company plans to initiate a phase 2 efficacy and tolerability trial in the second quarter this year to evaluate TRV130 in patients undergoing a bunionectomy (bunion removal) surgery. The trial will enroll approximately 400 patients and evaluate multiple dosing regimens of TRV130 compared to morphine 4mg every 4 hours. This is an adaptive dose ranging trial – the first 150 subjects will be randomized to one of the dose cohorts for TRV130 or to placebo (morphine) and findings from this group will help determine which dosing regimens to evaluate with the next group of patients and so forth. The primary endpoint is pain intensity measure over 48 hours and safety will be measured on the incidence of key adverse events. Results from this trial should be available some time in 1Q15. The second phase 2 trial should start in the second half of 2014 and will complete towards the end of 2015.

Trevena will be able to initiate a phase 3 pivotal trial following results from the first phase 2 trial. Assuming a start in the second half of 2015, we would expect results from the phase 3 trial to be available some time in the first half of 2017. Trevena will need to run a second phase 3 trial as well. We believe Trevena may receive FDA approval of TRV130 sometime in 2019. Outside the U.S., Trevena may look for a partner to commercialize TRV130 in international markets following phase 2 results.

If TRV130 is successfully developed, Trevena plans to expand TRVB130 into additional indications.

If TRV130 is successfully developed, Trevena plans to expand into additional indications such as for peri-operative use, non-surgical hospitalized patients such as burn victims, emergency service trauma care, military use, and for palliative care for terminal patients.

Market Potential and Product Positioning

Trevena estimates the global acute pain opioid market at approximately $3.95 billion, of which roughly 66% is in the US ($2.6 billion), 32% in Europe ($1.28 billion), and the remainder in other international markets. Trevena is targeting the post-surgical market in acute care hospitals with TRV130. Trevena estimates approximately 16 million invasive surgical procedures are performed globally each year, of which 6 million are in the U.S.

The opioid market is heavily genericized and Trevena estimates the average cost of these IV opioids at only ~$10-$15/day. Adding additional pain drugs increases this to $30-$140/day.

We believe a price in the range of $60-$90/day is appropriate for TRV130 – we have used a daily price of $75 in our model.

TRV130 will mainly be competing with currently available intravenous opioids such as morphine, hydromorphone, and fentanyl that are commonly used in the hospital setting. The opioid market is heavily genericized and Trevena estimates the average cost of these IV opioids at only ~$10-$15/day. However, additional pain drugs such as IV NSAIDs, Pacira's Exparel, and Cadence's Ofirmev are often added to therapy to provide incremental pain relief when adverse events limit the use of opioids. Adding in these products, the cost per day then increases to at least $30-$140 for these post-operative patients.

With hospitals as the primary customer, pricing for TRV130 will be important for the company to appropriately position the product in the market. We believe a price in the range of $60-$90/day is appropriate for TRV130 – we have used a daily price of $75 in our model. The company may have more pricing power if it is able to show a cost-effectiveness analysis that TRV130 is able to reduce adverse events, lead to a shorter length of hospital stay, or reduce readmission rates.

TRV734 – Oral Pain Compound

Trevena recently initiated a phase 1 trial for TRV734, an oral small molecule G protein biased ligand that targets the μ-opioid receptor for the treatment of moderate to severe chronic pain. Based on preclinical studies, Trevena believes targeting the G protein pathway will help enhance the analgesic effect while reducing the side effect profile (respiratory and GI events) commonly associated with current oral analgesics such as oxycodone. This first-in-human study will evaluate ascending doses of TRV734 in healthy patients and will measure tolerability and safety and also pupil constriction to measure the analgesic effect. Results are expected in 3Q14 and the company plans to find a partner to develop the product. We have not included any revenues from this product in our model given the lack of clinical data available.

Valuation

We are initiating coverage of Trevena with an Overweight rating and $14 price target. We arrive at price target using a probability-adjusted NPV analysis and using a discount rate of 10%. We estimate peak revenues of $757 million for TRV027 and peak royalties of $151 million, which translates to a NPV of $4/share. For TRV130 we estimate peak sales of $416 million, which also translates to a NPV of $6/share. Including ~$4/share in cash, we arrive at our $14 price target.

IGURE 9
Trevena Valuation Summary

Drug	Peak Sales ($M)	Peak Royalty ($M)	Stage	Estimated launch	Probability of Reaching Market	Probability Adjusted NPV ($M)	Per Share Value
TRV130	$416		Phase II	2019	37%	$156	$6
TRV027	$757	$151	Phase IIb	2020	22%	$115	$4
Total						$271	$10
Other ($M)							
Net Cash (Cash/Equivalents - Debt)						**$100**	**$4**
					Total ($M)	**$371**	**$14**
					Shares (M)	**27.0**	

Discount Rate	10%
Time of Valuation	2015

Source: Company data, Barclays Estimates

- **Upside scenario**: If TRV130 is successfully developed and phase 2b results for TRV027 are positive, we see upside potential at approximately $28/share.
- **Downside scenario:** If the phase 2b trial for TRV027 does not meet the primary endpoint and development for the product is stopped, we see valuation dropping to $8/share based on TRV130 and some cash value.

Risks

Development risks. While trial data to date for both TRV130 and TRV027 have been intriguing and have demonstrated signals of meaningful clinical benefit, there are always risks in replicating these results in larger pivotal trials.

Capital risks. As with any early development stage biotechnology company, there are risks in the company's ability to raise additional capital to further its development efforts. Trevena's current cash position should support the company through 2015.

Regulatory risk. The FDA is unpredictable and any setbacks in approvals will be significant for the company.

FRX/ACT not opting for TRV027. If Forest Labs/Actavis does not exercise the option to develop TRV027, Trevena will need to search for another partner or raise additional capital to develop the product internally.

Market risk with TRV130. Even if TRV130 is successfully developed and approved by the FDA, there could be market risks if the trial results do not demonstrate a meaningful improvement in safety and/or efficacy over currently marketed IV opioids, particularly given the lower costs of these genercized IV opioids.

Management Profiles

Maxine Gowen, Ph.D. (President and Chief Executive Officer)

Maxine Gowen is a co-founder, President, and Chief Executive Officer of Trevena. Dr. Gowen has significant experience in a variety of roles in the biotechnology industry. Prior to Trevena, Dr. Gowen spent 15 years in GlaxoSmithKline (GSK) serving various management roles. During her tenure in GSK, Dr. Gowen was the Senior Vice President for the Center of Excellence for External Drug Discovery ,where she developed the approach of externalizing drug discovery, after serving as the President and Managing Partner at SR One (venture capital subsidiary of GSK). Prior to GSK, Dr. Gowen was a senior lecturer in the School of Pharmacology, of the University of Bath, where she authored more than 100 scientific publications. Dr. Gowen received her B.Sc. in biochemistry from the University of Bristol, Ph.D. in cell biology from the University of Sheffield, and MBA from the Wharton School.

Michael W. Lark, Ph.D. (Chief Scientific Officer and Senior Vice President, Research)

Prior to joining Trevena in 2008, Dr. Lark was the Vice President of Biology at Centocor R&D and was responsible for therapeutic discovery strategy and execution in immunology, oncology, tissue remodelling and biomarkers. Prior to Centocor R&D, he was the Director of Musculoskeletal Diseases at GlaxoSmithKline (GSK) and also the Senior Investigator at Merck Research laboratories. Dr. Lark received his B.S. in Microbiology from the Pennsylvania State University, his Ph.D. in Molecular Biology and Microbiology from the Case Western Reserve University Medical School and completed his postdoctoral fellowship in the Department of Pathology at The University of Washington.

