COMPANY NOTE

Initiating Coverage

USA | Healthcare | Biotechnology

February 26, 2014

Jefferies

Trevena, Inc. (TRVN)

Initiate with A Buy: Biased Ligand Platform Offers Upside

BUY
Price target $11.00
Price $7.77

EQUITY RESEARCH AMERICAS

Key Takeaway

We believe TRVN's two candidates from its GPCR biased ligand platform offer upside to TRVN shares. TRV027 in acute heart failure has observed promising improvements in clinical efficacy parameters in Phase IIa studies. TRV130, which may offer effective analgesia without the harmful effects commonly associated with opioids, will begin a PII bunionectomy trial in Q2'14.

Jefferies was joint book-running manager for TRVN's IPO on January 31, 2014.

TRV027 - TRVN Can Adapt to Change in Regulatory Landscape for Acute Heart Failure. TRV027 is a biased ligand targeting AT1R for acute heart failure, an indication of high unmet medical need. Forest (FRX, $98.25, Buy) has the option to license TRV027, which would grant them WW rights. We believe PIIa data supports a favorable outlook for TRV027 as it begins its PIIb trial. TRVN is well-positioned to follow in Novartis' footsteps (NOVN VX, CHF74.40, Hold), as Novartis heads into its FDA Advisory Panel meeting in the next 1-2 mo for serelaxin. Serelaxin's PIII trial RELAX-AHF had mixed results, meeting the 1 EP of improvement in dyspnea (VAS AUC) but not the other (Likert scale) with a potential signal in mortality improvement at 6 mo. We expect the panel to discuss key issues on the trial design/dataset and relevance of dyspnea in AHF, which will guide TRVN/FRX on the pivotal PIII design for TRV027. Assuming a positive outcome on PIII, we believe TRV027 can generate WW royalty revenue for TRVN of $65M at peak ($41M in U.S.) (risk-adjusted).

TRV130 Could be a Game-Changer in Post-Operative Pain Management. TRV130 is a biased ligand against the m-opioid receptor for acute post-operative pain, which may exhibit more effective analgesia while reducing adverse events commonly associated with opioids. PI and preclinical data have been supportive where TRV130 showed superior analgesia v. morphine, while causing less respiratory depression, nausea, and vomiting. TRV130 will begin a PII bunionectomy trial in Q2'14. Assuming positive data expected H1 2015 and in the subsequent pivotal PIII trial, we estimate TRV130 approval in 2019. We anticipate U.S. revenues of $205M by 2031 (risk-adjusted). TRVN is also developing TRV734 as a follow-on program to TRV130, starting a PI trial, which could offer additional upside as an oral therapy for chronic pain.

Valuation/Risks

We arrive at our $11 PT based on DCF-methodology. Risks to our thesis include clinical trial failure, regulatory approval risks, and commercial launch risks.

USD	*Prev.*	2013E	*Prev.*	2014E	*Prev.*	2015E	*Prev.*	2016E
Rev. (MM)	--	0.1	--	0.0	--	0.0	--	42.3
EV/Rev		NM						2.3x
EPS								
Mar	--	(0.23)A	--	(0.33)	--	--	--	--
Jun	--	(0.30)A	--	(0.35)	--	--	--	--
Sep	--	(0.64)A	--	(0.37)	--	--	--	--
Dec	--	(0.56)	--	(0.38)	--	--	--	--
FY Dec	--	(1.76)	--	(1.44)	--	(1.64)	--	0.11
FY P/E		NM		NM		NM		70.6x

Financial Summary	
Net Debt (MM):	($101.2)
Long-Term Debt (MM):	$0.0
Cash & ST Invest. (MM):	$101.2
Cash/Share:	$3.94
Cash (MM):	$101.2
Market Data	
52 Week Range:	$8.98 - $6.35
Total Entprs. Value (MM):	$98.5
Market Cap. (MM):	$199.7
Shares Out. (MM):	25.7
Float (MM):	6.9
Avg. Daily Vol.:	NA

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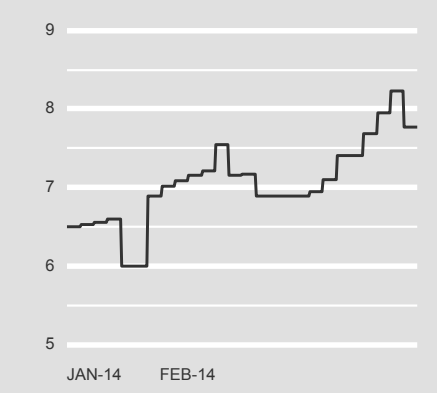
Price Performance



Trevena, Inc.

Buy: $11 Price Target

THE LONG VIEW

Scenarios

Target Investment Thesis

- Positive outcomes in TRV027's Phase II BLAST-AHF and Phase III trial, with US and EU approval in 2020. Assume Forest Labs exercises license option in H2 2015
- Expect TRVN to receive royalty revenue of $41M in the U.S. and $24M in EU/ROW for TRV027 at peak
- Positive outcome in TRV130's clinical trials and U.S. approval in 2019, with peak net sales of $205M (risk-adjusted)
- DCF-based PT: $11

Upside Scenario

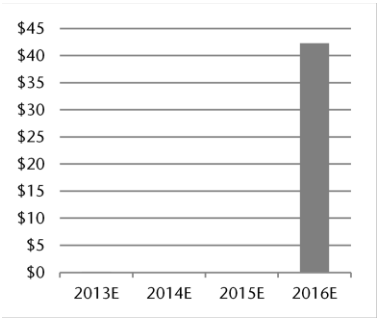
- Positive outcome in TRV734 clinical program for chronic pain
- Positive outcome in delta opioid program in CNS disorders
- DCF-based PT: $24

Downside Scenario

- Negative outcome in TRV027 clinical program, DCF-based PT: $8
- Negative outcome in TRV130 clinical program, DCF-based PT: $6
- On all clinical failure, including TRV734 and delta opioid program, cash-based PT: $4

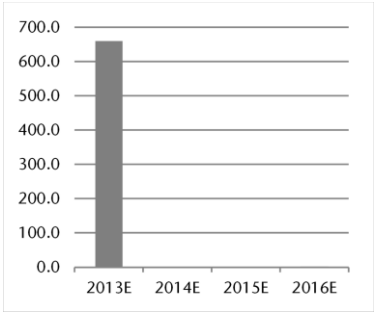
Long Term Analysis

Revenue (millions)



Source: Company data; Jefferies estimates

Enterprise Value (EV)/Sales



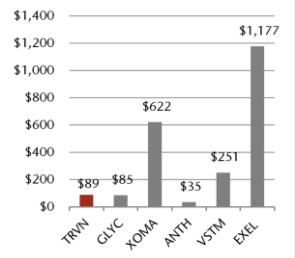
Source: Company data; Jefferies estimates

Other Considerations

We consider small-cap and mid-cap biotech companies with late-stage programs to continue to be attractive targets for partnering or M&A partnering with large-cap biotech and pharma companies, which we believe will be a driving factor for performance in the biotech sector 2014-2015.

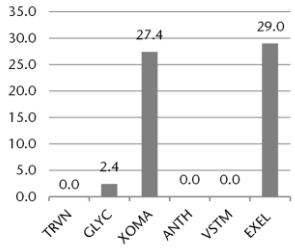
Peer Group

Group EV



Source: Factset, Jefferies estimates

Group EV/2014E Sales



Source: Factset, Jefferies estimates

Recommendation / Price Target

Ticker	Rec.	PT
TRVN	**Buy**	**$11**
GLYC	Buy	$13
XOMA	Buy	$11
ANTH	Buy	$18
VSTM	Buy	$21
EXEL	Hold	$5

Catalysts

- Initiation of Phase II bunionectomy trial for TRV130 in Q2 2014
- Data for Phase I trial for TRV734 in H2 2014
- Topline data for Phase II buniotectomy trial for TRV130 in H1 2015
- Topline data for Phase II (BLAST-AHF) for TRV027 in H2 2015

Company Description

Trevena is a biopharmaceutical company based in King of Prussia, PA, dedicated to the development of G-protein coupled receptor (GPCR) biased ligands. Trevena's lead product is TRV027, a β-arrestin2 biased ligand which is in Phase II evaluation for treatment of acute heart failure. Trevenas' pipeline also includes TRV130; a biased μ-opioid receptor ligand that will soon undergo Phase II clinical evaluation in post-operative pain, TRV734; a μ-opioid receptor ligand in pre-clinical trials for acute and chronic pain and Delta BL program which involves biased ∂-opioid receptor ligands for treating pain, depression and neurological disorders like Parkinson's disease.

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Executive Summary

Trevena is a biopharmaceutical company based in King of Prussia, PA, dedicated to the development of G-protein coupled receptor (GPCR) biased ligands. Trevena's lead product is TRV027, a ligand targeting the angiotensin II type I receptor (AT1R) which is in a Phase IIb trial for acute heart failure, an indication where effective therapies are lacking. As a biased ligand, TRV027 stimulates the β-arrestin pathway while antagonizing G-protein dependent signaling, potentially driving favorable effects without adversely affecting other organ functions. TRV027 has shown encouraging data in a Phase IIa study with decreased mean arterial pressure (MAP) and potentially pulmonary capillary wedge pressure (PCWP). Forest Laboratories (FRX, $99.55, Buy) has the option to license TRV027. If FRX exercises its option, Forest will have exclusive worldwide rights to develop and commercialize TRV027, which could be on the market in 2020. Trevena is also developing TRV130 for acute post-operative pain, another biased ligand that may allow for more effective analgesia while reducing adverse events associated with opioids. TRV130 will start a Phase II bunionectomy trial v. morphine to confirm earlier findings in Q2 2014. Assuming positive data in H1 2015 and in a subsequent Phase III trial, we estimate TRV130 approval in 2019. TRV734 is a follow-on program to TRV130, which is being developed as an oral therapy targeted towards acute and chronic pain, respectively. TRV734 and the delta opioid preclinical program for CNS disorders could drive additional upside to our estimates.

- **TRV027 - TRVN Will Have the Ability to Adapt to Change in Regulatory Landscape for Acute Heart Failure.** We believe promising Phase IIa data supports a favorable outlook for TRV027 in acute heart failure as it begins its Phase IIb trial. Furthermore, we believe TRVN is well-positioned to follow in Novartis' (NOVN VX, CHF74.85, Hold) footsteps, or change course if necessary, as it heads into the FDA Cardiovascular and Renal Drugs Advisory Committee Panel meeting in the next 1-2 months for serelaxin. Serelaxin is a recombinant form of human relaxin-2 being investigated for acute heart failure. It has completed a Phase III trial RELAX-AHF with mixed results, meeting one primary endpoint of improvement in dyspnea (VAS AUC) but not the other (Likert scale) with a potential signal in mortality improvement at 6 months. We expect the panel to discuss key issues on RELAX-AHF's trial design, serelaxin's controversial dataset, the relevance of dyspnea as an endpoint for approval in AHF, and appropriate endpoints that can be considered clinically meaningful for AHF. We believe the discussions and outcome of the FDA panel meeting will have implications for TRVN/FRX on how to best design the pivotal Phase III trial for TRV027, which we expect to start in H2 2016. Assuming a positive outcome, we believe TRV027 can be approved in 2020.

- **TRV130 Could Offer Advantages To Current Standard of Care in Post-Operative Pain Management.** Trevena is also developing TRV130 as a first-line treatment for patients experiencing moderate to severe acute post-operative pain. As a biased ligand, TRV130 may exhibit more effective analgesia while reducing adverse events as respiratory suppression and constipation commonly associated with opioids. Such a therapeutic profile would offer clear advantages over standard-of-care, which could help expedite recovery and hospital discharge, and ultimately reduce hospital costs. Early Phase I and preclinical data have been supportive, where TRV130 showed superior analgesia compared to high-dose morphine, while causing less respiratory depression, nausea, and vomiting. TRV130 will begin a Phase II bunionectomy trial in Q2 2014 to confirm earlier findings. Assuming positive data in

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the Phase II expected H1 2015 and in the subsequent pivotal Phase III trial, we estimate TRV130 approval in 2019.

- **TRV734 and Delta Opioid Program Offer Additional Value Proposition.** TRV734 is a follow-on program to TRV130 as a μ-opioid biased ligand may show potent analgesia without the adverse events associated with opioids. TRVN expects TRV734 will have pharmacokinetics that would make it amenable to chronic oral administration. TRVN has recently initiated a Phase I trial for TRV734 in healthy subjects, and as TRV734 develops, Phase II and III studies will evaluate the efficacy and tolerability in patients with acute and chronic pain. TRVN's delta opioid program involves developing a series of biased delta opioid receptor (DOR) ligands to treat pain, depression and Parkinson's disease, and TRVN will decide on the lead candidate for Parkinson's disease in 2014 and will file an IND in Q1 2015. Data from both of these programs over the next 18 months could provide additional value creation opportunities.

Valuation

We arrive at our $11 price target based on a DCF valuation model, which assumes a 14% WACC and outstanding shares of 25.7 million, driven by royalties from TRV027 and revenues from TRV130. We expect U.S. approval for TRV027 in 2020, reaching revenues of $612 million on an unadjusted-basis. Applying a 65% risk discount, we believe TRV027 will have U.S. revenues of $214 million by 2030, translating to royalty revenue of $41 million. We also expect ex-U.S. revenues of $126 million at peak on a risk-adjusted basis (65%), translating to royalty revenue of $24 million. For TRV130, we estimate approval in 2019 and total peak net sales for in- and out-patient surgical patients at $585 million in 2031 on an unadjusted-basis ($562 million for in-patient and $22 million for out-patient). Applying a 65% discount rate to reflect the risk associated with this early stage asset, we estimate risk-adjusted peak sales of $205 million by 2031. We expect TRVN to partner TRV130 for commercialization ex-U.S. and estimate royalty revenue of $82 million by 2031. We do not yet model TRV734 for pain management or TRVN's delta opioid program, both of which represent upside to our estimates.

Exhibit 1: DCF sensitivity analysis

Discount rate	Equity value	Price/ Share
10.0%	$401.4	$15.62
12.0%	$330.0	$12.84
14.0%	**$273.6**	**$10.65**
16.0%	$228.9	$8.90
18.0%	$193.1	$7.51

Source: Jefferies estimates

Risks

Clinical Failure: As with all companies in biotechnology and pharmaceuticals developing treatments of the future, a clinical failure can lead to delays in approval or possibly discontinuation of programs.

Regulatory Failure: The FDA could determine the Biologic Licensing Application is inadequate for one or more of TRVN's programs and could delay approval. Any delays in approval timelines could impact our earnings estimates, price target, and/or rating.

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Commercial Failure: We currently project $214 million (risk-adjusted) in U.S. sales for TRV027 in 2030, translating to royalty revenue of $41 million. We also project $205 million (risk-adjusted) in U.S. sales for TRV130 in 2031. Our estimates may rely on the success of the company/partners to receive drug reimbursement from private/public payors.

Financing Risks: We expect TRVN to have adequate cash until 2016, and may need additional financing from 2014 to 2016 to fund its R&D programs, and a sales and marketing infrastructure for a potential commercial launch of TRV130 (if approved). However, the company may partner ex-U.S. licensing rights and/or other pipeline candidates to offset the need for equity financing.

Company Overview

Trevena is a biopharmaceutical company based in King of Prussia, PA, dedicated to the development of G-protein coupled receptor (GPCR) biased ligands. Trevena's lead product is TRV027, a β-arrestin2 biased ligand which is in Phase II evaluation for treatment of acute heart failure. Trevenas' pipeline also includes TRV130; a biased μ-opioid receptor ligand that will soon undergo Phase II clinical evaluation in post-operative pain, TRV734; a μ-opioid receptor ligand in pre-clinical trials for acute and chronic pain and Delta BL program which involves biased ∂-opioid receptor ligands for treating pain, depression and neurological disorders like Parkinson's disease.

Exhibit 2: Company Pipeline

Drug	Mechanism of Action	Indication	Development Phase
TRV027	β-arrestin biased ligand against AT1R	Acute Heart Failure (AHF)	Phase IIb
TRV130	G-protein biased ligand against μ-opioid receptor	Pain management (acute post-operative)	Phase II
TRV734	G-protein biased ligand against μ-opioid receptor	Pain management (acute and chronic)	Phase I
Delta Opioid Program	Biased δ-opioid receptor ligands	Parkinson's Disease, Pain, Depression	Preclinical

Source: Company data.

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Exhibit 3: Key Upcoming Milestones.

Product	Indication	Event	Date
TRV027	**Acute Heart Failure (AHF)**	Enrollment completion of Phase II BLAST-AHF	H1 2015
		Topline data for Phase II BLAST-AHF	H2 2015
		FDA AdComm Panel for Novartis' serelaxin in AHF	Mar-Apr 2014
		PDUFA date for Novartis' serelaxin in AHF	Q2 2014
		EMA decision for conditional approval of Novartis' serelaxin in AHF	Q2 2014
		Forest Laboratories' exercise of license option (JEF est)	H2 2015
		Initiation of pivotal Phase III trial	H2 2016
		Topline data for pivotal Phase III trial	2019
		U.S. approval of TRV027	2020
		EU/ROW approval of TRV027	2020
TRV130	**Post-operative pain**	Initiation of Phase II trial (bunionectomy model)	Q2 2014
		Topline data for Phase II trial (bunionectomy model)	H1 2015
		Initiation of separate Phase II trial (alternative pain model)	H2 2014
		Initiation of pivotal Phase III trial	H2 2015
		Topline data for pivotal Phase III trial	2018
		U.S. approval of TRV130	2019
		EU/ROW approval of TRV130	2020
TRV734	**Moderate-to-Severe Pain**	IND filing	Q1 2014
		Initiation of Phase I trial for TRV734 in healthy subjects	*Feb 2014*
		Data for Phase I trial for TRV734	H2 2014
Delta Opioid Program	**Parkinson's Disease, Pain, Depression**	Candidate selection for Parkinson's Disease	2014
		IND filing	Q1 2015
		Initiation of Phase I trial	2015

Source: Company estimates, Jefferies.

TRV027

Acute Heart Failure

TRVN Uniquely Positioned to Adapt to Change in Regulatory Landscape

TRV027 is Trevena's lead candidate from its biased-ligand technology platform being investigated in Phase II as a treatment for acute heart failure (AHF). TRV027 is a polypeptide that targets the angiotensin II type I receptor (AT1R), stimulating the β-arrestin pathway while antagonizing G-protein dependent signaling, potentially driving favorable effects such as reduced blood pressure, increased cardiac contractility and performance without adversely affecting other organ functions. TRV027 has shown encouraging data in HF patients in a Phase IIa study with decreased mean arterial pressure (MAP) and potentially pulmonary capillary wedge pressure (PCWP), consistent with animal data and mechanism-of-action. TRVN is in an agreement with Forest Laboratories in which it granted Forest an exclusive option to license TRV027. If FRX exercises its option, the license agreement becomes effective and Forest will have exclusive worldwide rights to develop and commercialize TRV027. Assuming a positive Phase III trial, we believe TRV027 can make it to market in 2020, and AHF represents an opportunity of ~$214 million in revenues for TRV027 in the U.S. by 2030 (on a risk-adjusted basis). We

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model 15% in royalty revenue in 2020, increasing to 19% at peak and translating to royalty revenue of $41 million by 2030.

AHF is a complicated condition and the treatment paradigm has not changed significantly in the past several decades, being limited to angiotensin receptor blockers (ARB's), intravenous nitrates, inotropes, and diuretics/loop diuretics, none of which have been shown to improve long-term outcomes. Because of numerous feedback loops that occur within the renin-angiotensin system (RAS), it is difficult to determine the net clinical benefit of improving just one parameter. A successful candidate in AHF will improve one or more parameters while preserving organ functions.

Novartis' serelaxin, a recombinant form of human relaxin-2, may be a useful proxy. Serelaxin has shown mixed data from its Phase III RELAX-AHF trial, passing one of the co-primary endpoints in improvement in dyspnea, but not the other. There was also a post-discharge mortality benefit at 6 mo, which may or not have been due to chance. The FDA's Cardiovascular and Renal Drugs Advisory Committee was scheduled to meet on February 13 to discuss the results, but was canceled due to inclement weather. We expect the panel to re-convene within the next 1-2 months. We believe the discussions from this panel will be key in determining which factors and endpoints the FDA will deem as clinically meaningful in AHF. The discussion should help inform the pivotal Phase III design for TRV027, expected to begin in H2 2016. We believe TRVN is uniquely positioned to follow the path paved by Novartis, or adjust course if necessary should serelaxin fail to win approval.

TRV027 is currently in a Phase IIb trial and being evaluated at three doses compared to placebo in AHF patients. An interim analysis for this trial is expected after it enrolls ~300 patients, which we expect to occur in H2 2014. The primary endpoint of the study will be a composite endpoint of a spectrum of outcomes, including: 1) time from randomization to death through day 30; 2) time from randomization to heart failure re-hospitalization through day 30; 3) time to randomization to worsening heart failure through day 5; 4) change in dyspnea VAS score from baseline through day 5; 5) length of initial hospital stay (in days) from randomization. We expect final data in H2 2015.

U.S. Market Opportunity

Market Opportunity in Acute Heart Failure. It is estimated that >1.1 million hospitalizations due to acute heart failure (AHF) have occurred in 2004 (Fang, J. et al., *J Am Coll Cardiol*. 2008, 52, 428-434). The clinical classification for AHF is as follows: 1) worsening chronic HF with reduced or preserved LVEF which account for ~70% of all admissions; 2) de novo HF (i.e. after large myocardial infarction, or sudden increase in blood pressure on non-compliant LV which account for ~25% of admissions, and 3) advanced or refractory HF with severe LV systolic dysfunction, accounting for ~5% of admissions. TRV027 is currently in a Phase IIb trial, and we anticipate Phase III to begin in H2 2016. Assuming positive data in 2019, we expect U.S. approval in 2020. We assume +10% premium to Natrecor, which is priced at $800 per day (WAC). We assume peak penetration of 18% by 2030, reaching revenues of $612 million on an unadjusted-basis. Applying a 65% risk discount, we believe TRV027 will have revenues of $214 million by 2030.

Assuming Forest exercises its option and the license agreement becomes effective, TRVN could also receive tiered royalties between 10-20% of net sales worldwide. Royalty rates on net sales in the U.S. may be somewhat higher than those outside the U.S., although TRVN has not disclosed what the royalty rates may be. We model 15% in 2020, increasing to 19% at peak and translating to royalty revenue of $41 million by 2030.

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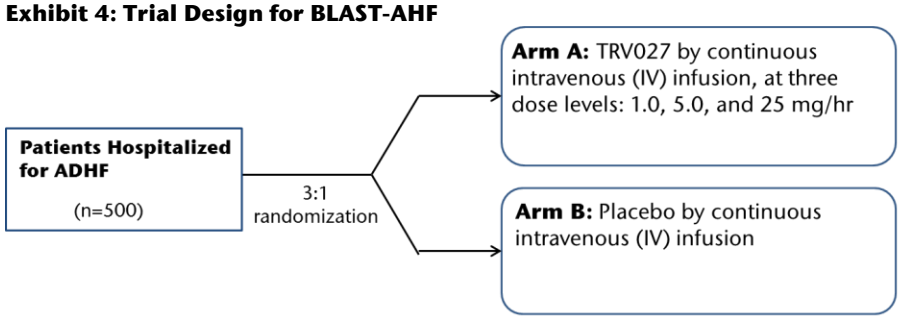
Phase IIb Trial (BLAST-AHF)

Nuts & Bolts: TRV027 is in a randomized, double-blind, placebo-controlled Phase II trial (BLAST-AHF) for patients hospitalized with Acute Decompensated Heart Failure (ADHF). The trial will enroll ~500 patients in clinical sites in the U.S. and Hungary. The trial will investigate three doses of TRV027 (1.0, 5.0, and 25 mg/hr) via continuous IV infusion and compared to placebo control. TRV027 will be administered for a minimum of 48 hours and up to 5 days. The primary endpoint will be a composite Z score of the following outcomes: 1) time from randomization to death through day 30; 2) time from randomization to heart failure re-hospitalization through day 30; 3) time to randomization to worsening heart failure through day 5; 4) change in dyspnea VAS score from baseline through day 5; 5) length of initial hospital stay (in days) from randomization. The component outcomes will be combined by deriving an average Z for each patient. The inclusion criteria are shown in Exhibit 4. The trial has just dosed its first patient in January 2014 and continues to enroll patients.

An interim analysis is expected after the trial enrolls ~300 patients. TRVN may drop one of the doses that are being investigated, restricting the trial to two doses for the remaining patients to be enrolled. We expect the interim analysis to occur in H2 2014.

Exhibit 4: Trial Design for BLAST-AHF



Endpoints
Primary:
- Composite score of:
  - Time from randomization to death through Day 30
  - Time from randomization to heart failure re-hospitalization through Day 30
  - Time to randomization to worsening heart failure through Day 5
  - Change in dyspnea VAS score from baseline through Day 5
  - Length of initial hospital stay (in days) from randomization

Inclusion Criteria:
- Presence of ADHF defined by:
  - BNP >400 pg/mL or NT-proBNP >1,600 pg/mL
  - At least two of the following: congestion on chest radiograph (CXR), rales by chest ausculatation, edema ≥+1 on a 0-3+ scale, indicating indentation of skin with mild digital pressure that requires ≥10 sec to resolve, elevated jugular venous pressure (≥8 cm H_2O)
- Systolic blood pressure ≥120 mmHg and ≤200 mmHg within 30 min of randomization
- Pre-existing diagnosis of heart failure
- Ventricular rate of ≤125 bpm
- Receipt of a IV loop diuretic at a minimum dose of 40 mg furosemide for treatment of dyspnea due to ADHF at least 1 hr prior to anticipated randomization

Source: ClinicalTrials.gov.

Phase III Design

A Phase III pivotal study is likely to begin in H2 2016. Primary endpoint will be determined on the basis of the Phase IIb results and discussions with the regulatory authorities. The study could enroll 1,500 patients and is likely to be placebo-controlled. The endpoint could include hospital length of stay, worsening heart failure during hospitalization, re-admission and/or mortality 30-180 days, improvement in dyspnea, or a hierarchical composite composed of these and other measures. The FDA Panel Meeting to review

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Novartis' serelaxin may give an indication on what endpoint the FDA will deem as clinically meaningful.

TRVN Can Follow the Path Paved by Novartis, or Change Course if Necessary

Novartis is developing serelaxin for AHF, a recombinant form of the peptide hormone human relaxin-2 that has been known to increase arterial compliance, cardiac output, and renal blood flow. Because serelaxin is ahead of TRV027 in clinical development, TRVN is uniquely positioned to follow the path paved by Novartis, or if necessary, change course should serelaxin fail to win approval. Serelaxin has completed a Phase III trial RELAX-AHF with mixed results, meeting one primary endpoint of improvement in dyspnea (VAS AUC) but not the other (on Likert scale). Novartis submitted regulatory filings for serelaxin to the FDA and EMA, and it was granted Breakthrough Therapy status in June 2013, which is granted when a drug shows substantial improvement over standard-of-care (SOC). The FDA's Cardiovascular and Renal Drugs Advisory Committee was scheduled to meet on February 13, 2014 to discuss serelaxin as a treatment to improve the symptoms of AHF through reduction of the rate of worsening of heart failure, but was canceled due to inclement weather. We expect the panel to re-convene within the next 1-2 months. The PDUFA date is expected in Q2 2014 (date not yet disclosed). We believe the outcome of the FDA panel will have implications on TRVN/FRX on how to best design the pivotal Phase III trial.

Because of numerous feedback loops that occur within the renin-angiotensin system (RAS) in HF, it is difficult to determine the net clinical benefit of improving just one parameter. None of the currently approved therapies improve long-term outcomes, and in some cases, can lead to poorer outcomes. For instance, inotropes improve the strength of muscular contractions, but are associated with increased mortality (ALARM-HF registry and OPTIME-CHF study). A successful candidate in AHF therefore will improve one or more parameters while preserving organ functions, such as renal function.

The controversy lies in the fact that in RELAX-AHF, serelaxin showed mixed results (Exhibit 5). For the primary endpoint, serelaxin showed a 19% improvement on dyspnea on VAS AUC (p=0.0075), but no difference in dyspnea relief on Likert scale at 24 h compared to placebo (27% v. 26%, p=0.70) (co-primary endpoint). Despite not having passed the latter endpoint, further analysis did show an improvement by day 5 (p=0.002). Serelaxin did not pass either of its secondary endpoints. Interestingly, at six months, all-cause deaths were reduced at Day 180, 7.3% in the serelaxin group versus 11.3% in the placebo group (HR=0.63, p=0.02), which makes RELAX-AHF the first trial to show an improvement in post-discharge mortality. However, the trial was not designed or powered as a mortality trial, and was an exploratory endpoint. Thus, while intriguing, it raises the question whether a confirmatory trial is needed. Serelaxin also improved worsening of HF before 14 days compared to placebo (11.4% v. 15.7%; HR=0.70, p=0.024).

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Exhibit 5: Summary of serelaxin data from RELAX-AHF.

Endpoint(s)	Detail of Endpoint	Serelaxin *n=581*	Placebo *n=580*	HR/Benefit	95% CI	p-value
Primary endpoint(s)	**Change in patient-reported dyspnea from baseline in the visual analogue scale area under the curve (VAS AUC) to day 5**	**2,756 mmxh**	**2,308 mmxh**	**448 mmxh**	**120-775**	**0.007**
	Proportion of patients with moderate or marked dyspnea improvement by Likert scale during the first 24 h	156 (27%)	150 (26%)	N/A	N/A	0.70
Secondary endpoint(s)	Days alive and out of the hospital to day 60	48.3 days	47.7 days	N/A	N/A	0.37
	Cardiovascular (CV) death or readmission to hospital for heart failure or renal failure before day 60 as adjudicated by the clinical events committee	76 events (13.2%	75 events (13.0%)	1.02	0.74-1.41	0.89
Other endpoint(s)	**Study day of moderately or markedly improved dyspnea before day 5**	**1.5**	**1.9**	**-0.40**	**-0.6 to -0.2**	**0.002**
	Study day of worsening heart failure before day 5	**5.8**	**5.5**	**0.30**	**0.1-0.4**	**0.0009**
	Worsening of heart failure before 14 days	**66**	**91**	**0.70**	**0.51-0.96**	**0.024**
	Total intravenous loop diuretic dose before day 5 (mg)	**161**	**213**	**-52.0**	**-88 to -15**	**0.006**
	Total oral loop diuretic dose before day 5 (mg)	193	183	10	-12 to 32	0.382
	Length of initial hospital stay (days)	**9.6**	**10.5**	**-0.9**	**-1.9 to 0.2**	**0.039**
	All-cause death or readmission to hospital for heart or renal failure before day 60	77.0	77.0	1.01	0.74-1.38	0.959
	Days alive out of hospital before day 30	20.9	20.4	0.5	-0.3 to 1.3	0.293
	Cardiovascular death before day 180	**35**	**55**	**0.63**	**0.41-0.96**	**0.028**
	All-cause mortality before day 180	**65**	**42**	**0.63**	**0.43-0.93**	**0.020**
	Days in intensive care unit or cardiac care unit	**3.5**	**3.9**	**-0.3**	**-1.1 to 0.5**	**0.029**
	Death before day 30	12.0	19.0	0.63	0.30-1.29	0.202
	Death or worsening heart failure or readmission to hospital for heart failure before day 30	90	110	0.79	0.60-1.04	0.089
	Cardiovascular death or readmission to hospital for heart or renal failure before day 30	43.0	40.0	1.1	0.70-1.66	0.726
	Cardiovascular death or readmission to hospital for heart or renal failure before 30 days after discharge	50	42.0	1.2	0.80-1.82	0.360

Source: Teerlink, J. R. et al., *Lancet*, 2013, 381, 29-39.
Positive results are highlighted in bold.

Three potential outcomes on PDUFA include full approval, accelerated (conditional) approval, and Complete Response letter. We examine these scenarios and their implications on TRV027:

- *Full Approval*: Should serelaxin receive full approval on its PDUFA, we believe this would a positive read-through for TRV027, as it would mean that FDA has a reasonably low bar for approval. While we see this scenario as unlikely, a full approval would mean that the FDA views dyspnea as clinically meaningful in AHF, and TRV027's Phase IIb trial explores that as an endpoint. It would also

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mean that the FDA views the 37% improvement in mortality at 180 days favorably despite that it was only an exploratory endpoint.

- *Accelerated approval*: Serelaxin could receive accelerated approval on the condition that RELAX-AHF-2 trial with cardiovascular death at 180 d met significance. We believe this to be the most likely outcome, as we believe the FDA may want to approve serelaxin given the clear lack of agents for the treatment of AHF. However, we expect the FDA to view the 37% improvement in mortality at 180 days with some scepticism and would want to see the findings confirmed in another trial, i.e. RELAX-AHF-2 (expected to complete sometime in mid-2016, according to ClinicalTrials.gov disclosure). Should the FDA lean towards wanting to see an improvement in survival, this endpoint could be incorporated into the Phase III design.

- *Complete Response*: The FDA may view serelaxin's data package as insufficient and require further studies. The FDA may simply not view dyspnea as clinically relevant, and may not see the mortality benefit as real. In this case, the FDA is likely to require the data from RELAX-AHF-2 before Novartis can file again, which may not occur until ~2017. Given the lack of effective treatments in AHF, we expect a low probability for this scenario. Nevertheless, in this scenario, TRVN would have to design the Phase III with care.

We explore some of the issues that may be discussed at the FDA Advisory panel:

- **How Relevant is Dyspnea in AHF?** Dyspnea (shortness of breath) is a very prominent and early symptom of AHF, causing extreme discomfort in patients. It is the principal symptom that will drive patients to seek medical assistance, and is often a sign of fluid overload. RELAX-AHF had two co-primary endpoints related to dyspnea. A key question for the FDA is the relevance of dyspnea to clinical benefit in HF. In RELAX-AHF, one of the endpoints evaluated dyspnea improvement were change from baseline in the visual analogue scale area under the curve (VAS AUC) to day 5 and the proportion of patients with moderate or marked dyspnea improvement by Likert scale during the first 24 h. Serelaxin showed a 19.4% improvement with a mean difference of 448 mm x hour (p=0.0075). However, there were no significant differences in the other primary endpoint of proportion of patients with dyspnea relief at 24 h (serelaxin 27% versus placebo 26%, p=0.70). Despite not having passed the latter endpoint, further analysis did show an improvement by day 5 (p=0.002). However, no studies in AHF have demonstrated a correlation of dyspnea to improvement in mortality. A *post-hoc* analysis of the PROTECT study of 303 AHF patients evaluating rolofylline (diuretic) showed an improvement in 60-day mortality but the authors admitted that larger trials are needed to confirm the findings (Metra, M. et al., *European Journal of Heart Failure*, 2010, 12, 499-507). One of the potential reasons for the lack of association between dyspnea and outcomes is that many of the drugs used to provide symptomatic relief may have concomitant effects on other areas that can modify mortality independently of its effects on dyspnea.

  Given that dyspnea is such a prominent and significant symptom of AHF, we expect the FDA will continue to view an improvement in dyspnea as clinically relevant whether a correlation to mortality exists. But the question that follows is which endpoint will the FDA give greater weight, dyspnea improvement as measured by VAS AUC or by Likert scale, where serelaxin showed benefit in the former but not the latter? VAS and Likert scale are the standard scales in

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measuring dyspnea in AHF, but may not be interchangeable in their assessment of dyspnea improvement in AHF. There is a lack of comparative information between these scales. TRV027's Phase IIb will investigate dyspnea by VAS AUC as part of its composite endpoint, but not Likert scale. The third question is what magnitude of benefit would be considered clinically meaningful. Serelaxin showed a 19% improvement with a mean difference of 448 mm x hour (p=0.0075). In the DOSE study investigating furosemide (high v. low dose), a significant improvement in the VAS AUC over 72 h for dyspnea was observed, and the effect size was a difference of 210 mm x h (p=0.04), less than what was observed in RELAX-AHF. Felker et al of the DOSE study showed no statistical differences in patients' global assessment of symptoms or mean change in the creatine level, and there was no difference in 60-day outcomes (death, rehospitalisation, or emergency room visit), suggesting that the dyspnea benefit observed in its trial had little relevance. Should the FDA view serelaxin's 19% improvement with a mean difference of 448 mm x h as meaningful, it could set a bar for TRV027.

- **What of the Mortality Benefit at 180 Days?** Interestingly, at six months in RELAX-AHF, cardiovascular deaths were significantly reduced in the serelaxin group at 180 days, 6% (n=35) in the serelaxin group versus 9.5% (n=55) (HR=0.63, CI 0.41-0.96, p=0.028, number needed to treat=29). Also, all-cause deaths during 180 days of follow up were reduced, 7.3% in the serelaxin group versus 11.3% in the placebo group (HR=0.63, 95% CI 0.43-0.93, p=0.02). A 37% reduction in all-cause mortality was observed even up to day 30, but was not significant (p=0.20). This result is consistent with the trend observed in Pre-RELAX-AHF (HR=0.53, p=0.16). Furthermore, when the results are combined in an exploratory analysis, the reduction in all-cause mortality at 180 d is confirmed (HR=0.62, p=0.0076; n=1,395) (Metra, M. et al., *J Am Coll Cardiol*, 2013, 61(2), 196-206). To our knowledge, this is the first trial to show a benefit on post-discharge mortality. But the trial was not designed or powered as a mortality trial, had a moderate number of death events and was an exploratory endpoint. Thus, while intriguing, it raises the question whether a confirmatory trial is needed. Mortality benefits earlier than 180 days did not reach statistical significance.

  We believe it is likely that the FDA will require Novartis to confirm the mortality results. Novartis has already begun enrolling patients for RELAX-AHF-2 for that purpose, with completion expected in mid-2016 (Clinicaltrials.gov disclosure). Under such a scenario, it would mean that the FDA is focused on improving mortality beyond short-term improvements in dyspnea. Given that serelaxin will set the bar, TRVN/FRX will have to consider how best to incorporate a mortality endpoint when designing their pivotal Phase III.

- **How Applicable is RELAX-AHF to the General AHF Population?** The AHF population can be heterogeneous. Part of the inclusion criteria of RELAX-AHF is that the systolic blood pressure had to be >125 mm Hg. Thus, the trial was enriched to investigate patients who are most likely to derive benefit from serelaxin while avoiding potential harm from unexpected hypotension. The patient population of RELAX-AHF may therefore not be representative of the general AHF population because it excludes patients with lower blood pressures at presentation. We note that TRV027's Phase IIb trial also requires systolic blood pressure of ≥120 mmHg as part of its inclusion criteria within 30 minutes of randomization, and this trial too is being enriched. We note that in the ADHERE registry of 187,565 patients presenting with AHF in U.S. hospitals, 186,805

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patients had blood pressure measured and 50% had systolic blood pressure >140 mm Hg. The patient population of the Phase IIb trial and RELAX-AHF thus still represents a significant portion of the general AHF population. Nevertheless, we expect this issue to be a topic of discussion at serelaxin's FDA panel meeting.

- **What is the Relevance of the Effects on Cardiac, Renal, Liver, and Decongestion Biomarkers?** Metra et al. conducted a *post-hoc* analysis of the effects of serelaxin on the cardiac, renal, liver, and decongestion biomarkers using the data from RELAX-AHF (Metra, M. et al., *J Am Coll Cardiol*, 2013, 61(2), 196-206). Serelaxin was found to significantly improve these biomarkers which are consistent with the prevention of organ damage. Furthermore, the authors showed that reductions in these biomarkers were all associated with lower mortality at 180 d, with exception of AST increase of ≥20% (Exhibit 7). While only a *post-hoc* analysis, it does support serelaxin as a differentiated product in AHF by improving certain parameters while avoiding widespread organ damage. We believe TRV027 can show similar findings in a large Phase IIb trial, and the FDA panel discussions for serelaxin can inform us as to whether the FDA will consider these changes as meaningful.

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Exhibit 6: Summary of serelaxin biomarker data from RELAX-AHF.

Variable	Serelaxin *n=581*	Placebo *n=580*	Treatment Effect	95% CI	p-value
Cardiac Damage					
hs-cTnT (µg/L)					
Relative change to day 2 (geometric mean change)	0.966	1.035	0.933	0.833-0.985	0.013
≥20% increase at day 2	16.5%	27.2%	0.530	0.39-0.71	<0.0001
Worsening renal function					
Serum creatinine (µmol/L)					
Mean change to day 2	-3.4	6.2	-9.5	-12.4 to -6.6	<0.001
≥0.3 mg/L (27 nmol/L) increase from baseline to day 2	10.9%	19.8%	0.50	0.35-0.70	<0.0001
Cystatin C (nmol/L)					
Relative change to day 2 (geometric mean change)	1.027	1.080	0.950	0.931-0.970	<0.001
≥0.3 mg/L (22 nmol/L) increase from baseline to day 2	16.0%	23.2%	0.63	0.46-0.85	0.0027
BUN (mmol/L)					
Change at day 2 (mmol/L)	0.2	0.8	-0.62	-0.96 to -0.28	<0.001
Uric acid (µmol/L)					
Change at day 2 (mmol/L)	-8.5	24.7	-33.0	-42 to -24	<0.001
Liver function					
ALT (U/I)					
Change at day 2 (mg/dL)	-6.4	-2.3	-4.16	-6.62 to -1.70	<0.001
≥20% increase at day 2	7.1%	11.4%	0.60	0.39-0.92	0.018
AST (U/I)					
Change at day 2 (mg/dL)	-7.6	-2.2	-5.33	-9.04 to -1.62	0.005
≥20% increase at day 2	7.0%	12.7%	0.51	0.33-0.79	0.0024
Albumin (g/L)					
Change at day 2 (mg/dL)	-1.3	-1.4	0.15	-0.23 to 0.53	0.450
Decongestion					
NT-proBNP (ng/L)					
Relative change to day 2 (geometric mean change)	0.492	0.607	0.81	0.753-0.876	<0.001
≥30% decrease from baseline at day 2	69.0%	58.0%	1.61	1.25-2.06	0.0002

Source: Metra, M. et al., *J Am Coll Cardiol*, 2013, 61(2), 196-206.

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Exhibit 7: Summary of serelaxin biomarker data from RELAX-AHF.

Biomarker Change from Baseline to Day 2	Death Through Day 180		HR	95% CI	p-value
	No	*Yes*			
Cardiac Damage					
Troponin (≥20% increase)	62/825 (7.6%)	30/231 (13.1%)	1.80	1.16-2.777	0.0076
Worsening renal function					
Creatinine (≥27 umol/L increase)	75/919 (8.2%)	23/167 (13.8%)	1.76	1.11-2.82	0.0160
Cystatin-C (≥22 nmol/L increase)	66/869 (7.7%)	32/212 (15.2%)	2.10	1.38-3.20	0.0004
Liver function					
AST (≥20% increase)	73/906 (8.1%)	13/99 (13.4%)	1.66	0.92-3.00	0.099
ALT (≥20% increase)	79/970 (8.2%)	15/99 (15.3%)	1.96	1.13-3.40	0.015
Decongestion					
NT-proBNP (≥30% decrease)	53/395 (13.5%)	45/686 (6.6%)	0.47	0.31-0.69	0.0001

Source: Metra, M. et al., *J Am Coll Cardiol*, 2013, 61(2), 196-206.

- **What Other Endpoints Could the FDA Find Clinically Meaningful Besides Mortality?** Given the clear paucity of effective agents in AHF, the FDA may consider other endpoints as clinically meaningful besides mortality. Such endpoints could include worsening of heart failure, length of hospital stay, total loop diuretic use, or reduction in readmission to hospital. Serelaxin did show an improvement in worsening of HF out to day 14 (HR=0.70, p=0.024), which could be highlighted at the FDA panel meeting. No previous study in AHF, including RELAX-AHF, has been able to show a significant reduction in readmission to hospital. The FDA panel could discuss several other possibilities, which TRVN may incorporate into their Phase III design.

- **Criticisms from CHMP Could Provide Insight**. In January 2014, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) took a negative stance on serelaxin for AHF, questioning the benefit of serelaxin for short-term dyspnea relief beyond 24 hours. Some benefit was shown over 5 days, but it was not clear this had clinical relevance. The CHMP also had concerns about the way the effectiveness in the study had been analyzed, describing that the results included calculated values for patients who had died or required additional treatment for worsening symptoms, and were excluded from the analysis. Furthermore, the CHMP questioned whether differences in background therapy between the active and placebo arms could have led to the differences. These issues could also be brought up during the FDA panel. Should the FDA reject serelaxin on the basis of trial design only, we believe this portends a favorable outlook for TRV027 since TRVN/FRX can avoid these pitfalls and adjust the Phase III appropriately. Novartis only included the RELAX-AHF study in the application and the CHMP recommended further studies be carried out to clarify its benefit. Novartis will submit a revised filing package with new data analyses for re-examination for conditional approval of serelaxin. A revised opinion could be granted later in Q2 2014.

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Early TRV027 Data Shows Improvement in Arterial Pressure, and May Not Compromise Renal Function

Phase IIa. TRV027 was investigated in a Phase IIa hemodynamics trial in advanced stable heart failure patients. The study enrolled 33 patients in 15 centers in the U.S. and Europe. The trial investigated three groups of patients: TRV027-treated high-PRA>5.82 (n=11), TRV027-treated normal-PRA <5.82 (n=13), and placebo (n=8). "PRA" stands for plasma renin activity and is a measure of the plasma enzyme renin, which plays a role in the regulation of blood pressure and urine output. A PRA level of 5.82 is the upper limit of normal for laboratory. Increased PRA may indicate activated RAS and reflect HF severity (Verna, S. et al. *European Heart Journal*, 2011, 32, 2135). Patients with high-PRA are expected to be representative of the HF patients in the Phase IIb trial.

Patients in the Phase IIa study were treated with either TRV027 (1.0, 3.0, and 10 µg/kg/min maximum dose levels) or placebo and dose-escalated in the first two hours, followed by ten hours of continuous steady-state infusion and a subsequent washout period (at hour 14). In the dose-escalation portion of the study, TRV027's dose-response relationship in high-PRA patients is comparable to the dose-response observed in HF dogs with respect to mean arterial pressure (MAP).

TRV027 was shown to have a clear effect in reducing MAP and potentially pulmonary capillary wedge pressure (PCWP) in patients with high-PRA. The decline in MAP was greater in the TRV027-treated high-PRA patients than placebo or TRV027 normal-PRA patients (although not observed for PCWP). PCWP was reduced in patients with high-PRA during the dose-escalating phase and was sustained in the maintenance phase, although the separation is not as clear-cut due to baseline drift in the placebo group (Exhibit 9). Additionally, when TRV027 was discontinued at hour 14 (washout period), the effects on MAP and PCWP reversed direction, indicating *reversibility*, which is a desirable feature in case of unexpected hypotension. The reversal effect of TRV027 on PCWP in the high-PRA patients was statistically significant versus those with normal-PRA (Exhibit 8).

TRV027 appeared safe and well-tolerated in patients with advanced heart failure, and did not adversely affect heart rate (HR), cardiac index (CI), or biomarkers, including cystatin-C, BNP, Ang II, PRA, or creatinine in normal PRA subjects. An increase in Ang II and PRA in high-PRA patients was observed. Cystatin-c and creatinine, which are biomarkers of renal function, were stable in either normal-PRA or high-PRA patients, suggesting that renal function is preserved. CI is an accepted hemodynamic parameter and measure of heart functioning by correlating the volume of blood pumped by the heart (cardiac output) with body surface area (BSA), therefore it appears that cardiac function from TRV027 is also preserved.

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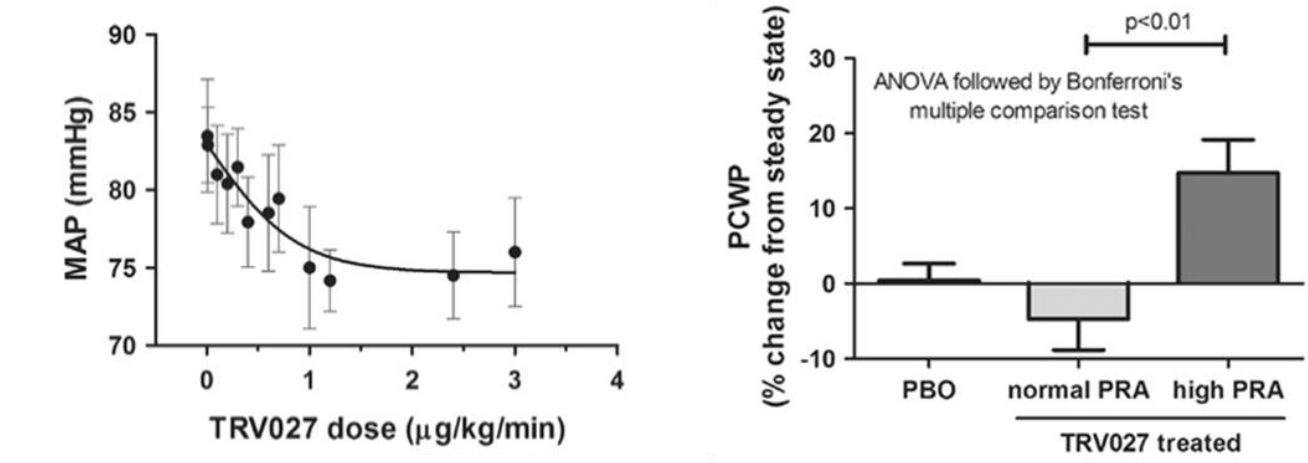
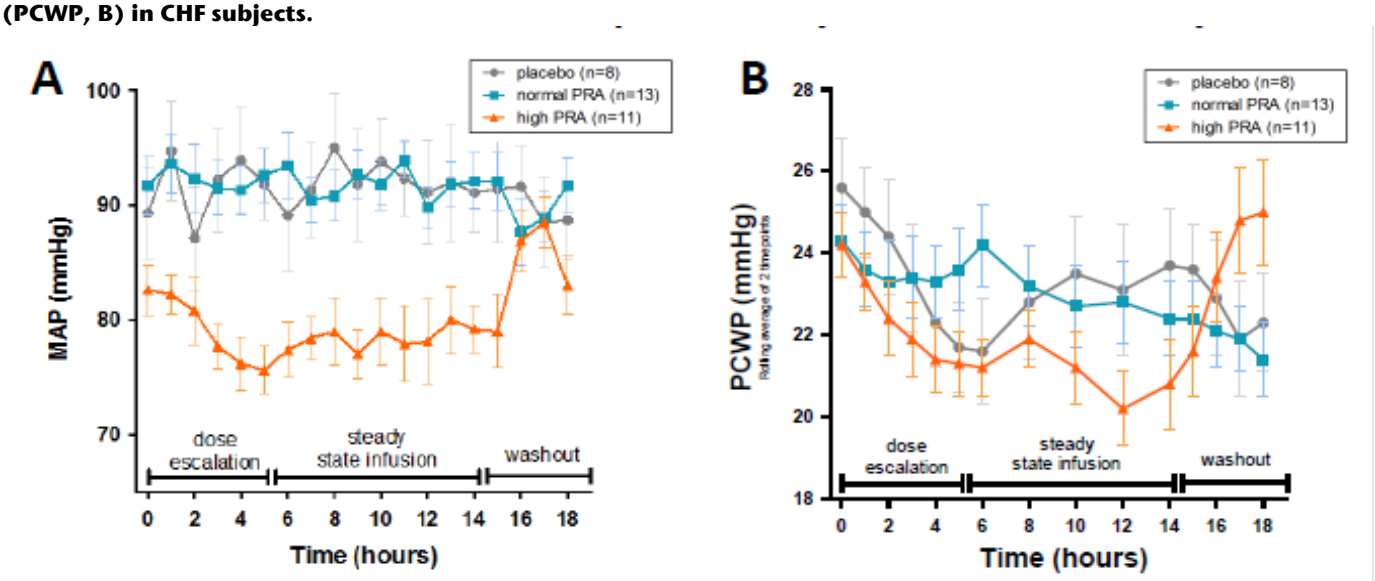
Exhibit 8: TRV027's dose-response with respect to mean arterial pressure (MAP) and pulmonary capillary wedge pressure (PCWP) in advanced stable heart failure patients with elevated PRA.



Source: Soergel, D. G. et al. *J Am Coll Cardiol*. 2013, 61, 10, Suppl A, 1221-284; Company data.
PRA=plasma renin activity
Note: Two of three high-PRA patients in cohort 3 had dosing errors, and were therefore excluded from the analysis.

Exhibit 9: TRV027's effect on mean arterial pressure (MAP, A) and potentially pulmonary capillary wedge pressure (PCWP, B) in CHF subjects.



Source: Soergel, D. G. et al. *J Am Coll Cardiol*. 2013, 61, 10, Suppl A, 1221-284; Company data.
PRA=plasma renin activity

TRV027 Well-tolerated in Renally-Impaired Patients. In a Phase Ib renal safety trial in 17 stable chronic HF patients (history of HF and concomitant renal dysfunction). TRV027 was investigated at 1.25, 6.25, and 31.25 mg/hr (equivalent to 0.35 ug/kg/min, 1.74 ug/kg/min, and 8.68 ug/kg/min, respectively, for a 60 kg person) without weight correction, and co-administered with furosemide, a diuretic. TRV027 was well-tolerated and there were no treatment-related serious adverse events reported. Furosemide can cause reduction in GFR that can be inhibited by blocking effects of elevated Ang II. In this trial, no effect of single dose of furosemide was observed on GFR or RPF, therefore a renal

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protective effect could not be demonstrated. But GFR and RPF was preserved by TRV027, and co-administration did not impair furosemide's effect on diuresis or urinary sodium excretion.

Collaboration Agreements

Forest Laboratories: TRVN entered into an option and license agreement with Forest Laboratories in May 2013 in which it granted Forest an exclusive option to license TRV027, which may be exercised at any time before the Phase IIb trial results and during a specified period of time thereafter. If Forest exercises its option, the license agreement becomes effective and Forest will have exclusive worldwide rights to develop and commercialize TRV027 and specified related compounds. Forest will be responsible for development, regulatory submissions/approval and commercialization. TRVN is conducting the Phase IIb trial at its own expense, and under the oversight of a joint development committee with equal number of representatives from TRVN and Forest. TRVN expects data from the Phase IIb trial in H2 2015. During the option period, TRVN may not negotiate or enter into another agreement with the third party for TRV027.

Forest has the right to renegotiate the terms of the license agreement. If Forest does not exercise the option, it will expire and TRVN would be free to enter into a new collaboration agreement with another party. If Forest chooses to exercise the option, Forest will have exclusive rights under the license agreement, and will develop and commercialize TRV027 under its own expense. Forest will consider in good faith whether to grant TRVN the right to co-promote in the U.S. but is not obligated to do so. TRVN could receive up to $430 million in the aggregate, including an option exercise fee of $65 million and milestone payments depending on the achievement of future development and commercial milestones. TRVN could also receive tiered royalties between 10-20% of net sales of licenses products worldwide. Royalty rates on net sales in the U.S. may be somewhat higher than those outside the U.S., although TRVN has not disclosed what the royalty rates may be. If Forest exercises the option, both TRVN and Forest have the right to terminate the license agreement and all licenses granted to Forest would terminate. If not terminated, the license agreement would remain in effect until expiration of the last royalty term.

Competitive Landscape

Novartis' Reasanz (serelaxin). Reasanz (serelaxin) would be TRV027's primary competitor in AHF. Serelaxin is a recombinant form of human relaxin-2, a peptide hormone that increases during pregnancy and mediates cardiovascular and renal adaptations in the mother, leading to increased arterial compliance, cardiac output, and renal blood flow. Serelaxin is being investigated in clinical trials for the treatment of AHF, since it binds to the receptors for relaxin in the blood vessels, causing the vessels to relax and widen and relieving the symptoms associated with AHF. The PDUFA date is expected in Q2 2014 (date not yet disclosed).

We have described serelaxin's data from RELAX-AHF trial and its controversies, and their implications to TRV027. Without analogous trials, it is difficult to compare efficacy between serelaxin and TRV027. We expect the FDA's Cardiovascular and Renal Drugs Advisory Committee to meet within the next 1-2 months following a cancellation on February 13, 2014, which will have implications on both products. In Europe, following the negative opinion on January 2014 by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), Novartis will submit a revised filing package with new data analyses for re-examination for conditional approval of serelaxin. A revised opinion could be granted in Q2 2014. If granted, the conditional approval would be conditional on meeting the primary endpoint of RELAX-AHF-2.

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RELAX-AHF-2 is a large, double-blind, placebo-controlled Phase III trial investigating serelaxin as an add-on to standard therapy in 6,375 AHF patients. The primary endpoint will be time to confirmed cardiovascular (CV) death during the follow-up period of 180 days. The study started in October 2013, and expected to complete in mid-2016. Beyond RELAX-AHF-2, Novartis is also running a Phase III European trial similar to RELAX-AHF known as RELAX-AHF-EU and another in Singapore investigating serelaxin added to standard-of-care in AHF.

Cardiorentis' ularitide. Cardiorentis (private) is developing ularitide, a natriuretic peptide, for AHF. Ularitide is a synthesized form of urodilatin, a human natriuretic peptide produced by the kidneys to regulate fluid balance and Na^+ hemostasis. Ularitide binds the natriuretic peptide receptor A, increasing intracellular cyclic guanosine monophosphone (cGMP) which leads to vasodilation and natriuresis and increasing blood flow.

Ularitide was investigated in a Phase IIb study (SIRIUS II) which was a placebo-controlled, double-blind, parallel-group study randomizing 221 patients with AHF to one of three doses of ularitide: 7.5 ng/kg/min (n=60), 15 nk/kg/min (n=53), and 30 ng/kg/min (n=55) or placebo (n=53). Ularitide and placebo were added on top of standard therapy. At 6 hours, 10.3-17.6% in change in dyspnea was observed in the three ularitide groups v. 34.0% in the placebo group. A greater proportion of subjects in the 7.5, 15, and 30 ng/kg/min dose reported marked or moderate improvement in self-assessed dyspnea v. placebo (39.7%, 47.1%, and 45.5% v. 24.5%, respectively) ($p<0.05$). All three doses of ularitide produced greater decrease in pulmonary capillary wedge pressure (PCWP). Also, the median time of hospitalization was shorter for the 15 and 30 ng/kg/min ularitide groups (122 and 158 h, respectively) v. placebo and 7.5 ng/kg/min dose (201 and 192 h, respectively). Mortality at Day 30 was also improved in the ularitide group v. placebo (3% across all dose groups and 13.2%, respectively). The most frequent drug-related adverse events included hypotension, sweating, dizziness, asthenia, headache, and decreased heart rate.

Ularitide is now being investigated in a Phase III study (TRUE-AHF) for 2,152 patients hospitalized for AHF. Ularitide will be investigated at 15 ng/kg for 48 h on top of standard-of-care. The primary endpoint will be an assessment of the clinical composite performed at 6, 24, and 48 h after ularitide IV infusion. Patients will be classified as 'improved' if they are: moderately or markedly improved at all three time points and do not fulfill criteria for 'worse' during the first 48 h (death, worsening heart failure, or moderate to marked worsening of their global assessment). The primary safety endpoint is all-cause mortality and cardiovascular re-hospitalization at Day 30 after start of infusion. The estimated completion date is around March 2015, according to ClinicalTrials.gov disclosure.

Amgen's AMG-423 (omecamtiv mecarbil). Amgen (AMGN, $124.36, Buy)/Cytokinetics (CYTK, $10.06, NC) are developing omecamtiv mecarbil, a small-molecule activator of cardiac myosin. It is in a broad clinical program in HF, including acute heart failure (ATOMIC-AHF) and chronic heart failure (COSMIC-HF). For AHF, the Phase IIb trial ATOMIC-AHF has been completed and results have been presented in September 2013. The primary endpoint of this trial was to evaluate the effect of 48 hours of treatment with IV omecamtiv mecarbil v. placebo on dyspnea (on 7-point Likert scale) in 613 patients with left ventricular systolic dysfunction AHF. The trial tested 3 dose cohorts (115 ng/mL, 230 ng/mL, and 310 ng/mL). Patients hospitalized w/ a history of heart failure and LVEF ≤ 40%, dyspnea due to HF at rest or w/ minimal exertion ≥ 2 hours after IV diuretic were enrolled in the trial. The trial excluded patients w/ a BP > 160/100 or SBP < 90 mm Hg.

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The trial defined dyspnea response as minimally, moderately, or markedly better at 6 hours and moderately or markedly better at 24 and 48 hours without worsening heart failure or death at 48 hours. Omecamtiv mecarbil treatment groups were not statistically different from the placebo group (p=0.33), however, cohort 3 observed an improvement in dyspnea (51% vs 41%; OR = 1.23) when compared to the pooled placebo response. However, when comparing vs. paired, cohort 3 observed a dyspnea response in 51% v. 37%, respectively (nominal p=0.03; OR = 1.41), and provides rationale to support a potential Phase III program. Death or worsening heart failure at day 7 were significantly lower across all 3 cohorts vs placebo. Omecamtiv mecarbil also did not show statistical significance in other endpoints, such as incidence of worsening heart failure within 7 days and median length of hospital stay. Rates of adverse events, serious adverse events, adjudicated deaths and hospitalizations were similar between groups.

A potential Phase III decision is expected in H1 2014. But as a cardiac myosin activating inotrope, it would be possible to combine omecamtiv mecarbil with TRV027 for potential synergies. Additionally, omecamtive mecarbil is also being developed as an orally delivered agent, and with the goal of moving both the intravenous and oral program into a Phase III program at the same time.

Background

About TRV027

TRV027 is a novel polypeptide β-arrestin-biased ligand that targets the angiotensin II type I receptor (AT1R). AT1R is part of a well-known class of cardiovascular G-protein-coupled receptors (GPCR), which are the largest class of therapeutic medicinal targets, accounting for ~1/3 of marketed pharmaceuticals (DeWire, S. M. et al., *Circulation Research* 2011, 109, 205-216). GPCR signaling can activate distinct signals, many of which are mediated by β-arrestins. Studies have shown that in knockout mice lacking β-arrestin or AT1Rs, their hearts failed to induce responses to mechanical stress, suggesting that β-arrestin may be cardioprotective (Rakesh, K. et al., *Sci Signal*. 2010, 3, 125: ra46). These findings led to the hypothesis that *biased ligands* could be used to antagonize certain AT1R functions while simultaneously stimulating others, allowing for functional selectivity.

As a biased ligand, TRV027 stabilizes distinct receptor conformations of AT1R, antagonizing G protein coupling while simultaneously stimulating β-arrestin mediated signaling. TRV027 competes with angiotensin II (Ang II), a peptide hormone that causes vasoconstriction and aldosterone secretion resulting in increasing blood pressure. It is a key product from the renin-angiotensin system (RAS), and elevated levels of Ang II are common in patients with HF. Increased blood pressure, initially to help compensate for heart failure, puts further strain on the heart, leading to worsening of the heart disease. A comparison of responses from TRV027 compared to a full agonist and full antagonist is shown in Exhibit 10.

Exhibit 10 shows the effect of Ang II to AT1R, resulting in vasoconstriction and increased blood pressure and cardiac work, putting further strain on cardiac function. TRV027, on the other hand, is competitive with Ang II at the AT1R and activates only the β-arrestin pathway, resulting in reduced Ang II-mediated hypertension, increased cardiac contractility, and increased cardiac performance. Indeed, TRV027 was able to demonstrate increased contractility in isolated murine cardiomyocytes and promotion of cardiac performance in vivo.

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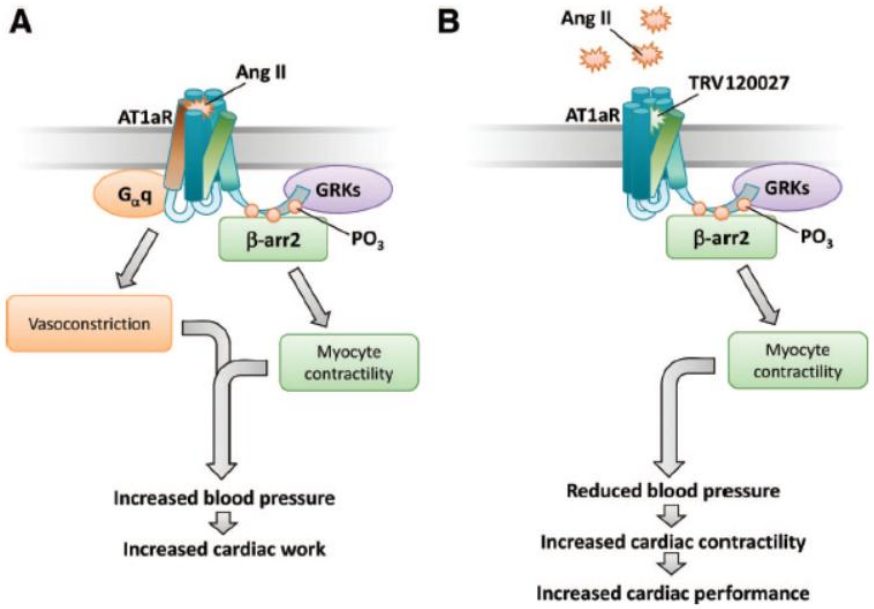
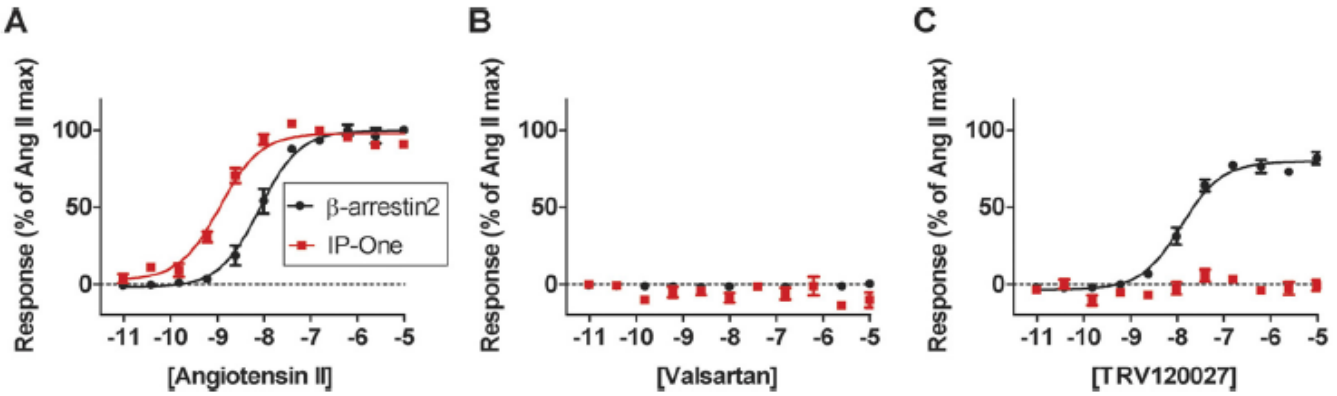
Exhibit 10: Mechanism and physiological effects of Ang II (A) versus TRV027 (B).



Source: DeWire, S. M. et al. *Circ Res*, 2011, 109, 205-216.

Exhibit 11: Comparison of responses from a full agonist (Ang II, A), a full antagonist (Valsartan, B), and a β-arrestin biased ligand (TRV027, C).



Source: Violin, J. D. et al., *Journal Pharmacology and Experimental Therapy*, 2010, 335, 572; Company data.
Note: Measure of β-arrestin2 recruitment (black circles) and G-protein coupling (red squares)

TRVN has an active IND for TRV027 for AHF since February 2010. TRVN has completed three clinical trials for TRV027: a Phase IIa study for patients with advanced stable heart failure, a Phase Ib study for patients with moderate heart failure and concomitant renal dysfunction, and a Phase I PK and tolerability trial in healthy subjects.

TRV027 showed in a single-center Phase I trial that it was safe and well-tolerated in 20 healthy subjects at doses ranging from 0.01 to 20 µg/kg/min (Soergel, D. G. et al., *The Journal of Clinical Pharmacology* 2013). No serious adverse events or clinically significant adverse events were reported in doses up to 20 times higher than expected therapeutic

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dose. A linear dose-response was observed, and TRV027 was rapidly cleared when infusion was ceased, indicating rapid reversibility. TRV027 also had a short-life (2.4-13.2 minutes). There was no urinary excretion of TRV027. Four subjects were subjected to salt restriction to induce measurable elevation in RAS (PRA ≥3 ng/hr/mL). Because salt restriction stimulates the renin-angiotensin system (RAS) which increases Ang II and activation of the AT1R, salt restriction is often used to test the pharmacological effects of agents inhibiting RAS. Modest decreases in MAP were observed in three of the four subjects, and no change in MAP was seen patients with normal PRA. TRV027 may thus help relieve load on the heart only in patients with elevated RAS.

Animal Data. TRV027 demonstrated benefits in a canine heart failure model. In the study, TRV027 was investigated in both healthy (n=4) and HF (n=6) dogs. TRV027 reduced blood pressure and pulmonary capillary wedge pressure while promoting cardiac output and preserving kidney function, in all cases with statistical significance. The data from the study are summarized in Exhibit 12. Additionally, upon discontinuation of TRV027, MAP quickly increased to baseline after 10 min, indicating rapid reversibility. The data is directionally quite encouraging, although care must be taken in extrapolating the effects to human patients.

Exhibit 12: Data summary of TRV027 on healthy and HF dogs.

	Healthy Dogs (n=4)	*p-value*	HF Dogs (n=6)	*p-value*
Δ Mean Arterial Pressure (MAP)	↓	0.008	↓	<0.0001
Δ Pulmonary Capillary Wedge Pressure	↓	<0.0001	↓	<0.0001
Δ Cardiac Output	↑	<0.0001	↑	0.012
Δ Renal blood flow	↑	<0.0001	↑	<0.0001
Δ Renal vascular resistance	↓	<0.0001		
Δ Plasma Renin Activity	↑	0.0027		
Δ Filtration Fraction			↓	0.0004
Δ Aldosterone			↓	0.0034

Source: Boerrigter, G. et al, *Circulation: Heart Failure* 2011, 4:770-778; Company data.

TRV027's effect on mean arterial pressure (MAP) and cardiac contractility was demonstrated in normal rats and compared to telmisartin, an ARB that inhibits both G-protein and β-arrestin AT1R pathways (Violin, J. D. et al., *The Journal of Pharmacology and Experimental Therapeutics*, 2010, 335, 3, 572-579). TRV027 was able to show increased cardiac contractility independent of its effects on blood pressure.

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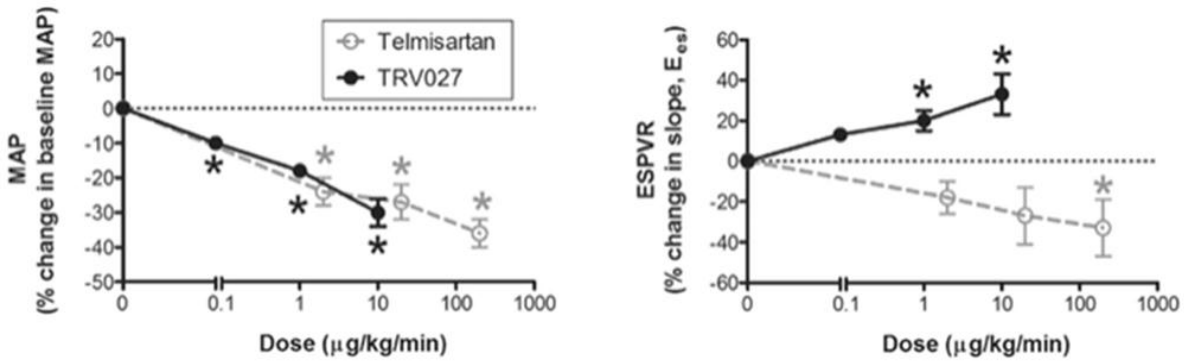
Exhibit 13: TRV027's effect on mean arterial pressure (MAP) and cardiac contractility in rats.



Source: Violin, J. D. et al., *The Journal of Pharmacology and Experimental Therapeutics*, 2010, 335, 3, 572-579; Company data.

Patent Estate: TRV027 is protected by a composition-of-matter (COM) patent (8,486,885) that grants protection until July 2031. Methods-of-use and broader composition claims are being pursued in U.S. applications. Foreign applications are pending in Australia, Canada, China, Europe, Hong Kong, India, Japan, and New Zealand.

About Acute Heart Failure (AHF)

Heart failure (HF) refers to the condition where the heart is unable to provide sufficient action to maintain blood flow to the rest of the body and lungs (insufficient cardiac output). It is estimated that >1.1 million hospitalizations due to heart failure (HF) have occurred in 2004, and it is the leading cause of hospitalization in patients >65 years of age (Fang, J. et al., *J Am Coll Cardiol*. 2008, 52, 428-434; McCullough, P. A. et al., *J. Am Coll Cardiol*. 2002, 39, 60-9). Chronic heart failure (CHF) is a persistent and progressive condition that worsens over time. Acute heart failure (AHF) is characterized by a significant worsening of HF signs and symptoms (such as dyspnea and fluid build-up), primarily from severe pulmonary congestion, which generally lead to hospitalization. CHF can be punctuated by acute heart failure (AHF). AHF can be life-threatening.

Concurrent conditions of HF include coronary heart disease (CHD), hypertension, valvular heart disease, atrial arrhythmias, renal dysfunction, diabetes and anemia which can precipitate or complicate AHFS. The clinical classification for AHF is as follows: 1) worsening chronic HF with reduced or preserved LVEF which account for ~70% of all admissions; 2) de novo HF (i.e. after large myocardial infarction, or sudden increase in blood pressure on non-compliant LV) which account for ~25% of admissions, and 3) advanced or refractory HF with severe LV systolic dysfunction, accounting for ~5% of admissions.

Pathophysiology. HF is caused by any condition which reduces the pumping efficiency of the heart, either through damage (i.e. myocardial infarction) or overload. Causes of HF include ischemic heart disease, and less frequently, cigarette smoking, hypertension, obesity, diabetes, and valvular heart disease. As a compensatory mechanism, the renin angiotensin system (RAS), the hormone system that regulates blood pressure and fluid balance, is activated in HF. RAS contributes to the maintenance of perfusion of vital organs by increasing levels of angiotensin II (Ang II), a peptide hormone that causes vasoconstriction and stimulates release of aldosterone from the adrenal cortex, which promotes sodium (Na^+) retention in the distal nephron in the kidney. Both actions increase blood pressure.

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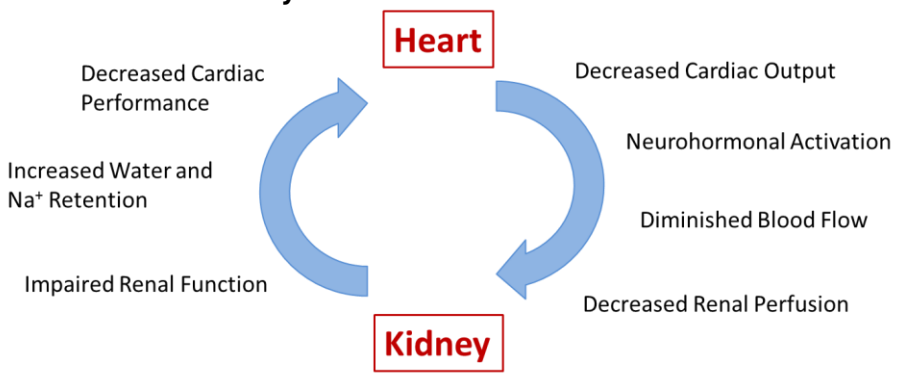
The increased blood pressure has maladaptive consequences. Vasoconstriction and fluid retention increases hydrostatic pressure in the capillaries, which increases interstitial fluid formation, promoting pulmonary congestion and peripheral edema. The increased volume load also puts further strain on the myocardium, leading to worsening of the ischemic heart disease. Each AHF episode results in worsening health and damage to vital organs, including potential renal impairment, decreasing the likelihood of survival during subsequent AHF episodes. The one-year mortality rate is ~30% (ADHERE Heart Failure Registry).

Exhibit 14: Cardiorenal Syndrome of HF



Source: Medscape.org (adapted).

Diagnosis. