COWEN
AND COMPANY

Biotechnology

Trevena

Equity Research

Initiating Coverage

December 19, 2014

Price: $4.97 (12/18/2014)

Price Target: $13.00

OUTPERFORM (1)

Ritu Baral
646.562.1379
ritu.baral@cowen.com

Kenny Lalwani
646.562.1425
kenny.lalwani@cowen.com

Key Data

Symbol	NASDAQ: TRVN
52-Week Range:	$9.95 - 3.80
Market Cap (MM):	$187.0
Net Debt (MM):	$(38.0)
Cash/Share:	$39.64
Dil. Shares Out (MM):	37.6
Enterprise Value (MM):	$116.6
ROIC:	NA
ROE (LTM):	NA
BV/Share:	$2.44
Dividend:	NA

FY (Dec)	2014E	2015E	2016E
Earnings Per Share			
Q1	$(0.59)	$(0.44)	-
Q2	$(0.44)	$(0.49)	-
Q3	$(0.59)	$(0.52)	-
Q4	$(0.39)	$(0.58)	-
Year	$(1.93)	$(2.01)	$(1.59)
P/E	NM	NM	NM
Consensus EPS	$(2.17)	$(1.48)	$(1.14)

Consensus source: Thomson Reuters

Revenue (MM)			
Year	-	$65.0	$15.0
EV/S	-	1.8x	7.8x

Initiation: TRVN's Biased Ligands Leave Us Biased Toward Upside

The Cowen Insight

We believe Trevena's TRV130 for acute postoperative pain has potential to bypass current postoperative pain relief treatment options. We believe TRV027 has potential to become a key therapy for AHF and benefit from an Actavis milestone payment.

We think TRVN has a very promising GPCR biased ligand technology platform that has the potential to generate multiple blockbuster therapies.

TRVN's ABLE platform has the potential to generate biased GPCR ligands. which can preferentially activate one of two intra-cellular signaling pathways (G Protein or beta-arrestin) associated with GPCR's. One pathway often confers clinical benefit and the other, side effect. Biased ligands may allow TRVN to develop therapies that have optimized clinical profiles to currently available treatments.

TRV130 Could Surpass Current Suboptimal Post-op Pain Options; Recent Phb Trial Data Support Advancement into Ph3 with Better Pain Relief Than Morphine

Despite first-line morphine, adjunct, and rescue treatment options, 50-75% of post-op patients still suffer from moderate to severe pain. Traditional opiate side effects, such as respiratory depression, nausea, and vomiting, are of great concern to clinicians. These drawbacks present a tremendous opportunity for optimized front-line treatment options, which would be well-received by clinicians. Ph2b bunionectomy data hit the primary endpoint of better analgesia over PBO. Importantly, data showed significantly better analgesia vs morphine at 3 mg of TRV130. 100% of responders in the 3 mg cohort showed either"very much" or "complete" pain relief versus only 10% with morphine. We believe this data and data from the next Ph2 trial will support a Phase 3 program in early 2016.

TRV027: Next-Gen AHF Drug Has the Potential to Become a Critical Therapy in an Innovative and Emerging Class of AHF Drugs

TRV0127 appears to strike the right balance by helping cardiac contractility without increasing blood pressure and fluid retention. There are no currently available heart failure therapies that safely improve cardiac output. Diuretics such as furosemide are the standard of care and act by reducing fluid load in patients until they are stable so vasodilators can then be utilized to moderate blood pressure. KOLs we have spoken to highlight heart tissue damage with even moderate use and, therefore, seldom use first-generation inotropes.

We Model $866M TRV130 Peak US sales; $646M Peak US Sales of TRV027 with driving $129M Peak Potential Royalties to TRVN

We model $866M in peak US sales for TRV130 as a postop, first-line treatment assuming a blended 16% peak market share. For AHF, we believe the Ph2b trial design will elucidate TRV027's effectiveness and inform a Ph3 pivotal design. We believe Actavis would trigger its TRV027 option on positive data which would relieve Trevena of Ph3 clinical costs and trigger a $65 million payment.

Please see addendum of this report for important disclosures.

At A Glance

Our Investment Thesis

We believe Trevena's TRV130 for acute post-op pain and TRV027 for AHF are only the beginning of potential blockbuster candidates from the (ABLE) platform. TRV130 could bypass current suboptimal postoperative pain relief options as a vital front-line treatment option with less side effects and potential to reduce length of hospital stay. TRV027 is a next-generation inotrope that improves heart contractility without stressing heart tissue and has the potential to become a critical therapy in an innovative and emerging class of AHF drugs. We also highlight TRV734, currently in a Ph1 trial, an oral version of TRV130 for acute or chronic, moderate to severe pain. TRV734 could have an even greater market opportunity but would come with more strict commercial constraints given the greater abuse potential in outpatient setting.

Forthcoming Catalysts

- 1Q15: TRV734 Ph1 multiple ascending dose data
- Mid-2015: TRV130 Ph2a/b soft tissue surgery data vs. morphine
- 4Q15: TRV027 Ph2b data
- 1Q16: TRV130 Ph3 initiation

Base Case Assumptions

- TRV130 becomes critical postop pain treatment bypassing suboptimal current treatments
- TRV027 becomes key therapy in AHF treatment
- Actavis triggers $65M opt-in 4Q15 for TRV027
- TRV734 POC data helps land partner in 1H15

Upside Scenario

- Stronger than expected Ph2 TRV130 data indicating TRV130 has even stronger, more rapid relief than morphine
- Better than expected benefit in CV outcomes data
- Better pharmacoeconomic data indicating either '734, '027 reduces length of stay by at least 36hrs may drive higher uptake
- TRV734 lands partner earlier than expected due to strength in TRV130

Downside Scenario

- TRVN's Ph2 trials may be confounded by statistics, a common event in pain trial due to unusual placebo response
- TRV130 Ph2a/b soft tissue trial is unsuccessful
- TRV027 misses primary endpoint; Actavis does not activate option thereby restricting TRVN's cash balance
- Any potential issues with TRV130 cascade into TRV734's potential

Price Performance

Source: Bloomberg

Company Description

Trevena is a biopharmaceutical company focusing on novel treatment therapies targeting G protein coupled receptors (GPCRs). Based on the proprietary development platform, Trevena has three product candidates in clinical trials: TRV130 for the treatment of moderate to severe acute pain intravenously, TRV027 for acute heart failure, and TRV734 as an oral treatment for acute and chronic pain. Trevena recently announced data from TRV130's Phase 2a/b trial, with another TRV130 trial in soft tissue will commence by the end of 2014. TRV027 is currently in a Phase 2b trial and TRV734 is currently in a Phase 1 trial. Trevena was founded in 2007 with its platform based on Dr. Robert Lefkowitz's work in GPCR's who is a scientific founder of the company. The company is based in Pennsylvania and has approximately thirty employees.

Analyst Top Picks

	Ticker	Price (12/18/2014)	Price Target	Rating
Raptor Pharmaceutical Corp.	RPTP	$9.10	$24.50	Outperform
Intercept Pharmaceuticals	ICPT	$150.14	$420.00	Outperform

Investment Thesis

We believe Trevena's TRV130 for acute postoperative pain and TRV027 for acute heart failure are only the first of more potential blockbuster candidates from the company's G protein biased signaling technology platform (ABLE). We consider Trevena's ABLE drug discovery platform as a distinct, versatile new approach to drug candidate profile selection and optimization. Drug candidates derived from Trevena's ABLE platform can harness the power and broad applicability of G proteins. They should have a superior safety and efficacy profile compared to the currently available class of GPCR-based drugs.

TRV130 could bypass current suboptimal postoperative pain relief options as a differentiated front-line treatment option. Despite first-line morphine treatment, adjunct treatment, and rescue treatment options, 50-75% of post-operative patients still suffer from moderate to severe pain. Also, traditional side effects of opiates, such as respiratory depression, nausea, and vomiting, are of great concern to clinicians. They tend to worsen patient outcomes and satisfaction, thereby increasing healthcare costs and length of hospital stay (which is crucial to payors). These drawbacks present a tremendous opportunity for optimized front-line treatment options and we predict they would be well-received by clinicians. TRV130 is a biased ligand of the G-protein signaling pathway of the μ-opioid receptor. It is believed the μ-opioid receptor activation elicits G protein signaling mediated pain relief without activating undesirable side effects of the β-arrestin mediated pathway: respiratory depression, nausea and vomiting.

Recent Data from Phase 2a/b Bunionectomy Trial Supports TRV130 Advancement into Phase 3 with better pain relief than morphine. Data from this trial achieved the primary endpoint of better analgesia over placebo at 2 mg and 3 mg TRV130 doses. Importantly, the statistically significant improvement in analgesia versus morphine at 3 mg of TRV130 in a 48 hour duration was promising. Over the first three hours of treatment at the 2 mg and 3 mg doses, TRV130 showed better analgesia than morphine as early as five minutes after dosing. 100% of responders in the 3 mg cohort showed "very much" and "complete" pain relief versus approximately 10% with morphine. TRV130 at these doses had comparable safety to 4 mg of morphine with less nausea, vomiting, itching, and constipation and no serious adverse events in any groups. From the Phase 1b trial, TRV130 demonstrated less respiratory depression and better efficacy which suggests a unique and enhanced therapeutic profile. TRV130 had a statistically significant increase in intolerable pain latency and pupil restriction which is an accepted opiate analgesic biomarker. We believe the bunionectomy data and data from the next Phase 2 trial (starting December 2014 in soft tissue) will provide sufficient safety and efficacy data to support a Phase 3 program in early 2016.

We believe Trevena will self-commercialize TRV130; we model $866M in TRV130 peak US sales. Trevena has stated its intent to self-commercialize TRV130 with a 75-100 hospital rep-based sales force. The company plans on implementing a strategy comparable to AcelRx's for its drug sublingual sufentanil tab Zalviso (which has a first quarter 2015 FDA resubmission date). We model $866M in peak US sales for TRV130 as a postoperative, first-line treatment assuming a blended 16% peak market share (surgical inpatient and outpatient peak market share values of 25% and 20%, respectively, and non-surgical inpatient and outpatient peak market share values of 15% and 2%, respectively).

TRV734: Same Mechanism As TRV130 Should Be Equally Efficacious

TRV734 is an orally available, small molecule G protein μ-opioid biased agonist that has the same mechanism as TRV130 and may, therefore, be equally efficacious. Trevena intends to develop TRV734 as a treatment for acute and chronic pain in both the moderate to severe areas in the outpatient setting which could represent a larger market opportunity. However, this opportunity would be vulnerable to more strict commercial constraints because of the greater abuse potential in the outpatient setting. Preclinical studies indicated TRV734 has a comparable drug candidate profile to TRV130 both in vivo and in vitro. TRV734 achieved analgesia similar to that of oxycodone with reduced constipation. Preclinical data implies TRV734's analgesic efficacy may be separable from opioid-related adverse effects. There were no severe or serious adverse events reported nor were there any clinically significant changes in vital signs, laboratory values or ECG parameters. We expect safety and efficacy data from the Phase 1b trial in 1Q15. Trevena has retained all worldwide development and commercialization rights to TRV734 but we think the company may commercialize TRV734 with a partner that has deep outpatient chronic pain management expertise.

TRV027 is a next-generation acute heart failure drug that improves heart contractility without stressing heart tissue and has the potential to become a critical therapy in an innovative and emerging class of acute heart failure (AHF) drugs. TRV027 is a β-arrestin biased agonist of the Angiotensin 2 Type 1 receptor (AT1R). ATR1 β-arrestin signaling enhances cardiac contractility, a beneficial effect for AHF patients. However, AT1R signaling is actually blocked by current AHF treatments since its G protein pathway signaling causes elevation of blood pressure and fluid retention which worsens the condition by making the heart work harder to pump blood. TRV027 appears to strike the right balance by helping cardiac contractility without increasing blood pressure and fluid retention. There are no currently available heart failure therapies that safely improve cardiac output. Diuretics such as furosemide are the standard of care and act by reducing fluid load in patients until they are stable so vasodilators can then be utilized to moderate blood pressure. KOLs we have spoken to highlight heart tissue and heart damage in long-term care and, therefore, seldom use first-generation inotropes.

Phase 2a data highlights TRV027's ability to improve critical heart function biomarkers and vascular and renal health. Phase 2a stable AHF data demonstrated statistically significant mean arterial pressure dose-dependent decreases in a patient subgroup with verified RAS activation (a class representing approximately half of all heart failure patients). Patients treated with TRV027 also had numeric decreases in pulmonary capillary wedge pressure (PCWP). Additionally, TRV027 demonstrated stable cardiac index, a marker of cardiac muscle function and contractility. This is in contrast to treatment with ATR1 signal antagonists like angiotensin receptor blockers (ARBs) which have been associated with reductions in cardiac index. Safety in this Phase 2 population was positive, with only transient mild low blood pressure (a potentially meaningful data point given the medically fragile state of the patients). This trial demonstrated no increase in heart rate which is considered a marker for stress on cardiac tissue.

We consider Trevena's well-designed TRV027 Phase 2b trial as having a suitable chance of success potentially prompting an opt-in by Actavis: we model $646M peak US sales potential with 18%, or $129M, of these peak sales belonging to Trevena after the Actavis opt-in. We believe the Phase 2b trial design, which utilizes a composite endpoint including standard CV outcomes, length of stay, and dyspnea, will elucidate TRV027's effectiveness and potentially inform a Phase 3 pivotal trial design. Based on Phase 2a's response strength indicated with 14 hours' infusion, we believe a longer

follow-up period with a larger trial will demonstrate clinically meaningful benefit in support of a Phase 3 trial. We believe Actavis would trigger its TRV027 option on positive data which would relieve Trevena of Phase 3 clinical costs and provide Trevena with a $65 million option payment. Trevena is eligible for an additional $365 million in milestones and 10-20% royalties on sales.

Overview of Financials

We reach a price target of $13 based on our pNPV analysis of Trevena.

We predict TRV130 will launch in the US by the end of 2018 for treatment in first-line postoperative pain. We project postoperative pain peak TRV130 market share of 10-15% in US inpatient/outpatient non-surgical setting and 20-30% in US inpatient and outpatient surgeries. We assume it will take eight years from launch to reach peak sales in 2026, given the need for formulary adoption.

For TRV130 in the inpatient setting, we believe Trevena will price a 2.5-day course at approximately $200 and an eight-hour course in the outpatient setting at approximately $15 in the US at launch. We think superior pharmacoeconomics and safety profile from research will prove our estimates conservative. We forecast peak sales for TRV130 in 2026 of ~$866M. We have not forecasted any potential sales or royalties outside the US which, we believe, presents potentially significant upside from our current estimates.

We believe TRV027 will launch in the beginning of 2020 and we estimate TRV027 will achieve peak market share of 30% in the US. We think this peak market share will come to fruition in 2026, six years from launch.

We predict TRV027's ongoing Phase 2 trial will generate positive data by the end of 2015 which is when Actavis will trigger the opt-in rights to the TRV027 program. We posit the Trevena/Actavis union will price a treatment course of TRV027 at approximately $2,500 in the US at launch. Overall, we forecast peak 2026 sales for TRV027 of approximately $646M. With an 18% blended tiered US royalty, Trevena could receive royalties of $129M from peak year sales. Similar to our TRV130 forecasts, we have not forecasted any potential sales or royalties outside the US which, we believe, presents potentially significant upside from our current estimates.

Trevena reported cash and cash equivalents of $72.2M as of September 30, 2014 and recently raised $40M net proceeds from a recent public offering. In addition to an optional $16.5M debt tranche, we believe Trevena has enough cash to fund its operations and clinical candidates through the fourth quarter of 2016. We also believe Trevena's cash position will be meaningfully bolstered in the fourth quarter of 2015 when we believe Actavis could pay Trevena the $65M opt-in payment, which would make Actavis responsible for all costs related to the ongoing research and development and 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 1 – TRVN pNPV Table

Trevena, Inc.

Assumptions / Results	
Total NPV	**13.3**
Number of Shares (m)	37.6
Pharma PE	13.0x
Discount rate	25%
Current year	2014.75

Product Development

Drug name	Indication	Status	Launch	Success	Sales (US$m)	Royalty	Profitability	NPV (US$)
TRV130	Acute postoperative pain	Phase 2b	2018	55%	866.0	100%	90%	12.04
TRV027	Acute heart failure	Phase 2b	2020	40%	645.9	18%	100%	1.31
							Total	**13.35**

Source: Cowen and Company

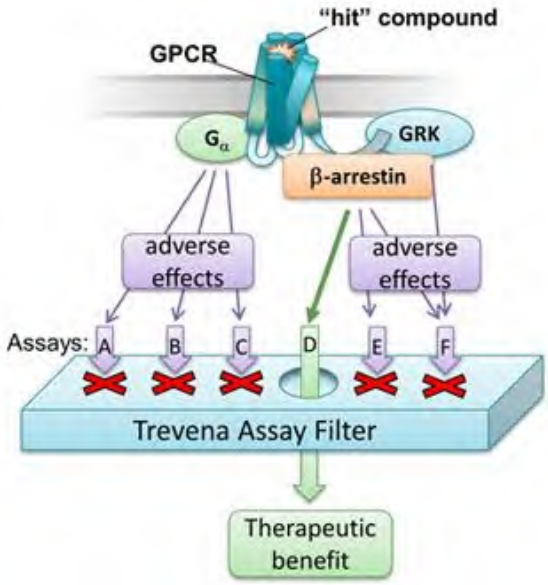
Company Overview

Trevena is a biopharmaceutical company focusing on novel biased ligand therapies targeting G protein coupled receptors (GPCRs). Based on the proprietary development platform, Trevena has three product candidates in clinical trials: TRV130 for the treatment of moderate to severe acute pain intravenously, TRV027 for acute heart failure, and TRV734 as an oral treatment for acute and chronic pain. Trevena recently announced data from TRV130's Phase 2a/b trial, with another TRV130 trial in soft tissue will commence by the end of 2014. TRV027 is in a Phase 2b trial and TRV734 is in a Phase 1 trial. Trevena was founded in 2007 with its platform based on Dr. Robert Lefkowitz's work in GPCR's who is a scientific founder of the company. The company is based in Pennsylvania and has approximately thirty employees.

The Advanced Biased Ligand Explorer (ABLE) Platform

Trevena monopolizes its ABLE platform by finding more specific ligands that have the ability to inhibit or activate EITHER the intracellular G protein or β-arrestin pathways. This is unique to other available pharmaceuticals that use a GPCR mechanism. Usually, one intracellular pathway is associated with a desired therapeutic effect while the other can cause undesirable adverse events. The ability of Trevena's proprietary ligands to activate one of the pathways while repressing the other allows for high signaling specificity and a highly differentiated, more effective, and safer therapeutic. Trevena's ABLE product platform can fuel a pipeline with the company's broad range of knowledge of the biology and ability to identify unique GPCR ligands that can manipulate the process of cellular activation. The G protein and β-arrestin pathways are involved in cellular function as well as numerous processes such as sensory systems, mood and behavioral regulation, immune system activity and inflammation, autonomic nervous system transmission, cell density sensing, growth and metastasis of certain tumors, and homeostasis.

Figure 2 – Trevena's ABLE Platform: Targeting Specific Pathways

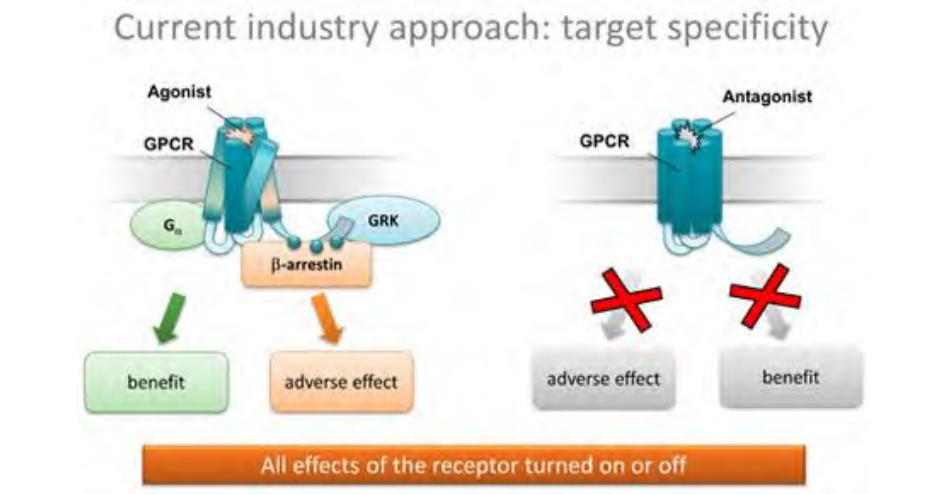


Source: Trevena

GPCRs and Biased Ligands

G protein coupled receptors (GPCRs) are a group of transmembrane receptors that detect molecules outside a cell and can then activate a response via signal transduction pathways. Current estimates vary but it is believed that 30% to 50% of all marketed drugs act by binding to GPCRs. Common drugs with GPCR mechanisms include Lilly's Zyprexia, Schering-Plough's Clarinex, GSK's Zantac, and Novartis's Zelnorm. Most GPCR modulating drugs weren't initially targeted to attack a specific protein. Rather, they were developed on observed functional activity. GPCRs target the G protein and β-arrestin pathways. Available treatments today that focus on GPCRs lack signal specificity. For example, as highlighted in Figure 3, treatments either inhibit both the G protein and β-arrestin pathways and are considered antagonist ligands or activate both pathways and are considered agonist ligands. This lack of signal specificity in pathway activity results in an inferior therapeutic profile since one pathway may help with therapeutic benefit while the other frequently is linked to undesired side effects.

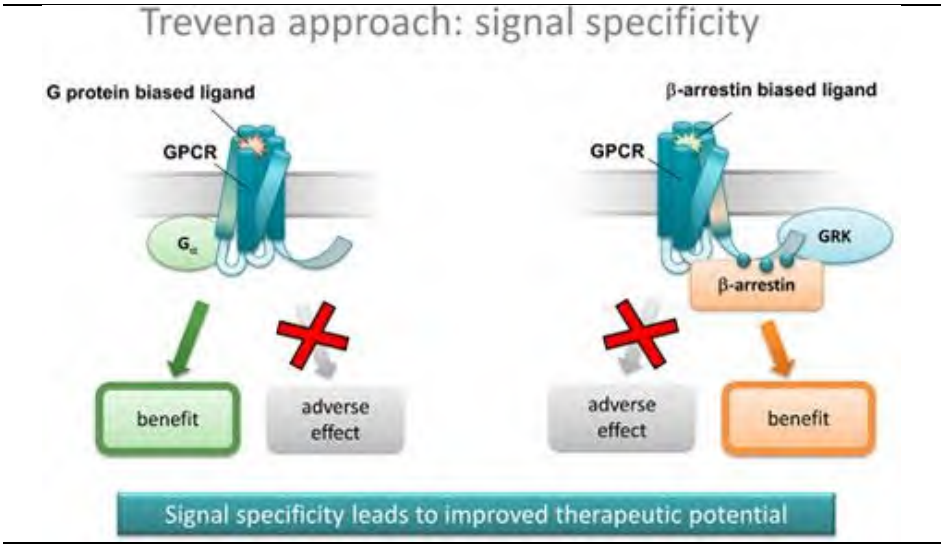
Figure 3 – The All-Or-Nothing Approach of Current GPCR Targeted Therapies



Source: Trevena

Trevena's research approach is to focus on signal specificity, highlighted below.

Figure 4 – TRVN's Signal Specific Approach Can Lead to Better Therapeutic Outcomes



Source: Trevena

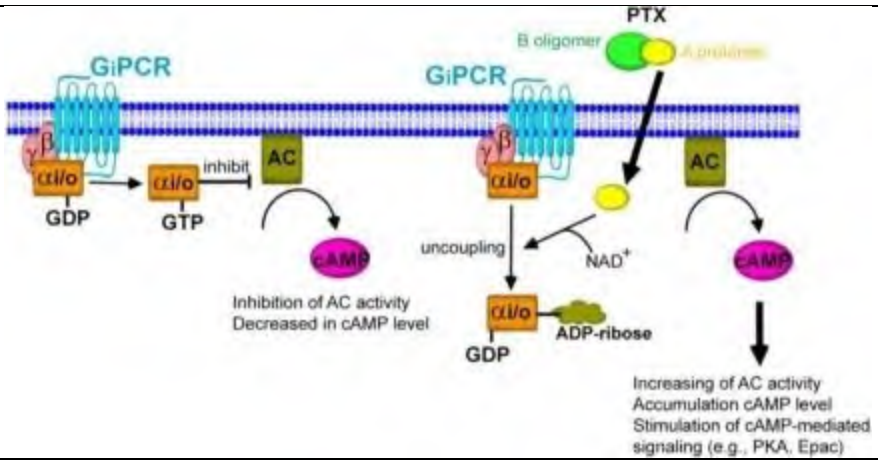
G Proteins. G proteins are unique proteins than can bind to and phosphorylate (or dephosphorylate) guanosine triphosphate (GTP) and guanosine diphosphate (GDP). G proteins that are linked to GPCRs are heterotrimeric with alpha, beta, and gamma subunits. The alpha and gamma units are attached to the plasma membrane by lipid anchors. The alpha subunit can bind to either GTP or GDP which is contingent upon the activity of the protein (active status is linked to GTP and inactive status to GDP). A ligand binds to the GPCR and institutes a conformational change that allows the GPCR to act as a GEF and dephosphorylate a GTP into a GDP. The conformational change allows the portion of the GPCR inside the cell to split into it's a and b effectors that are then used to create a cellular response. This reversible reaction can allow for the GPCR to return to its intact conformation, when it acts as a GAP and is phosphorylated. At this point, the a and b effectors bind and the cellular response is thereby inhibited. G proteins are often referred to as being a switch-like, or all-or-none mechanism because their activation is binary based on the presence of a ligand.

G protein coupled receptors (GPCRs) are a group of transmembrane receptors that detect molecules outside a cell and can then activate a response via signal transduction pathways. These, in turn, can lead to cellular response pathways. A ligand binds to the GPCR and institutes a conformational change that allows the GPCR to act as a GEF and dephosphorylate a GTP into a GDP. The conformational change allows the portion of the GPCR inside the cell to split into it's a and b effectors that are then used to create a cellular response. This reversible reaction can allow for the GPCR to return to its intact conformation, when it acts as a GAP and is phosphorylated. At this point, the a and b effectors bind and the cellular response is thereby inhibited.

G Proteins Target Second Messengers. The activation G proteins can cause an amplified effect as one G protein can influence production of hundreds to thousands of second messenger molecules (such as cyclic AMP [cAMP], diacylglycerol [DAG], inositol 1, 4, 5-triphosphate [IP3]). These second messengers are small molecules that can initiate and facilitate intracellular signaling pathways. Adenylyl cyclase is an

enzyme linked to the membrane that is targeted by G proteins. When it is activated by the GTP-bound alpha subunit, it catalyzes synthesis of cAMP from ATP molecules. In humans, cAMP is involved in sensory input, nerve transmission, hormones, and various other cellular messaging pathways. Another common target of activated G proteins is phospholipase C which is another membrane-associated enzyme that can catalyze the synthesis both DAG and IP3 from lipid phophatidyl inositol, a membrane lipid. This pathway is key to various activities in the body such as blood clotting.

Figure 5 – Uncoupling of G proteins from GPCR

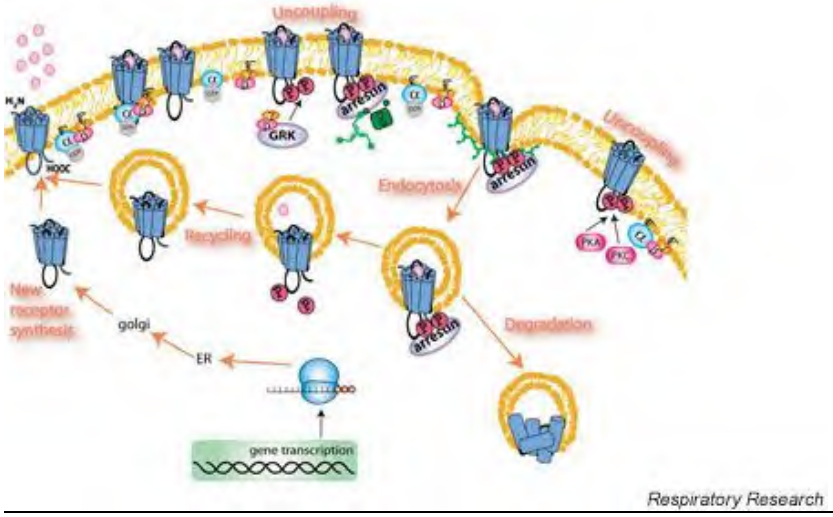


Source: NIH - Openi

β-arrestin

β-arrestins are versatile, adaptable proteins that translocate to the cell membrane and bind to receptors that are linked to agonists. β-arrestins comprise four members: arrestin 1 and 4 which are expressed in the retina, and 1 and 3 which have robust expression and play a critical role in GPCR transduction. Once β-arrestins bind to receptors, the G protein and receptor disconnect, causing desensitization. Recent research indicates β-arrestins also operate as scaffold proteins which interact with various cytoplasmic proteins and connect GPCRs to intracellular signaling pathways such as MAPK cascades. The latest research also indicates as certain GPCRs are activated, β-arrestins move into the nucleus from the cytoplasm and associate with transcription factors p300 and cAMP-response element-binding protein (CREB) to promote transcription. β-arrestins also interact with transcription regulators to indirectly regulate transcription. It is currently believed that this β-arrestin-controlled transcription regulation is critical in cell growth, apoptosis, and modulation of immune functions.

Figure 6 – GPCR Regulation in Airway Smooth Muscle



Source: NIH - Openi

Acute and Postoperative Pain

Postoperative pain comprises a significant component of the general acute pain market. According to HHS estimates, over 46 million inpatient and 53 million outpatient surgeries are completed every year in the US. Moderate-to-severe pain is usually treated with injectable analgesics for the inpatient setting with IV analgesics in the US market consisting primarily of μ-opioid agonists. Examples of these drugs are morphine, hydromorphone, fentanyl, and non-opioid analgesics like IV ketorolac generics, Caldolor (IV form of ibuprofen), Toradol, and Ofirmev (IV form of acetaminophen). The postoperative pain market grew to $5.9 billion in 2010 which is approximately 20% of the entire pain therapeutics market.

Multimodal treatment paradigm, the standard of care in treating acute postoperative pain, is based on the administration of two or more drugs with different analgesic mechanisms of action (usually an opioid plus non-opioid) to help reduce adverse events. The patient is transitioned to a prescription oral pain medication upon discharge, allowing him/her to self-administer relatively strong analgesics on his/her own (referred to as the IV-to-oral "step-down" process).

During the immediate postoperative period, strong μ-opioid analgesics are the common method of pain treatment. These drugs are typically accompanied by serious side effects such as: postoperative opioid-related nausea and vomiting, postoperative opioid-induced respiratory depression, and opioid-induced bowel dysfunction. The latter of these side effects can contribute to the severity of postoperative ileus. In 30% of patients, opioid-induced respiratory depression can occur unexpectedly. This lengthens hospital stay and increases the total cost of treatment. Post-operative opioid-related nausea and vomiting strikes one-third of all surgical patients which makes it a critical factor in determining length of stay post-surgery. The CDC estimates the resulting annual cost to the US healthcare system at around $1 billion. Adverse events related to μ-opioids considerably increase the cost of care and can hinder recovery.

Non-opioid analgesics formulated for injection or infusion (such as IV acetaminophen and IV ibuprofen) can serve as alternatives to μ-opioids in reducing patients' acute pain but are only moderately effective. Acetaminophen has potentially fatal liver toxicity while NSAIDs are linked with risk of bleeding, kidney damage, serious gastrointestinal adverse events, and serious cardiovascular thrombotic events (heart attack and stroke).

Available Therapies for Acute Pain

Innovation in new analgesics has been stagnant despite the large pain market. Most of the new and recent approvals are reformulated versions of existing drugs with different delivery methods. Despite the safety drawbacks intrinsic to their respective mechanisms, μ-opioids are still the most prescribed drugs for pain management. Physicians tend to prescribe suboptimal doses of μ-opioids which leads to suboptimal pain relief. We see the postoperative pain market as one with an unmet need. Our conversations with clinicians indicate they would like superior options to balance pain management with reduced risk of causing severe adverse events.

In 2010 there were 46 million inpatient surgical procedures in which almost all patients experienced postoperative acute pain of differing intensity and length which depended on the type, length, and tissue damaged in surgery. Pain is the most severe in the first initial days immediately following the operation and studies estimate that ~50% of patients self-report inadequate pain relief with available therapies.

Conventional immediate-release formulation of bupivacaine was FDA-approved many years ago under the name Marcaine. The drug is now available generically and is commercially available via various US manufacturers: Hospira distributes both branded and generic versions of bupivacaine and APP Pharma, a subsidiary of Fresenius SE, distributes Sensorcaine which is the branded generic.

Figure 7 – Drugs Typically Used in Continuous Wound Infiltration

Local anesthetic	Number of procedures (mil)
Ropivacaine	0.6
Bupivacaine	7
Lidocaine	15

Treatment drug	Half-life (hrs)	Typically Used
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: Cowen and Company

Opioids. The standard of care and common opioids prescribed for postoperative pain include morphine, hydromorphone, oxycodone and fentanyl which are frequently administered intravenously by patient-controlled analgesia (PCA) pumps. Each year in the US and globally, 300M and over 650M IV units of opioids are used, respectively.

These treatments are popular due to their potency, consistent efficacy, and multiple modes of administration for opioids.

Morphine is cleared through the kidneys and poses an additional toxicity risk for renal-impaired patients. The morphine metabolite morphine-6-glucuronide (M6G) crosses the blood-brain-barrier more slowly is a stronger analgesic than morphine itself. We see morphine as a less than ideal treatment option in renally impaired patients.

Non-steroidal anti-inflammatories (NSAIDs). NSAIDs are a less potent opioid alternative but they do come with complications. NSAIDs inhibit cyclooxygenase-1 and 2 (COX) and play a critical role in inflammation via COX's involvement in the construction of prostaglandins. Medications such as ketorolac, diclofenac, ofirmev, and ibuprofen inhibit both COX-1 and 2 but lack the risk of respiratory depression or constipation typical of steroids. Aside from being less potent analgesics, NSAIDs can cause ulceration, diarrhea, and renal dysfunction.

NSAIDs have utility in postoperative pain management given their antipyretic activity but can cause fluid retention in renally impaired patients which can exacerbate hypertension. Ketorolac is the most commonly used NSAID in the post-operative realm and can be administered intravenously which means it can be used in patients that cannot hold down oral solids but have wound infiltration. This drug class has played a role in reducing opioid consumption and is considered to be safer than opioids.

Figure 8 – Classes of Drugs Used in Postoperative Pain Management

	Sodium channel blockers	Acetaminophen	Opioids	NSAIDs
Description	Blocks, binds to sodium channels on nerve cells preventing depolarization	Centrally acting analgesic and universal antipyretic	Most frequently used in acute postoperative pain; binds to opioid receptors that mediate pain	Reduces inflammation by inhibiting pro-inflammatory COX
Common names	Lidocaine Bupivacaine Ropivacaine	Mapap Ofirmev Panadol	Morphine Fentanyl Oxycodone	Ibuprofen Ketorolac Aspirin
Usage	Direct wound administration; nerve block and epidural	Used in combination with NASIDs and opioids; help to maintain baseline control	Management of break through pain and administered through IV PCA	Often combined with opioids and helps maintain baseline control
Advantages	Systemic exposure is limited	Antipyretic and orally administered	Postoperative pain's most efficacious treatment option	No respiratory depression risk
Drawbacks	Efficacy is less than 3.5hrs	Least potent	Multiple SAEs	GI/bleeding risk

Source: Cowen and Company

Ofirmev. Ofirmev is an IV formulation of acetaminophen used in treating patients suffering from postoperative pain (launched by Cadence Pharmaceuticals in 2011). Ofirmev was tested in 1020 adults and 355 children (greater than two years of age) and was well tolerated in clinical trials. The overall safety and effectiveness of ofirmev was similar between elderly and younger subjects. The most common adverse events in adult patients were nausea, vomiting, headache, and insomnia. Pediatric patients experienced nausea, vomiting, constipation, pruritus, agitation, and atelectasis (partial lung collapse).

Long-acting approaches in postoperative pain management. Oral opioids such as Vicodin and Xolox have a slower onset of action and reduced efficacy than intravenous administration which limits use in the postoperative setting. PCA pumps are the most common postoperative IV opioid administration method.

In the U.S over 13 million patients receive PCA pumps each year. Despite their popularity, PCA pumps have room for improvement. Irrespective of the administration path, the active analgesic is still an opioid, like morphine, with all the identical risks, costs, and complications. All patients using the pump are bound to an intravenous post that delays recovery and ambulation. Any adverse events linked to opioid usage will further decrease the discharge process and increase hospital related costs. Although PCA pumps are controlled by patients, these devices require considerable efforts from hospital staffs to set up and monitor: nurses must program the devices, initiate intravenous access, educate patients, and routinely monitor pump usage. Despite extensive efforts from hospital staffs, poor or faulty programming of devices and usage interruption due to technical issues are still common for these pumps.

Continuous wound infiltration. Before the process of suturing commences at an incision site, a local anesthetic such as a sodium channel blockers like bupivacaine and ropivacaine, is directly injected at the site of incision. This injection gives the patient immediate and broad postoperative pain relief while permitting additional pain treatments to be used in unison as required with limited side effects. Treatments that end in the "-caine" category are universally utilized by anesthesiologists and surgeons due to their familiarity and a rich safety and tolerability database going back a decade. Treatments have a short half-life and analgesic duration. Bupivacaine, for example, which is the longest acting drug in the 'caine class, lasts less than 3.5 hours in adults. Since repeat injections at a surgical site are not feasible post-surgery, most patients are put on additional systemic treatments that have longer-durations in pain management (such as opioids and non-steroidal anti-inflammatories (NSAIDs). We estimate there are ~23M continuous wound infiltrations performed in the US each year.

The Market Opportunity

More than 13 million patients receive PCA in the US each year. The approximate cost for three days of therapy on opioid intravenous PCA can exceed $500, excluding any impact of potential opioid-related adverse events. In 2006 the CDC noted 48% of morphine PCA patients reported opioid-related adverse events with 8% reporting respiratory depression. A recent study indicated ORAEs increase hospital stay duration by 2.7 days resulting in a $10,000 higher total hospital cost per patient per visit.

Pain is classified as acute or chronic and is graded via severity as mild, moderate or severe. Acute pain is typically triggered by an injury causing tissue, nerve, or bone damage. Acute pain is expected to wane in severity as tissues heal. Postoperative pain falls under the acute injury category that is a specific part of the acute pain market. Chronic pain is different from acute pain in that it can last longer, even for years, and can result from an acute injury or a current disease, such as neuropathic pain caused by diabetes.

There are approximately 100 million US adults with chronic pain. Events such as childbirth, surgery, injury, and acute/episodic illness cause acute pain. The total pain therapies revenue estimate in the seven major pharmaceutical markets of the US, France, Germany, Italy, Spain, UK and Japan exceeded $37 billion in 2011.

The severity of pain is the primary factor of determining the appropriate pain therapy. Pain that falls in the mild or mild-to-moderate category can usually be treated with OTC products such as oral aspirin, acetaminophen, and ibuprofen. Moderate-to-severe pain is traditionally treated with μ-opioid analgesic drugs. These drugs are considered very effective but they have a poor side-effect and abuse profile which remains a major headwind to their use. Opioid analgesics may be the only successful method of treating moderate to severe pain. They are among the largest US prescription drug classes with opioid analgesics representing 71% of the 341 million prescriptions administered in 2012 with over $8.3 billion in sales according to IMS.

TRV130: For Acute Post-Operative Pain

TRV130 is a first-line, IV treatment for patients experiencing moderate to severe pain. TRV130 is a small molecule G protein biased ligand that acts at the μ-opioid receptor, a well-established analgesic target, which inhibits the β-arrestin pathway. The μ-opioid receptor is targeted by common analgesics such as fentanyl and morphine that act as unbiased agonists of the μ-opioid receptor. This action by TRV130 enables the clinical benefit of activating the μ-opioid receptor to help reduce pain while inhibiting the β-arrestin pathway which is associated with constipation and depression.

TRV130: A Differentiated, Potentially Powerful Analgesic

TRV130 is differentiated by its: efficacy (improved analgesia, reduced time to peak effect, novel ligand bias) and safety and tolerability (reduced risk of respiratory depression, reduced postoperative nausea and vomiting [PONV], reduced postoperative ileus [POI] and constipation).

Novel Ligand Bias Targets Established Moderate to Severe Acute Pain Mechanism: As a G protein biased ligand at the μ-opioid receptor, TRV130 has shown equivalent or superior analgesic efficacy when compared to morphine in multiple preclinical pain models and in an evoked-pain model in Trevena's clinical testing. The entrenched μ-opioid analgesics such as morphine, fentanyl, and hydromorphone come with severe adverse events. TRV130 exhibits activity on the same mechanism as the aforementioned analgesics but without triggering the undesirable effects.

Improved Analgesia and Safety Profile: In a Phase 2 trial, TRV130 showed superior analgesia versus placebo at the 2 mg and 3 mg doses. At 3 mg, TRV130 demonstrated statistically significantly better analgesia over morphine. In a Phase 1b trial with healthy subjects, TRV130 showed superior analgesia when compared to 10 mg of morphine. This trial also highlighted TRV130's ability, in comparison to morphine, to have less respiratory depression, less nausea, and less vomiting. We have confidence in TRV130's overall therapeutic profile given superior analgesia and safety profile at the 3 mg dose.

Reduced Time to Peak Effect: In a Phase 2 trial, more patients reported a statistically significant greater peak pain relief during the first dosing period for 2 mg and 3 mg TRV130 versus 4 mg morphine. During this period complete pain relief was 13%, 31%, and 52% of patients receiving 1 mg, 2 mg, and 3 mg TRV130, respectively, compared to 0% and 8% for those patients receiving placebo and 4 mg morphine, respectively. In the Phase 1 trial TRV130 also reached full pharmacodynamics response as indicated by pupil constriction in humans ten minutes after dosing. This is considered a well-established analgesic efficacy surrogate for opioid drugs. If TRV130 can continue to

show this response time in further trials, it could take market share from fentanyl which is the most prescribed therapeutic in the peri-operative pain market.

Reduced PONV: Data from a Phase 2 trial of patients treated with TRV130 suggested less nausea and vomiting versus morphine with no unexpected side effects and no serious adverse in any groups. In a Phase 1 trial, patients on TRV130 had less nausea and vomiting at a dose eliciting greater analgesia versus a high morphine dose. This data aligns with another Phase 1 study where TRV130 demonstrated no nausea or vomiting at doses eliciting equivalent or greater pupil constriction versus twenty to thirty percent PONV incidence with morphine or fentanyl. We believe KOLs will view the PONV reduction as an advantage to TRV130.

TRV130's Clinical Data

Phase 2a/b Study of TRV130 in Acute Postoperative Pain (Bunionectomy)

This was a randomized, double-blind, placebo- and active-controlled trial of TRV130 versus morphine in moderate-to-severe postoperative acute pain. At 2 mg and 3 mg TRV130 doses administered at three hour intervals the study successfully achieved its primary endpoint of statistically significant greater pain reduction than 4 mg morphine in a 48 hour period (measured by TWA0-48, the time-weighted average change in pain score, LS mean). At 2 mg TRV130 reduced average pain score by 1.4 points ($p=0.0024$) compared to placebo. At 3 mg TRV130 reduced LS mean by 2.4 points ($p<0.0001$ versus placebo) and by 1.0 points compared to morphine ($p=0.014$). Morphine reduced LS mean change by 1.3 points compared to placebo ($p=0.0023$). Baseline pain rating was about 7/10 which is considered severe pain. TRV130 reduced pain intensity by 6 points with notable efficacy at 5 minutes which is the first pain assessment post-dosing.

Figure 9 – Phase 2a/b: A Study of TRV130 for the Treatment of Pain After Bunionectomy

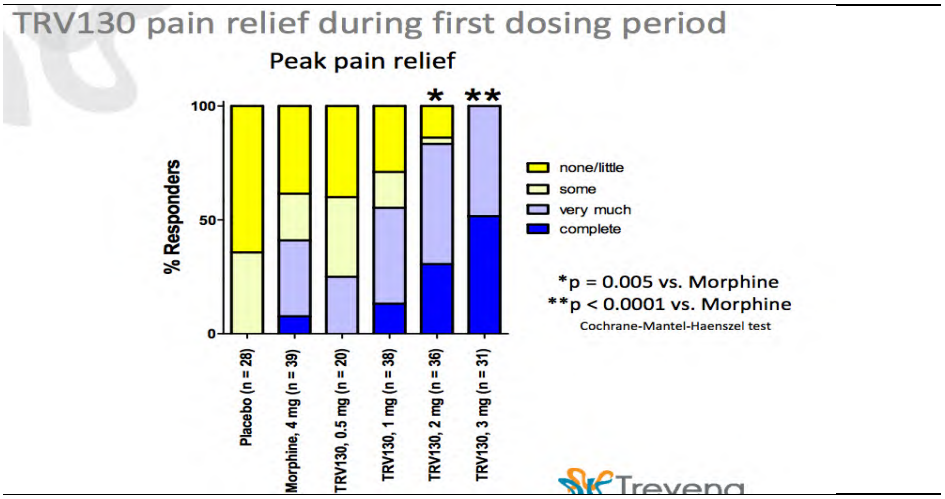
Study Design	Randomized, parallel assignment, double blind
Treatment duration	48 hours
Enrollment	333
Dose	1, 2, 3, and 4 mg IV TRV130 administered every 4 hours for 48 h Active Comparator 4 mg morphine IV administered every 4 hours for 48 h Placebo Comparator of 5% dextrose in water IV administered every 4 hours for 48 h
Primary Endpoint	Reduction of pain intensity following bunionectomy which is to be evaluated by an 11-point numeric rating scale versus placebo in 48 hours
Secondary Endpoints	Efficacy and safety of TRV130 compared to morphine; pharmacokinetics of TRV130 and morphine
Key Inclusion Criteria	• Subject has undergone primary, unilateral, first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures • Subject experiences a pain intensity rating of ≥ 4 on an 11 point NRS
Key Exclusion Criteri	• Subject has ASA Physical Status Classification System classification of P3 or worse • Subject has surgical or post-surgical complications • Subject has clinically significant medical conditions or history of such conditions that may interfere with the interpretation of efficacy, safety, or tolerability data obtained in the trial, or may interfere with the absorption, distribution, metabolism, or excretion of drugs • Subject has previously participated in another TRV130 clinical study
Data released	November 2014

Source: Cowen and Company

During the first 3 hours after the initial dose, which is when pain was most severe, TRV130 at 1 mg, 2 mg, and 3 mg showed a statistically significant reduction in pain (TWA0-3) compared to placebo (LS mean change -1.0, -2.4, -3.0, respectively; p=0.021, p<0.0001, p<0.0001, respectively). TRV130 at 2 mg and 3 mg showed a statistically significant reduction in pain compared to 4 mg morphine during the same time period (LS mean change of: TRV130 2 mg -1.2 vs. morphine, p = 0.0029; TRV130 3 mg -1.8 vs. morphine, p<0.0001).

More patients reported a statistically significant greater peak pain relief during the first dosing period for 2 mg and 3 mg TRV130 versus 4 mg morphine (p = 0.005 and p < 0.0001 for TRV130 2 mg and 3 mg vs. morphine, respectively). During this period complete pain relief was 13%, 31%, and 52% of patients receiving 1 mg, 2 mg, and 3 mg TRV130, respectively, compared to 0% and 8% for those patients receiving placebo and 4 mg morphine, respectively.

Figure 10 – Phase 2 Bunionectomy Trial First Dosing Period Pain Relief



Source: Trevena

The trial's key secondary endpoints determined the difference between treatment of TRV130 from morphine at a standard reference dose of 4 mg every 4 hours. The 2 mg and 3 mg doses of TRV 130 demonstrated statistically significant superior analgesic efficacy versus 4 mg morphine in the first 3 hours of dosing. In these doses patients reported maximum pain relief during the first dosing period that was statistically superior compared to morphine. TRV130 at 2 mg and 3 mg demonstrated similar tolerability to morphine 4 mg over 48 hours. Adverse events associated with both TRV130 and morphine were common in opioid-related events (dizziness, headache, nausea, somnolence, flushing, vomiting, and itching).

Figure 11 – TRV130 Phase 2 Bunionectomy Trial Data of Pain Relief vs. Placebo

Success on primary endpoint:
pain relief vs. placebo over 48 hours (TWA0-48)

Additionally: TRV130 3 mg demonstrated pain relief superior to morphine

Stage B data

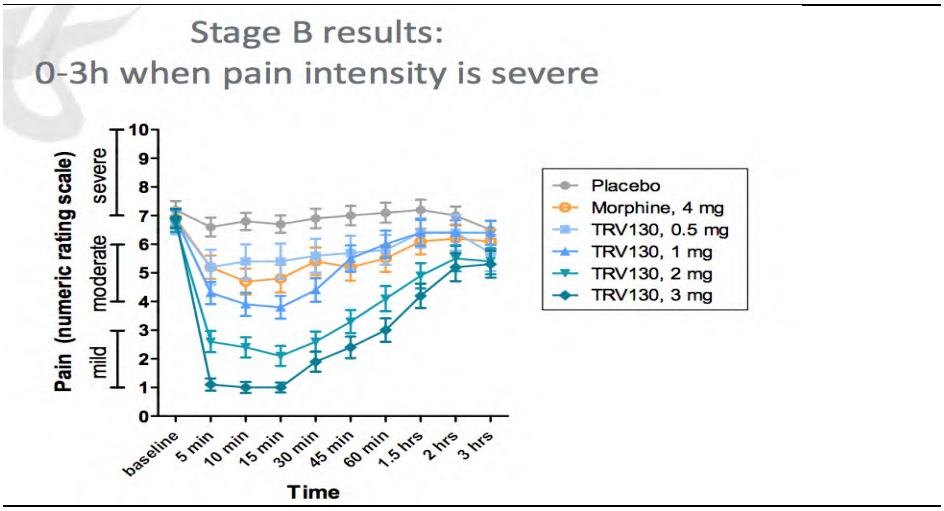
Dose (mg)	Interval (hr)	Patients (n)	LS mean Δ TWA 0-48	p (vs. Placebo)	p (vs. Morphine)
Placebo	3 or 4	28	-	-	-
TRV130 (0.5 mg)	3	20	-0.5	0.18	0.95
TRV130 (1 mg)	3	38	-0.3	0.23	0.99
TRV130 (2 mg)	3	36	-1.4	**0.0024***	0.48
TRV130 (3 mg)	3	31	-2.4	**<0.0001***	**0.014****
Morphine (4 mg)	4	39	-1.3	**0.0023***	-

**statistically significant vs. placebo*
***statistically significant vs. morphine*
1 sided p values
TWA0-48 = time weighted average pain intensity difference from 0 to 48 hours

Source: Trevena

Data from the Phase 2 bunionectomy trial achieved the primary endpoint of better analgesia over placebo at the 2 mg and 3 mg TRV130 doses. Additionally, the data demonstrated a statistically significant better analgesic effect versus morphine at the 3 mg TRV130 dose over a 48 hour trial duration. Over the first three hours of treatment at the 2 mg and 3 mg doses, TRV130 showed better analgesia than morphine with pain improvement as early as five minutes after being treated. Responders on the 2 mg and 3 mg TRV130 treatment who had 80% and 100%, respectively, "very much" and "complete" pain relief during the first dosing period.

Figure 12 – Phase 2 Bunionectomy Trial Pain Intensity Over Time



Source: Trevena

Safety in Trevena's Phase 2 bunionectomy trial also indicated better safety versus 4 mg of morphine at the 2 mg and 3 mg TRV130 doses. The data suggests less nausea, vomiting, constipation, and itching. There were no unexpected side effects which is associated with opioids and there were no serious advents in any groups. Oxygen desaturation data, the measurement used for quantifying respiratory depression, implies dose dependent improvement versus morphine.

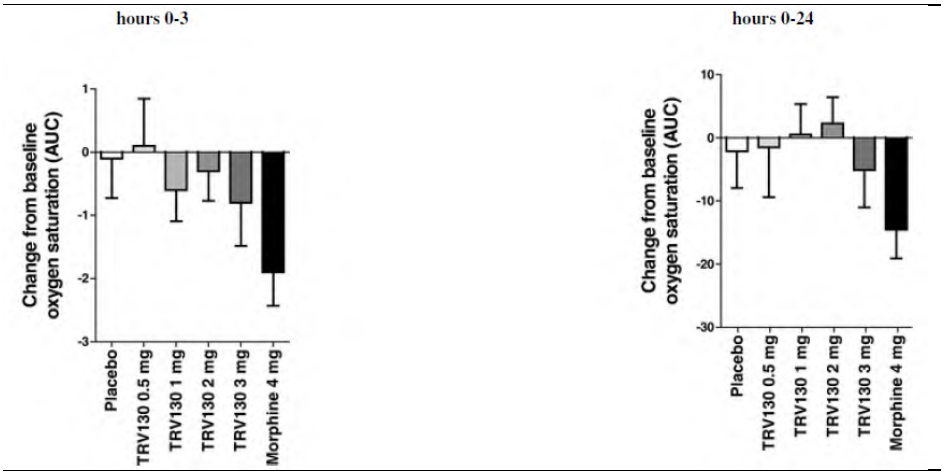
Figure 13 – Phase 2 Bunionectomy Data on Spontaneously Reported Opioid-Related Adverse Events

	Placebo	TRV130				Morph
	(n=51)	0.5 mg (n=20)	1 mg (n=38)	2 mg (n=36)	3 mg (n=31)	4 mg (n=64)
constipation	2	2	6	3	5	6
dizziness	6	4	22	17	18	28
dry mouth	2	0	2	4	1	3
feeling hot	0	0	0	2	4	1
flushing	0	0	3	6	3	4
hot flush	0	0	2	5	4	4
headache	8	5	10	7	7	16
hyperhidrosis	0	0	0	3	5	2
nausea	10	7	13	20	23	38
pruritis	3	0	1	4	3	6
pruritis generalized	0	0	0	1	2	6
somnolence	4	4	5	4	4	15
vomiting	1	0	4	10	17	23

"n"= number of patients in each cohort
Bar length corresponds to proportion of patients reporting the adverse event
Placebo and morphine data pooled from first and second parts of trial;
TRV130 dose data from second part of trial

Source: Trevena

Figure 14 – Phase 2 Bunionectomy Data Change from Baseline in Oxygen Desaturation Levels from 0-3 and 0-24 hours



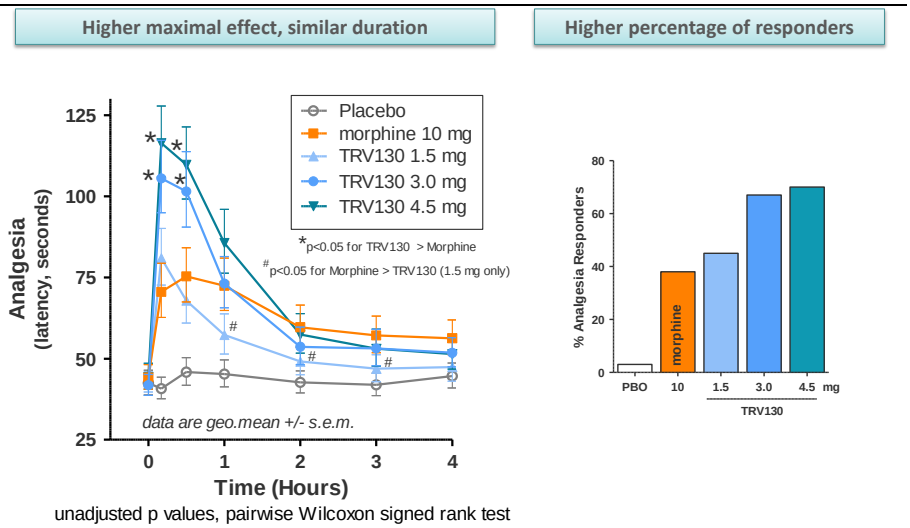
Source: Trevena

Phase 1b Proof-of-Concept (POC) Exploratory Trial

TRV130's safety and analgesic effects were compared to a ten milligram dose of morphine in a POC double-blind, five-period crossover design. Thirty healthy male subjects were randomized into three dose levels of TRV130 (1.5 mg, 3.0 mg, 4.5 mg), 10 mg of morphine, and placebo for a 2 minute infusion. A cold pain test was used to evaluate the analgesic effects of TRV130. Time to hand removal was measured via a temperature-controlled cold water bath. Nausea was documented on the visual analog scale and respiratory depression was reported via ventilator response to hypercapnia.

At the 3.0 mg and 4.5 mg doses, TRV130 demonstrated statistically significant efficacy versus 10 mg of morphine dose ($p<0.05$) at ten and thirty minutes after dosing. The durability of the analgesic effect was similar to morphine as shown in Figure 15 below. Morphine demonstrated a more rapid time to peak effect, and there were more responders at the 3.0 mg and 4.5 mg TRV130 dose levels compared to morphine.

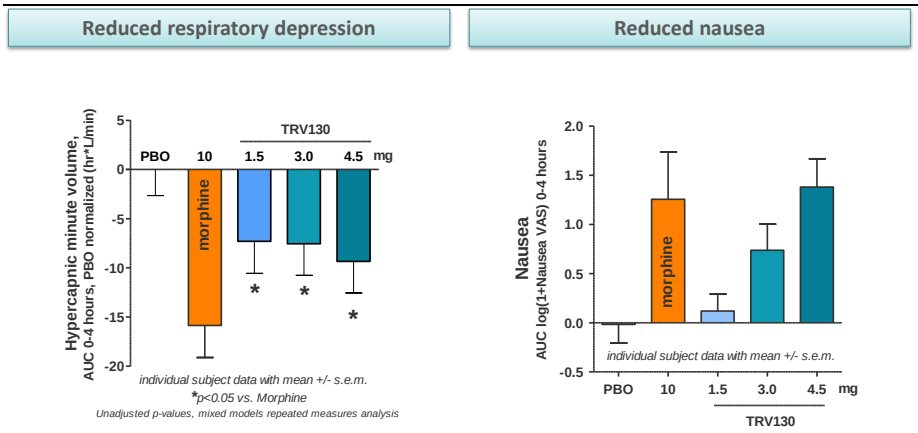
Figure 15 – Ph1b of TRV130's Showed Superior Analgesia to Morphine



Source: Trevena

Overall, this Phase 1b trial indicated that TRV130 is well tolerated and subjects on experimental treatment showed less nausea, less vomiting, and respiratory depression at the 1.5 mg and 3.0 mg doses versus 10 mg dose of morphine. TRV130 subjects also demonstrated less respiratory depression versus morphine (measured by minute volume – MV) highlighted in Figure 16 below. MV measures the volume of air exhaled in one breath and is a product of respiratory rate and tidal volume. MV has been used as a measurement to capture the ability of the body to expel carbon dioxide.

Figure 16 – SPID24 following postoperative treatment in CLIN2002



Source: Trevena

Three-part Phase 1 trial in healthy subjects

The pharmacodynamics data collected from all three trials indicates TRV130 can be administered by continuous IV bolus infusion. We believe TRV130 can be conveniently administered through a patient-controlled analgesic device which could help drive uptake in the postoperative setting.

These studies also demonstrated that TRV130 is well tolerated. Part A showed TRV130, when administered as a one-hour infusion, caused no nausea or vomiting until dose levels reached 4 mg/hour which then lead to a pupil diameter reduction. At increased dose levels of 7 mg/hour, four subjects on TRV130 reported nausea and four reported vomiting. Subjects that were treated with TRV130 for over one hour produced strong pupil constriction at doses beginning at 1.2 mg/hour. At a 7 mg/hour dose mean pupil diameter decrease by as much as 3.5 mm. TRV130 produced a mean reduction in pupil diameter of approximately 2.5 mm at the well-tolerated 4 mg/hour dose which was higher than effective morphine or fentanyl doses. At the effective doses of morphine and fentanyl, 25% of the subjects reported nausea and vomiting. The 4 mg/hour dose may be as effective as morphine and fentanyl without the opioid-induced nausea and vomiting.

In Part A, one subject on 0.25 mg/hour of TRV130 experienced a severe episode of vasovagal syncope which was classified as a serious adverse event. This subject eventually recovered with no medical intervention and did not experience any known adverse consequences afterward. Trevena addressed this issue by using a dose escalation up to 7 mg/hour. No additional vasovagal syncope events were reported in the study.

TRV130 demonstrated a dose-dependent increase in exposure and its primary metabolism through CYP2D6 and CYP3A4 liver enzymes. In approximately thirteen percent of the population low levels of CYP2D6 activity was observed. TRV130 was evaluated in a group of poor metabolizers to assess whether dose adjustments would be necessary in Part B of the trial. The maximum amount of TRV130 plasma concentration in this study group was on the upper end of normal metabolizers. These poor metabolizers exhibit similar TRV130 tolerability to those subjects that are not considered poor metabolizers. Poor metabolizers demonstrated a 50% reduction in

clearance and a lower dosing frequency may be required to achieve effective pain relief.

A reduction in infusion time when administering TRV130 as a bolus in Part C did not significantly change exposure. This lends credence to TRV130's viability as an intermittent bolus infusion without compromising exposure of the drug. In Part C, six subjects were treated with TRV130 on successive days with a 1.5 mg dose and an infusion time of thirty minutes, fifteen minutes, five minutes, and one minute. TRV130 was well tolerated with a pupil constriction of about 1 mm.

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 on treatment experienced mild nausea when 3.5 mg TRV130 was administered. No subjects on the lower doses reported nausea. When patients were administered 3.5 mg of TRV130 pupil diameter decreased by approximately 2 mm from baseline which is a figure that is in line with high-dose morphine or fentanyl.

Drug Interaction Phase 1 Study

TRV130 was administered as a single dose to healthy subjects in conjunction with ketoconazole which is a CYP3A4 inhibitor. Results indicated that TRV130 was safe and well-tolerated in the presence of ketoconazole with no meaningful change in TRV130 exposure.

Commercial strategy

In patients for whom IV administration is preferred, Trevena plans to first position TRV130 as the treatment of moderate to severe, acute postoperative pain. However, we also see success in TRV130's potential in perioperative use, burn victims and other non-surgical hospitalized patients, and end-of-life palliative care patients. We also see potential additional uses in emergency service trauma care and military applications pending data. Trevena can also expand TRV130's commercial potential via alternative dosage forms such as oral or transdermal administration.

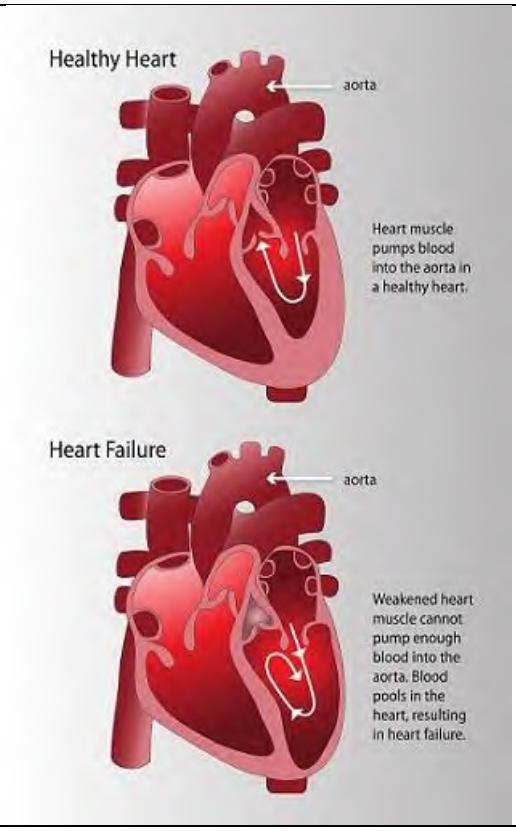
Trevena intends to develop and commercialize IV TRV130 alone, and it will build out an infrastructure for acute care in the US and fully retain rights to the treatment in the US. TRVN may seek pharmaceutical partners to commercialize TRV130 ex-US.

Trevena's TRV027 and AHF

Heart Failure

Congestive heart failure, also referred to simply as heart failure, is a potentially fatal and progressive condition in which a weakened heart is unable to pump sufficient blood through the body. This results in body tissues that are chronically deprived of oxygen at a normal resting and is worse in periods of physical exertion. Fluid accumulation is also a result of heart failure and is common in the extremities, abdomen, and lungs.

Figure 17 – A Healthy and Weakened Heart



Source: Center for Disease Control and Prevention – Division for Heart Disease and Stroke Prevention

Pathology

Damage to heart muscle caused by chronic or acute oxygen deprivation is classified as heart failure. Oxygen deprivation can be caused by a heart attack or by impaired blood flow to the heart which is frequently caused by coronary artery disease. Cardiomyopathy, which is also referred to ask cardiac hypertrophy, or thickening of the heart walls is typically the body's response to a lack of oxygen. The body causes overgrowth of the heart muscle tissue to help increase the heart's pumping power. Heart valve disease can also cause heart failure since malfunctioning heart valves potentially can interfere with normal blood flow and cardiac function. Severe congenital heart disease can also be a driver of heart failure.

Heart failure can be classified as either chronic or acute, and chronic heart failure is significantly more common. The disease is segregated via heart function impairment severity. Half of the patients with the most advanced stage of heart failure die in less than one year. Chronic heart failure separated into either systolic or diastolic dysfunction:

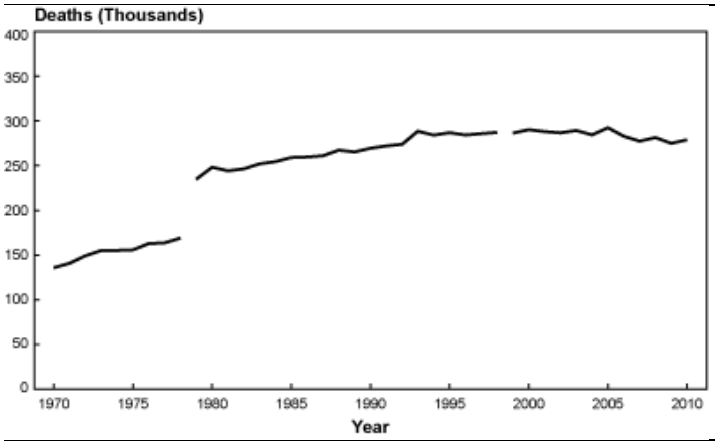
Systolic Dysfunction: This dysfunction occurs when the heart is weak. Ejection fraction (EF), is a common clinical measurement that quantifies the amount of blood ejected out of the left ventricle in a heartbeat, also called stroke volume, and is divided by the maximum volume in the left ventricle at the end of diastole, or relaxation, phase. Systolic heart failure patients have and ejection fraction of less than 50% while a normal, healthy patient will have an ejection fraction exceeding 50%.

Diastolic Dysfunction: This dysfunction occurs when the heart is stiff or inflexible, especially during diastole when it is in a relaxed state and filling with blood, but can still contract normally with a normal ejection fraction. This dysfunction prevents the heart from filling with blood and causes fluid backup to flow into the lungs and, therefore, produce heart failure symptoms. Diastolic heart failure results in less blood flow to the body despite a normal ejection fraction. This type of heart failure is more common in patients that are over 75 years of age and particularly in females with high blood pressure.

Acute heart failure. AHF is often a period of acute disease exacerbation usually observed in patients already suffering with chronic heart failure. Acute heart failure patients' symptoms normally involve severe shortness of breath and other symptoms but not with the chest pain that is distinctive of a heart attack. AHF patients requiring hospitalization could potentially have mortality rates as high as 20%.

Incidence/prevalence of heart failure. Over 5.7 million people in the US have heart failure every year; approximately 670,000 people are diagnosed with some stage of heart failure. The AHA approximates 300,000 deaths in the US from the condition each year. According to The World Health Organization, there are approximately 23 million people in the world with congestive heart failure. However, some estimates are as high as 65-70 million patients with two million new cases of CHF diagnosed every year. CHF accounts annually for 12-15 million office visits, approximately 6.5 million hospital days, comprising an aggregate medical cost exceeding $29 billion.

Figure 18 – Deaths Attributed to Heart Failure in the U.S., 1970-2010

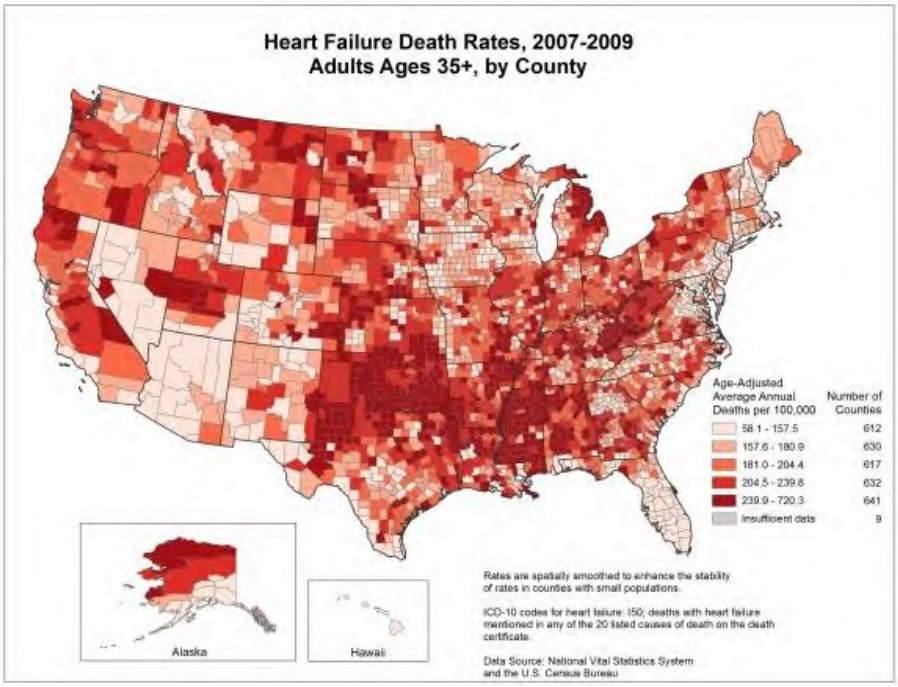


Source: NIH Factbook

Individuals over 65 years of age are at the highest risk for heart failure, the leading cause of hospitalization for individuals in this age group. African Americans frequently have worse disease and prognosis and have a higher risk for developing heart failure than other races. Another high risk group is overweight and obese patients, given weight often causes high blood pressure, and, therefore, greater strain on the heart.

The incidence of heart failure, the most rapidly growing cardiovascular disorder in the US, is increasing despite decreasing incidence rates of other heart diseases such as heart attacks. Heart failure prevalence doubles each decade of life after the age of 50. Experts predict the prevalence and incidence of heart failure will continue to grow given the increasing average age of the general population and the worldwide incidence increase in excessive weight and obesity.

Figure 19 – Geographical Breakdown of Heart Failure Death Rates of Adults 35+ Years of Age



Source: Center for Disease Control and Prevention – Division for Heart Disease and Stroke Prevention

Market Size and Drivers

Current estimates place the heart failure drug market over $3 billion which grew tremendously from $1.33 billion in 2004. Most of the drugs commonly used to treat heart failure also treat blood pressure. This means many AHF drugs are used in high blood pressure patients that do not have heart failure which, therefore, makes exact market size for heart failure drugs difficult to quantify. The economic burden of congestive heart failure is enormous, with an estimated cost to the US health care system in 2011 of $37 billion.

It is commonly believed by cardiovascular and clinical experts that the incidence and prevalence of heart failure is growing due to the aging population which is compounded further by contributing factors such as obesity and diabetes. Additionally, the rate of heart attack survivors is improving which is also driving growth in the heart disease population. Long-term clinical data has established combination therapy with drugs like ACE inhibitors, diuretics, and beta blockers as the most successful methods of treatment in relieving heart failure symptoms and in preventing progression of the disease.

Trevena's TRV027 in Heart Failure

TRV027 is a peptide β-arrestin biased ligand targeting the AT1R mechanism. It inhibits G protein signaling and activates β-arrestin signaling for the treatment of acute heart failure (AHF) and designed is to be used in combination therapy with standard diuretic treatments. ATR1 β-arrestin signaling enhances cardiac contractility, a beneficial effect for AHF patients. However, AT1R signaling is blocked by current AHF treatments since its G protein pathway signaling causes elevation of blood pressure

and fluid retention which worsens the condition by making the heart work harder to pump blood. In Trevena's Phase 2a study, TRV027 reduced blood pressure while preserving cardiac and renal function. There are no currently available heart failure therapies that safely improve cardiac output. Diuretics such as furosemide are the standard of care and act by reducing fluid load in patients until they are stable so vasodilators can then be utilized to moderate blood pressure. KOLs we have spoken to highlight heart tissue and heart damage in long-term care and, therefore, seldom use first-generation inotropes.

As of December 2014, Trevena has enrolled 250 out of the 500 objective patients in its Phase 2b clinical trial to evaluate the safety and efficacy of TRV027 in AHF with top-line data expected in the fourth quarter of 2015. We think TRV027 has potential to be a first-line, in-patient AHF treatment based on strong scientific rationale and a clean safety profile. Furthermore, if TRV027 demonstrates improvements in AHF symptoms in upcoming trials, reduced length of stay, and reduced readmission and mortality rates post-discharge, it may be well-received by physicians which could drive rapid uptake.

TRV027 targets the RAS mechanism which is a central mechanism to AHF. Currently there is no approved AHF therapy that has been proven to improve patient outcomes in the long-term. Several studies have indicated that blocking RAS activity is linked with reduced morbidity and mortality in chronic heart failure. TRV027 has the potential to be the first therapy in the acute realm that modulates RAS. This potential benefit would allow physicians to improve blood circulation without harming the heart and kidneys. Additionally, TRV027 reduced blood pressure only in subjects that had elevated RAS activity. This adherence to target pathophysiology is critical for any drug utilized in emergency hospital departments since the first diagnosis may not be certain.

TRV027's Point of Differentiation

TRV027 could benefit the blood vessels, heart, and kidneys. TRV027 reversibly and rapidly lowered blood pressure and pulmonary capillary wedge pressure (PCWP). PCWP is a crucial heart failure marker that frequently correlates with improvement in dyspnea and is regularly referred to as wedge pressure. TRV027's benefit to blood pressure and PCWP-lowering effect permits the heart to function with less resistance and pump blood throughout the body more effectively which preserves cardiac performance. Renal function markers indicate TRV027 may also preserve kidney function. Therefore, treatment with TRV027 could potentially result in improvements in heart failure outcomes (such as hospital readmission rates, mortality, and length of stay).

Improves diuretic effects on wedge pressure. Furosemide, a customary diuretic treatment, is used as a first-line treatment in approximately 90% of patients with AHF. Furosemide helps to lower blood pressure and stress on the heart by causing a patient's body to excrete excess fluid. Furosemide, however, has renal safety concerns that limit its usage and results in suboptimal dosing. Around fifty percent of AHF patients remain symptomatic at the time of hospital discharge partially due to this safety limitation. Combination treatment of TRV027 with furosemide could potentially improve dyspnea by reducing heart and lung pressure without triggering RAS (renin angiotensin system, a G protein) activation. In a trial dog model of heart failure, when combined with furosemide versus furosemide monotherapy, TRV027 exhibited additional significant decreases in wedge pressure levels. TRV027's and furosemide's combined synergy with may resolve dyspnea more quickly, reduce the length of hospital stay, and reduce AHF symptoms which would reduce hospital readmissions.

TRV027's safety profile is favorable. In a Phase 1 trial, healthy volunteers administered with TRV027 showed no significant AEs even at doses 20 times greater than the expected therapeutic level. TRV027 showed no reported SAEs in a Phase 2a trial which involved fragile and severe chronic heart failure patients. Preclinical toxicology findings of TRV027 aligned with this clean tolerability profile.

Dose-dependent decrease in blood pressure. TRV027 demonstrated a dose-dependent decrease in blood pressure up to doses of 1 µg/kg/min in a Phase 2a clinical trial. No further reduction in blood pressure was reported at doses up to 3 µg/kg/min. However, this effect could still offer a safety benefit versus current vasodilators which have harsh drawbacks due to hypotension.

TRV027-induced blood pressure reduction is quickly reversible. TRV027 had a very short half-life in the aggregate clinical data collected to date and its effects were rapidly reversible. This benefit should permit the physician in the acute care setting to modify the dose quickly so prolonged hypotension can be prevented.

TRV027's Clinical Data

Phase 2a Hemodynamics Trial in Subjects with Advanced Stable Heart Failure

This study evaluated TRV027 safety and efficacy in 24 advanced stable heart failure subjects utilizing a step-wise dose titration method over a five hour period. The highest dose was no more than 10-fold higher than the beginning dose. The highest dose was administered for nine hours after titration in a steady-state infusion to assess the stability of TRV027's hemodynamic effects. The reversibility of TRV027's effects was analyzed for four hours after discontinuation of treatment. A total of fourteen different doses were studied over 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.

TRV027's hemodynamic effect was expected to correlate with a patient's elevated RAS activity (referred to as patients with high plasma renin activity, PRA) based on precedents set forth in previous clinical data. TRV027 exhibited a dose-dependent reduction in mean arterial pressure (MAP), which reversed in the washout period after the end of the infusion. This reversal of effect was statistically significant versus both placebo and normal PRA subjects ($p<0.01$, $p<0.001$, respectively).

High PRA subjects demonstrated an initial reduction in wedge pressure during dose titration. This effect was sustained throughout the infusion period and reversed during the washout period. After discontinuation the increase in PCWP of TRV027 infusion was evident in high PRA versus normal PRA subjects ($p<0.01$). There were no notable changes observed in cardiac index or heart rate following TRV027 administration.

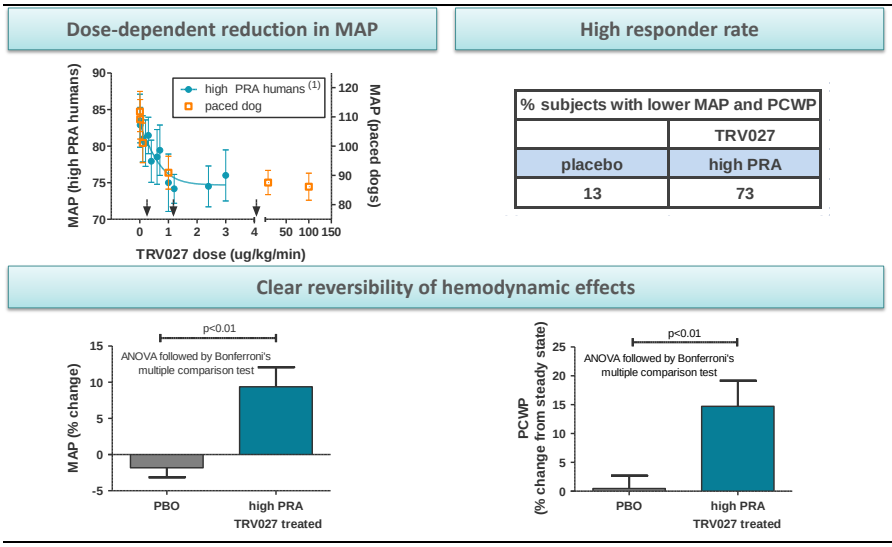
There was one subject who exhibited hypotension requiring a dose reduction and subsequently discontinued TRV027 treatment. No other drug-related SAEs were reported aside from this incident. Additionally, high-PRA subjects on TRV027 treatment exhibited less increases in brain natriuretic peptide (BNP), a cardiac stress marker, compared to low-PRA groups and placebo. This data implies TRV027 may possess cardiac stress-relieving characteristics. No spike in heart rate or cystatin-C and creatinine levels was observed despite the significant MAP reduction in TRV027 high-PRA subjects. These results are consistent with preclinical findings and the renal function biomarkers imply kidney function was preserved while the blood pressure declined.

Figure 20 – Phase 2a TRV027 Hemodynamics in Advanced Stable Heart Failure Subjects

Study Design	Randomized, double blind
Treatment duration	14 hours
Enrollment	33 (24 with TRV027, 9 with placebo)
Dose	Step-wise dose titration over 5 hours with dose increased to 10-fold higher target dose which was continued for 9 hours in steady state: 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 Placebo Comparator
Primary Endpoint	Characterize TRV027's tolerability and safety in subjects with advanced stable heart failure and to measure its effects on blood circulation (hemodynamics) in magnitude, sustainability, reversibility (MAP--mean arterial pressure, PCWP--pulmonary capillary wedge pressure)
Secondary Endpoints	TRV027 Pharmacokinetics, additional hemodynamic variables, biomarkers on renal function and neurohormonal activation
Key Inclusion Criteria	• Diagnosis of congestive heart failure made at least 3 months befores creening • NYHA Class III or IV heart failure, ejection fraction ≤35%, and in the opinion of the investigator, right-heart catheterization is clinically indicated. • Baseline mean PCWP ≥ 20 mmHg • Systolic blood pressure at screening must be ≥ 100 mmHg. Heart rate at screening must be ≥ 90 bpm.
Key Exclusion Criteri	• Any significant conflicting disease or condition • Significant valve disease • Current signs or symptoms of acute myocardial ischemia or acute coronary syndrome (ACS) or coronary revascularization in the past 3 months. • Sustained or uncontrolled ventricular arrhythmia. Inclusion of patients with atrial fibrillation with a heart rate ≤ 90 bpm is permitted.
Data released	November 2014

Source: Cowen and Company

Figure 21 – Phase 2a hemodynamics trial in subjects with advanced stable heart failure results



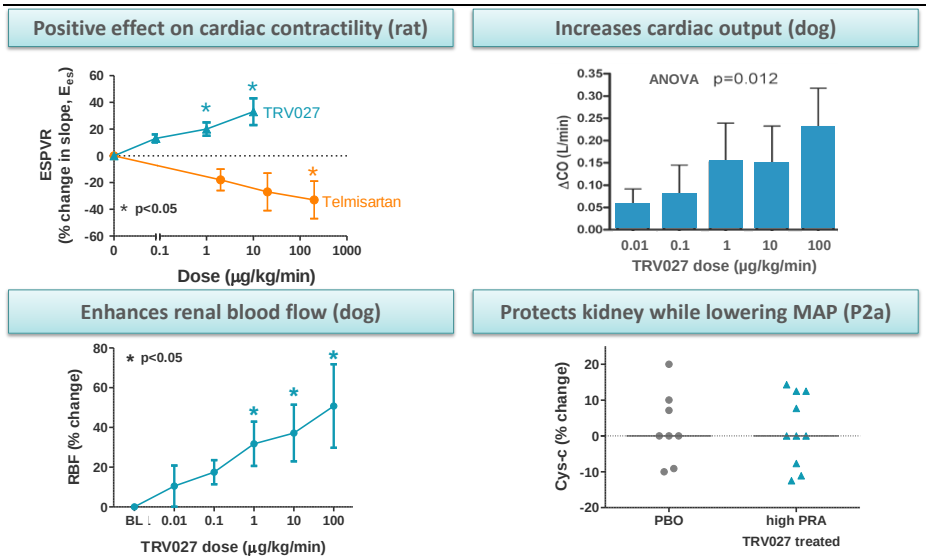
Source: Trevena

The AHF patients considered most sick frequently have the highest PRA and these subjects tend to have higher BNP levels and a lower ejection fraction. AHF patients experiencing high PRA levels should be responsive to TRV027 given TRV027's body of clinical data to date. In this trial, 21 of 24 TRV027 subjects were on ACE inhibitors (ACEis). These inhibitors and other drugs were withheld on the day of dosing, but this was not enough to washout background ACEi levels which suggests TRV027 was effectively studied in combination with ACEis in this trial.

Phase 1b Renal Safety Trial in Stable Chronic Heart Failure Subjects

This was a two-period Phase 1b trial where TRV027 was co-administered with furosemide in 17 heart failure subjects (split into three cohorts of six, six, and five) exhibiting renal dysfunction. The following TRV027 doses were administered without weight correction: 1.25 mg/hour, 6.25 mg/hour and 31.25 mg/hour. On a per kilogram basis, resulting plasma concentrations were no different from TRV027. We believe that a standard dosing method without adjustment could be advantageous in the emergency hospital treatment venue where patients are not regularly weighed. There were no drug-related adverse events and TRV027 was well tolerated.

Figure 22 – Phase 1b Renal Safety Trial Summary



Source: Cowen and Company

The Phase 1 clinical trial

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

After dose discontinuation TRV027 was rapidly cleared which could make it easy to reverse any unforeseen hypotensive effects. There was a dose-dependent linear increase in TRV027 exposure and no urinary excretion of TRV027 was observed. A brief sodium restriction model that activates RAS induced the pharmacodynamic effects of TRV027. Subsequently, four of the 20 subjects demonstrated a notable RAS elevation. Three of the four subjects with elevated RAS demonstrated modest MAP decreases.

Ongoing Phase 2b BLAST-AHF: TRV027's Efficacy in patients Hospitalized for Decompensated AHF—Data 4Q2015

This study is a randomized, double-blind, placebo-controlled trial in 500 AHF patients. TRV027 will be administered as continuous IV infusion for 48-96 hours as needed in each subject. There are a total of three doses of TRV027 (1, 5, 25 mg/hour) and placebo. The primary endpoint of this trial is to evaluate the impact of TRV027 on clinically important outcomes: dyspnea, worsening heart failure during hospitalization, length of stay in days, and 30-day readmission/mortality. Approximately 250 patients have been enrolled and the trial has over 65 sites open in 12 countries. Recruitment for the trial is on schedule to be completed by the third quarter of 2015 with top-line data expected in the fourth quarter of 2015.

Figure 23 – Phase 2b (BLAST-AHF): TRV027's Efficacy in Patients Hospitalized for Decompensated AHF

Study Design	Randomized, parallel assignment, double blind
Treatment duration	48 - 96 hours as needed
Enrollment	500
Dose	1, 5, and 25 mg IV TRV027 continuously administered 48-96 hr as needed Placebo IV comparator continuously administered 48-96 hr as needed
Primary Endpoint	Composite z score of clinically important outcomes: dyspnea (change in VAS score), worsening heart failure during hospitalization, length of stay (days), 30-day readmission/mortality
Key Inclusion Criteria	• Men or women between 21 - 85 years (women of non-child-bearing potential) • Pre-existing diagnosis of heart failure • Systolic blood pressure ≥120 mmHg and ≤ 200 mmHg within 30 minutes of randomization • Ventricular rate ≤125 bpm Presence of ADHF defined by: • 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 AND at least two (2) of the following: • Congestion on chest radiograph (CXR) • Rales by chest auscultation • Edema ≥ +1 on a 0-3 + scale • 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 Criteri	• Women who are pregnant or breast-feeding • Acute coronary syndrome in the 3 months prior to screening or planned during current admission. • Temperature >38.5 degrees celsius • Clinically significant anemia • Current or planned ultrafiltration, paracentesis, hemofiltration or dialysis at time of screening • Any mechanical ventilation • CPAP/BiPAP discontinued less than 1 hour prior to randomization • History of primary pulmonary hypertension • History or current use of left ventricular assist devices (LVADs) or intra-aortic balloon pumps (IABPs) • Intravenous radiographic contrast agent within 72 hours prior to screening or presence of acute contrast induced nephropathy at the time of screening • Presence of clinically significant arrhythmia • Nitroprusside or nesiritide • Intravenous nitrates • Use of inotropes • Use of ARBs within 7 days of prior to randomization • Use of any investigational medication within 30 days • Clinically significant hypersensitivity or allergy to, or intolerance of, angiotensin receptor blockers • Major surgery within 8 weeks prior to screening
Data Expected	4Q15

Source: Cowen and Company

Exclusive Licensing Arrangement with Actavis

Trevena entered into an option agreement with Actavis in May 2013 granting Actavis the exclusive option to license TRV027. This option may be exercised at any time before Phase 2b trial results are released to Actavis and for a specified time thereafter. In the scenario Actavis exercises the option, Actavis will have exclusive worldwide rights to develop and commercialize TRV027 and other specific compounds. Subsequent development, regulatory approval, and commercialization costs are the responsibility of Actavis. Additionally, if Actavis exercises the option, Trevena would receive up to $430 million in sum. This sum includes an upfront option exercise fee of $65 million and milestone payments contingent upon development and commercial milestones. Trevena could also receive 10-20% tiered royalties on worldwide net sales of licensed products (US royalties would be higher than ex-US royalties).

Available Therapies for AHF

There are several chronic oral drugs for acute heart failure patients that we detail below:

ACE (angiotensin-converting enzyme) inhibitors. Proven ACE data indicates this class of drug improves patient survival and heart failure symptoms. ACEs are vasodilators that reduce blood pressure, improve blood flow, and decrease overall heart workload by dilating blood vessels. Common ACE inhibitors include enalapril (Vasotec), lisinopril (Prinivil, Zestril) and captopril (Capoten). This class of drug also mediates the effects of hormones that supports salt and water retention. A side effect of severe cough is common with these drugs and is serious enough to warrant treatment discontinuation.

Angiotensin II (A-II) receptor blockers (ARBs). These drugs, such as losartan (Cozaar) and valsartan (Diovan), possess similar clinical blood pressure benefits as ACE inhibitors since they work through the same hormonal pathways. ARBs are a potential alternative for people who can't tolerate ACE inhibitors as they do not cause the persistent cough that is associated with ACE inhibitors.

Digoxin (Lanoxin). In high doses, this drug increases heart muscle contraction strength and reduces the heart rate. Digoxin's mechanism of action is not yet understood, however, it likely inhibits cardiac cell sodium and chloride ion pumps which leads to higher cardiac muscle cell calcium levels. This effect may result in better heart function via stronger contraction. Digoxin data also indicates it reduces heart failure symptoms and increases patient survival rates. Experts posit that meaningful benefit in heart muscle contractility occurs only at very high doses uncommon in the clinical setting.

Beta blockers. These drugs reduce both blood pressure and heart rate. Common beta blockers are carvedilol (Coreg), metoprolol (Lopressor) and bisoprolol (Zebeta). These drugs can also decrease the risk of abnormal heart patterns, improve heart function, and reduce signs and symptoms of heart failure.

Diuretics. This class of drug is frequently referred to as water pills. Diuretics increased urination which helps to decrease excess body fluid. These drugs also decrease lung fluid, a trait linked to certain types of heart failure. Commonly prescribed heart failure diuretics include bumetanide (Bumex) and furosemide (Lasix). Since diuretics can cause potassium and magnesium deficiency they may need to be given as treatment in unison with supplement and, therefore, may require regular blood monitoring.

Calcium channel blockers. This class of drug is used in the treatment of diastolic heart failure. These drugs block the number of electrical signals that induce heart muscle contractions and heartbeats which aids in reducing the heart rate. This class of drug

also helps slow the heart rate by giving the organ more time to fill with blood between heartbeats. These drugs help reduced blood pressure which may help treat diastolic heart failure since the heart does not have to work as rigorously to pump blood. We note that these drugs can worsen systolic heart failure since they reduce heart rates.

Aldosterone antagonists. Drugs such as spironolactone (Aldactone) and eplerenone (Inspra) fall into this category of AHF treatment. These drugs are potassium-sparing diuretics that also improve heart function and can potentially reverse scarring in the heart after a heart attack which can help improve survival rates. One side effect of spironolactone is that it can raise the blood level of potassium to hazardous levels.

Inotropes. Inotropes are IV treatments used in severe heart failure patients to help improve heart pumping function and to maintain blood pressure by changing the force of muscle contractions. There are both positive (agents that increase myocardial contractility) and negative (agents that decrease myocardial contractility) inotropes. Positive inotropes tend to increase the level of calcium in muscle cytoplasm while negative inotropes attempt to reduce these calcium levels. Side effects of inotropic agents include cell damage due to increased energy expenditures, exacerbation of relaxation abnormalities, and the potential of arrhythmogenic side effects.

Device-based therapy or transplantation is the only alternative for patients with advanced congestive heart failure (CHF). Many patients with advanced CHF have been fitted with left ventricular assist devices. This field has various promising technologies such as biventricular pacing and defibrillators, ventricular assist devices, and ventricular remodeling.

Research indicates a 50% medication compliance in the pharmacy approach for AHF patients. High cost of medicine, intolerable side effects, and high dosage frequency or low dosage rates (many practicing physicians prescribe lower doses due to adverse event concerns) are some of the reasons for the poor compliance rates.

Novartis' LCZ696 – Impressive, Well Received Phase 3 Results

On August 30, 2014, data from Novartis' PARADIGM-HF trial demonstrated LCZ696's impressive results. The primary endpoint of the trial was death from CV causes or hospitalization for heart failure which the drug reduced by 20%. The difference in patients treated with LCZ696 occurred early which is another beneficial factor. There were less patients on LCZ696 versus enalapril that stopped treatment because of an adverse event (10.7% vs. 12.3%, respectively, P=0.03). LCZ696 patients did have more probability of having symptomatic hypotension. Angiodema occurred more in patients on LCZ696 than enalapril (19 vs 10, respectively, p=0.13). No patients required angioedema or intubation.

There may be some questions regarding the small sample size of North American patients in the PARADIGM-HF trial (approximately 7%) given the different background therapies in the US and EU. Overall the subgroup data showed good results with each subgroup showing favorable activity for LCZ. Some of the subgroups had a p-value that was greater than 0.05 (Asians, Blacks, Western Europeans, patients with Class III-IV heart failure, and patients on no prior ACE therapy). Whether a patient was on background mineralcorticoid receptor antagonists did not impact study results.

Novartis intends to file its marketing authorization application with the FDA by the end of 2014 and with the EU in early 2015.

Serelaxin

Serelaxin is a recombinant form of human relaxin-2, a hormone of various functions and is created during pregnancy and mediates hemodynamic fluctuations. This hormone may also have protective effects against organ damage. Novartis' phase 3 RELAX-AHF trial evaluated serelaxin's effects in subjects with AHF with serelaxin demonstrating improvement in one out of two primary endpoints. Serelaxin improved VAS but did not impact the relief of dyspnea ascertained via the Likert scale at 6, 12, and 24 hour periods. The drug also did not indicate a reduction in cardiovascular death or heart failure readmissions through day 60, or days alive, and out of the hospital through the same 60 day period. We highlight the all-cause pre-specified 180-day mortality was significantly reduced with serelaxin treatment and that these results were comparable to the results from the Phase 2 Pre-RELAX-AHF trial.

Phase 3 Results

In this Phase 3 trial, 1161 patients were randomly assigned to serelaxin (n=581) or placebo (n=580) which studied serelaxin's effects of on dyspnea reduction and 60-day outcomes. Serelaxin significantly reduced dyspnea which is calculated by change from baseline on a 100-point visual analogue scale over a five day period versus with placebo (p=0.007). Serelaxin did not have significant effect on the other primary endpoint which involved the Likert scale (placebo, p=0.70).

Treatment with serelaxin did not impact 60-day readmissions or death (p=0.89 and p=0.37, respectively), largely due to the lack of a treatment effect on readmissions. Serelaxin treatment was linked to other beneficial effects on length of stay in the hospital intensive care unit, congestion, and length of initial hospital stay, and a reduction of 180-day all-cause mortality (p=0.019).

Serelaxin FDA Rejection Follows EU rejection

On May 15, 2014, FDA followed the voting decision of the AdComm panel and rejected serelaxin which followed a January rejection from the EU. The FDA requires further evidence of the synthetic form of the relaxing hormone is efficacious in treating heart failure patients. The FDA is following the AdComm decision which detailed the agency's issues with trial design (another trial or one with two or more independent studies), method of imputation ascertaining episodes of worsening heart failure, lack of objective measuring of worsening heart failure, conflict over intent of trial design versus broader target, subjective patient-reported outcomes and investigator decisions, and that the primary endpoint only accounted for dyspnea instead of including other symptoms. Novartis has an ongoing Phase 3 trial of 6,300 patient outcomes with results expected in 2016.

Ularitide – Cardiorentis' IV AHF Treatment

Cardiorentis' ularitide is an advanced natriuretic peptide currently in Phase 3 development as an IV AHF infusion treatment. Ularitide is the pharmaceutical version of synthesized urodilatin. Urodilatin is a hormone comprised of 32 amino acids and is a member of the natriuretic peptide group which is secreted from the kidney. Urodilatin is response of the kidney to decompensating heart failure by protecting renal function. This function occurs by binding urodilatin to specific natriuretic peptide receptors. The result of this binding increases intracellular cyclic guanosine monophosphate (cGMP) thereby relaxing smooth muscle tissues which causes vasodilation and increased blood flow.

TRV734 and Emerging CNS Portfolio

TRV734 is an orally available, small molecule μ-opioid G protein biased ligand agonist. Trevena intends to develop TRV734 as a treatment for acute and chronic pain in both the moderate to severe areas. Preclinical studies indicated TRV734 has a comparable drug candidate profile to TRV130 both in vivo and in vitro. TRV734 achieved analgesia similar to that of oxycodone with reduced constipation. TRVN intends to initiate several Phase 1 studies to assess the safety, tolerability, and PK/PD of TRV734 in 76 healthy adult males. TRV734 was orally available with dose-related increases in plasma concentrations. Peak plasma concentrations were reached about one hour post-dosing and exhibited a terminal half-life consistent with use involving acute pain treatment. At doses of at least 80 mg pupil constriction indicative of analgesia was observed with mild-to-moderate adverse effects reported at the maximum investigated dose of 250 mg. This data implies TRV734's analgesic efficacy may be separable from opioid-related adverse effects. There were no severe or serious adverse events reported nor were there any clinically significant changes in vital signs, laboratory values or ECG parameters.

Trevena has completed enrollment in a second Phase 1 multiple ascending dose clinical trial. We expect to data from this trial in the first quarter of 2015. Trevena has retained all worldwide development and commercialization rights to TRV734 but we believe the company is open to commercializing TRV734 with a partner possessing deep chronic pain management expertise. In this scenario, Trevena would retain US rights in hospital and specialist markets.

Intellectual Property

Trevena has filed various applications to protect its clinical candidates for several years. The company has an issued US patent covering TRV130 including compositions of TRV130 and methods utilizing TRV130 which is expected to expire no earlier than 2032. The company also filed a Patent Cooperation Treaty (PCT) for TRV130 in S. Korea, Europe, Eurasian Patent Office, Australia, Brazil, China, Canada, Israel, India, Japan, and New Zealand that, if issued, should extend protection at least until 2032.

Trevena has three issued US patents covering the composition of matter and method of use for TRV027 that should not expire any earlier than 2031 and 2029, respectively. The company has also been issued patents in New Zealand and China. The patent portfolio in the US also includes two pending applications which cover a genus of compounds encompassing TRV027 and methods of using such compounds that, if issued, would offer protection through 2029. Outside the US, TRV027 has pending applications in Australia, Canada, the European Patent Office, Hong Kong, India, and Japan that could offer protection through 2029. TRV027's patent portfolio also includes two U.S. provisional applications covering the synthesis of TRV027, including crystalline and amorphous forms, and methods of preparing the compound.

For TRV734 the company has filed patent applications covering methods of use. TRVN also has patent applications covering compounds that modulate various opioid receptors (δ-opioid receptors and other GPCRs, and peptides and peptide mimetics) that target AT1R that are beta-arrestin effectors. Except for two patents, Trevena has filed 33 U.S. provisional patent applications, foreign applications, U.S. non-provisional patent applications, and PCT applications that cover compositions and methods of making and using compounds that target G protein coupled receptors.

Management

Figure 24 – Management Background & Experience

Officer name	Title	Experience	Education	Joined Trevena:
Maxine Gowen, Ph.D.	Founding President, CEO	GSK, SR One, CEEDD, Human Genome Sciences	B.Sc. Biochemistry, University of Bristol; Ph.D. Cell Biology, University of Sheffield; MBA University of Pennsylvania	2007
Michael Lark, Ph.D.	CSO, SVP Research	Centocor, GSK, Merck	B.S. Microbiology, Pennsylvania State University; Ph.D. Microbiology Case Western Reserve University Medical School; Postdoctoral Fellowship University of Washington	2008
Roberto Cuca, CFA	CFO	Endo Health, moksha8, JPMorgan	MBA, University of Pennsylvania; J.D., Cornell Law School; A.B., Princeton University	2013
David Soergel, M.D.	SVP Clinical Development	Concert Pharmaceuticals, GSK	M.D., Cornell University; Pediatric Cardiology, Johns Hopkins; B.A. Johns Hopkins	2009
Rosamond Deegan	SVP Business Development & Operations	GSK, Immuno-Inflammation, KPMG	MBA, INSEAD; First Class B.A. Natural Sciences, Cambridge	2008
John Limongelli	SVP General Counsel & Corporate Secretary	Cigna, Adolor, Cephalon, Morgan, Lewis & Bockius, KPMG, Bell Atlantic	J.D. and MBA, Temple University	2014

Source: Cowen and Company, Trevena filings

Figure 25 – TRVN TRV130 Market Model

TRV130 (post-op pain) market model

US population (mil)	1.0%	321.3	324.5	327.8	331.1	334.4	337.8	341.2	344.7	348.2	351.7	355.2	358.8	362.4
Hospital inpatient setting		15,317,007	15,627,973	15,945,252	16,268,973	16,599,266	16,936,264	17,280,104	17,630,925	17,988,868	18,354,078	18,726,703	19,106,893	19,494,801
Incidence	1.0%	*4.8%*	*4.8%*	*4.9%*	*4.9%*	*5.0%*	*5.0%*	*5.1%*	*5.1%*	*5.2%*	*5.2%*	*5.3%*	*5.3%*	*5.4%*
Surgical		10,614,686	10,830,185	11,050,060	11,274,398	11,503,291	11,736,831	11,975,112	12,218,231	12,466,286	12,719,376	12,977,605	13,241,077	13,509,897
% of hospital inpatient	0.0%	*69%*	*69%*	*69%*	*69%*	*69%*	*69%*	*69%*	*69%*	*69%*	*69%*	*69%*	*69%*	*69%*
Non-surgical		4,702,321	4,797,788	4,895,192	4,994,575	5,095,975	5,199,433	5,304,992	5,412,694	5,522,583	5,634,702	5,749,098	5,865,816	5,984,904
% of hospital inpatient	0.0%	*31%*	*31%*	*31%*	*31%*	*31%*	*31%*	*31%*	*31%*	*31%*	*31%*	*31%*	*31%*	*31%*
Hospital outpatient setting		33,755,698	35,122,939	36,545,559	38,025,801	39,565,998	41,168,580	42,836,072	44,571,105	46,376,413	48,254,844	50,209,359	52,243,039	54,359,092
Incidence	3.0%	*10.5%*	*10.8%*	*11.1%*	*11.5%*	*11.8%*	*12.2%*	*12.6%*	*12.9%*	*13.3%*	*13.7%*	*14.1%*	*14.6%*	*15.0%*
Surgical		10,801,823.35	11,239,341	11,694,579	12,168,256	12,661,119	13,173,945	13,707,543	14,262,754	14,840,452	15,441,550	16,066,995	16,717,773	17,394,909
% of hospital outpatient	0.0%	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*	*32%*
Non-surgical		7,345,240	7,642,752	7,952,314	8,274,414	8,609,561	8,958,283	9,321,129	9,698,672	10,091,508	10,500,254	10,925,556	11,368,085	11,828,538
% of hospital outpatient	0.0%	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*
Total addressable patients		33,464,070	34,510,065	35,592,145	36,711,643	37,869,946	39,068,492	40,308,777	41,592,351	42,920,828	44,295,883	45,719,254	47,192,751	48,718,249
TRV130														
% of inpatient - surgical						*1.0%*	*4.0%*	*10.0%*	*15.0%*	*20.0%*	*22.0%*	*23.0%*	*24.0%*	*25.0%*
Number of pts on Tx						115,033	469,473	1,197,511	1,832,735	2,493,257	2,798,263	2,984,849	3,177,858	3,377,474
% of inpatient - non-surgical						*1.0%*	*3.0%*	*5.0%*	*8.0%*	*10.0%*	*12.0%*	*13.0%*	*14.0%*	*15.0%*
Number of pts on Tx						50,960	155,983	265,250	433,016	552,258	676,164	747,383	821,214	897,736
% of outpatient - surgical						*1.0%*	*5.0%*	*10.0%*	*12.0%*	*14.0%*	*16.0%*	*18.0%*	*19.0%*	*20.0%*
Number of pts on Tx						126,611	658,697	1,370,754	1,711,530	2,077,663	2,470,648	2,892,059	3,176,377	3,478,982
% of outpatient - non-surgical						*0.0%*	*1.0%*	*1.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*
Number of pts on Tx						-	89,583	93,211	193,973	201,830	210,005	218,511	227,362	236,571
Number of pts on TRV130						292,604	1,373,736	2,926,726	4,171,254	5,325,009	6,155,080	6,842,802	7,402,811	7,990,763
Blended TRV130 penetration						*1%*	*4%*	*7%*	*10%*	*12%*	*14%*	*15%*	*16%*	*16%*
Gross price - inpatient	3.0%					200.00	206.02	212.22	218.61	225.19	231.97	238.95	246.14	253.55
Gross price reduction						*0%*	*10%*	*20%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
Net price - inpatient						200.00	185.42	169.78	163.96	168.89	173.98	179.21	184.61	190.16
Net revenue - inpatient (mil)						33.20	115.97	248.34	371.49	514.36	604.47	668.86	738.25	812.99
Gross price - outpatient	3.0%					15.00	15.45	15.92	16.40	16.89	17.40	17.92	18.46	19.02
Gross price reduction						*0%*	*10%*	*20%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
Net price - outpatient						15.00	13.91	12.73	12.30	12.67	13.05	13.44	13.85	14.26
Net revenue - outpatient (mil)						1.90	10.41	18.64	23.43	28.87	34.98	41.81	47.13	52.99
Total TRV130 Revenue						**35.10**	**126.38**	**266.98**	**394.92**	**543.24**	**639.44**	**710.67**	**785.38**	**865.98**

Source: Cowen and Company.

Figure 26 – TRVN TRV027 Market Model

TRV027 (acute heart failure) market model														
US population (mil)	1.0%	321.3	324.5	327.8	331.1	334.4	337.8	341.2	344.7	348.2	351.7	355.2	358.8	362.4
Primary population		1,108,356	1,142,053	1,176,775	1,212,552	1,249,418	1,287,404	1,326,545	1,366,876	1,408,433	1,451,253	1,495,376	1,540,840	1,587,686
Incidence	2.0%	*0.34%*	*0.35%*	*0.36%*	*0.37%*	*0.37%*	*0.38%*	*0.39%*	*0.40%*	*0.40%*	*0.41%*	*0.42%*	*0.43%*	*0.44%*
Secondary population		1,091,847	1,119,429	1,147,708	1,176,700	1,206,426	1,236,902	1,268,148	1,300,184	1,333,028	1,366,703	1,401,228	1,436,625	1,472,917
Incidence	1.5%	*0.34%*	*0.34%*	*0.35%*	*0.36%*	*0.36%*	*0.37%*	*0.37%*	*0.38%*	*0.38%*	*0.39%*	*0.39%*	*0.40%*	*0.41%*
Hospitalization due to AHF		1,215,890	1,251,733	1,288,639	1,326,637	1,365,761	1,406,044	1,447,520	1,490,225	1,534,195	1,579,468	1,626,084	1,674,081	1,723,501
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		607,945	625,867	644,319	663,319	682,880	703,022	723,760	745,112	767,098	789,734	813,042	837,040	861,750
incidence	0.0%	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Total addressable patients		607,945	625,867	644,319	663,319	682,880	703,022	723,760	745,112	767,098	789,734	813,042	837,040	861,750
TRV027 penetration rate	0.0%							*3.0%*	*8.0%*	*15.0%*	*20.0%*	*24.0%*	*28.0%*	*30.0%*
Number of pts on TRV027								21,785	59,683	115,141	158,026	195,211	234,455	258,611
Gross price	3.0%							2,484.61	2,559.40	2,636.43	2,715.79	2,797.54	2,881.74	2,968.48
Growth to net	1.0%							2,090.59	2,153.51	2,218.34	2,285.11	2,353.89	2,424.74	2,497.73
TRV027 Revenue (mil)								45.54	128.53	255.42	361.11	459.51	568.49	645.94
ACT royalty to TRVN (mil)	18.0%							9.11	25.71	51.08	72.22	91.90	113.70	129.19

Source: Cowen and Company.

Figure 27 – TRVN Income Statement

	2011A	2012A	2013A	Q1/14A	Q2/14A	Q3/14A	Q4/14E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E
TRV130	-	-	-	-	-	-	-	-	-	-	-	35.1	126.4	267.0	394.9	543.2	639.4	710.7
Product revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**35.1**	**126.4**	**267.0**	**394.9**	**543.2**	**639.4**	**710.7**
Grant revenue	2.4	0.8	0.1	-	-	-	-	-	-	15.0	-	50.0	15.0	75.0		-	-	-
Total revenues	**2.4**	**0.8**	**0.135**	**-**	**-**	**-**	**-**	**-**	**-**	**15.0**	**-**	**85.1**	**141.4**	**342.0**	**394.9**	**543.2**	**639.4**	**710.7**
Cost of goods sold		-	-	-	-	-	-											
Gross Profit	**2.4**	**0.8**	**0.1**	**-**	**-**	**-**	**-**	**-**	**-**	**15.0**	**-**	**85.1**	**141.4**	**342.0**	**394.9**	**543.2**	**639.4**	**710.7**
R&D expense	15.1	13.3	18.2	7.6	9.0	13.0	12.0	41.7	66.0	70.0	50.0	50.0	50.0	50.0	50.5	51.0	51.5	52.0
SG&A expense	3.1	3.1	4.0	2.0	2.5	2.5	2.7	9.7	11.4	6.6	50.0	60.0	63.0	66.2	69.5	72.9	76.6	80.4
Other operating expense			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total operating expense	**18.2**	**16.4**	**22.3**	**9.7**	**11.5**	**15.5**	**14.7**	**51.4**	**77.4**	**76.6**	**100.0**	**110.0**	**113.0**	**116.2**	**120.0**	**123.9**	**128.1**	**132.4**
Operating income	**(15.8)**	**(15.6)**	**(22.1)**	**(9.7)**	**(11.5)**	**(15.5)**	**(14.7)**	**(51.4)**	**(77.4)**	**(61.6)**	**(100.0)**	**(24.9)**	**28.4**	**225.8**	**275.0**	**419.3**	**511.4**	**578.2**
Net Interest/Investment income	0.0	-	0.0	0.0				0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
(interest expense)	(0.1)	(0.2)	0.0	-		0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Other non-operating income (expense)	0.0	0.2	-	0.2	0.0	0.0		-	-	-	-	-	-	-	-	-	-	-
Change in fair value of warrant liability				0.1														
Interest and other, Net	(0.1)	(0.0)	-	0.3	-	-	-	0.3	0.6	1.1	2.2	4.5	8.7	17.4	34.8	69.7	139.1	277.6
Pre-tax income	**(15.8)**	**(15.6)**	**(22.1)**	**(9.4)**	**(11.5)**	**(15.5)**	**(14.7)**	**(51.3)**	**(77.3)**	**(61.5)**	**(99.9)**	**(24.8)**	**28.4**	**225.9**	**275.0**	**419.4**	**511.4**	**578.3**
Income tax expense (benefit)	-	-	-	0.0				-	-	-	-	-	-	-	-	-	-	-
Net income (loss)	**(15.8)**	**(15.6)**	**(22.1)**	**(9.4)**	**(11.5)**	**(15.5)**	**(14.7)**	**(51.3)**	**(77.3)**	**(61.5)**	**(99.9)**	**(24.8)**	**28.4**	**225.9**	**275.0**	**419.4**	**511.4**	**578.3**
Basic EPS	**(0.96)**	**(0.95)**	**(1.18)**	**(0.59)**	**(0.44)**	**(0.59)**	**(0.39)**	**(1.93)**	**(2.01)**	**(1.59)**	**(2.57)**	**(0.64)**	**0.72**	**5.72**	**6.92**	**10.51**	**12.75**	**14.34**
Diluted EPS	**(0.96)**	**(0.95)**	**(1.18)**	**(0.59)**	**(0.44)**	**(0.59)**	**(0.39)**	**(1.93)**	**(2.01)**	**(1.59)**	**(2.57)**	**(0.64)**	**0.72**	**5.72**	**6.92**	**10.51**	**12.75**	**14.34**
Basic shares outstanding	16.5	16.5	18.8	16.0	26.3	26.4	37.6	26.6	38.5	38.7	38.9	39.1	39.3	39.5	39.7	39.9	40.1	40.3
Diluted shares outstanding	16.5	16.5	18.8	16.0	26.3	26.4	37.6	26.6	38.5	38.7	38.9	39.1	39.3	39.5	39.7	39.9	40.1	40.3

Source: Cowen and Company.

Valuation Methodology And Risks

Valuation Methodology

Biotechnology:

In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe there are any good methodologies for assigning a specific target price to such stocks.

Investment Risks

Biotechnology:

There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

Risks To The Price Target

Additional trials may show TRV027 and TRV130 as having an unacceptable safety and/or tolerability profiles, and the trials themselves may not be successful. Despite Ph3 success, TRV130 may not be approved by the FDA and/or EMA or scheduling/REMS restriction may considerably hinder the drug's probability of success. Both TRV027 and TRV130 face entrenched, inexpensive competition that could limit either or both drugs' adoption.

Addendum

Stocks Mentioned In Important Disclosures

Ticker	Company Name
ICPT	Intercept Pharmaceuticals
RPTP	Raptor Pharmaceutical Corp.
TRVN	Trevena

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Cowen and Company, LLC. New York (646) 562-1000 **Boston** (617) 946-3700 **San Francisco** (415) 646-7200 **Chicago** (312) 577-2240 **Cleveland** (440) 331-3531 **Atlanta** (866) 544-7009 **London** (affiliate) 44-207-071-7500

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Market Perform (2): The stock is expected to have a total return that falls between the parameters of an Outperform and Underperform over the next 12 months

Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

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Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

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Points Of Contact

Analyst Profiles

Ritu Baral
New York
646.562.1379
ritu.baral@cowen.com

Ritu Baral is a senior analyst covering the biotechnology sector. She joined Cowen in 2014, having previously worked at Canaccord.

Kenny Lalwani
New York
646.562.1425
kenny.lalwani@cowen.com

Kenny Lalwani is an associate covering the biotech sector. He has an MBA from the University of Michigan and an engineering background.

Reaching Cowen

Main U.S. Locations

New York
599 Lexington Avenue
New York, NY 10022
646.562.1000
800.221.5616

Boston
Two International Place
Boston, MA 02110
617.946.3700
800.343.7068

Cleveland
20006 Detroit Road
Suite 100
Rocky River, OH 44116
440.331.3531

San Francisco
555 California Street, 5th Floor
San Francisco, CA 94104
415.646.7200
800.858.9316

Atlanta
3399 Peachtree Road NE
Suite 417
Atlanta, GA 30326
866.544.7009

Chicago
181 West Madison Street
Suite 1925
Chicago, IL 60602
312.577.2240

International Locations

Cowen International Limited

London
1 Snowden Street - 11th Floor
London EC2A 2DQ
United Kingdom
44.20.7071.7500

Cowen and Company (Asia) Limited

Hong Kong
Suite 1401 Henley Building
No. 5 Queens Road Central
Central, Hong Kong
852 3752 2333