Roberto Cuca (Chief Financial Officer)

Roberto Cuca joined Trevena in 2013 and brings 20 years of experience in the pharmaceutical and biotechnology industries. Before Trevena, Mr. Cuca was the Treasurer and Senior Vice President of Finance at Endo Health Solutions, Director of Corporate and Business Development at Moksha8 Pharmaceuticals. Prior to, Cuca was an equity research analyst covering the U.S. pharmaceutical space at JPMorgan. Mr. Cuca received an MBA from the Wharton School, a JD from Cornell Law School, and an AB from Princeton University.

David Soergel, M.D. (Senior Vice President, Clinical Development)

Dr. Soergel joined Trevena in November 2009. Prior to, he was Senior Director of Clinical Development at Concert Pharmaceuticals and was responsible for clinical operations and strategy for a number of therapeutic areas. Before Concert, he was Director of Discovery Medicine at GlaxoSmithKline. Dr. Soergel completed his clinical training at Johns Hopkins Hospital in Pediatric Cardiology and also trained at the Children's Hospital of Philadelphia in the Heart failure and Transplant division.

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I, Ying Huang, Ph.D., hereby certify (1) that the views expressed in this research report accurately reflect my personal views about any or all of the subject securities or issuers referred to in this research report and (2) no part of my compensation was, is or will be directly or indirectly related to the specific recommendations or views expressed in this research report.

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Primary Stocks (Ticker, Date, Price)

Trevena Inc. (TRVN, 25-Feb-2014, USD 7.77), Overweight/Neutral, A/C/D/J/L

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Gilead Sciences (GILD)	GlycoMimetics Inc. (GLYC)	Halozyme Therapeutics Inc. (HALO)
Idenix Pharmaceuticals (IDIX)	Incyte Corp. (INCY)	Intrexon Corp. (XON)
Medivation Inc. (MDVN)	Regeneron Pharmaceuticals (REGN)	Tetraphase (TTPH)
Trevena Inc. (TRVN)	Vertex Pharmaceuticals (VRTX)	

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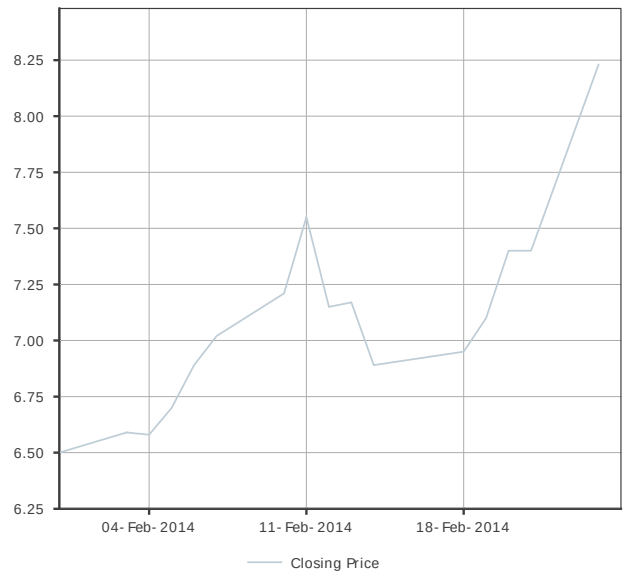
IMPORTANT DISCLOSURES CONTINUED

Trevena Inc. (TRVN)	Stock Rating	Industry View
USD 7.77 (25-Feb-2014)	**OVERWEIGHT**	**NEUTRAL**

Rating and Price Target Chart - USD (as of 25-Feb-2014) **Currency=USD**

Date	Closing Price	Rating	Adjusted Price Target



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Valuation Methodology: We arrive at our price target using a probability-adjusted NPV analysis. We value the two foremost pipelien products - TRV130 at $6/share and TRV027 at $4/share. Including cash value of $4/share, we arrive at our price target of $14.

Risks which May Impede the Achievement of the Barclays Research Price Target: Downside risks include failure of trials results for both TRV130 and TRV027, ACT/FRX not opting to license TRV027, and inability to raise additional capital in the future.

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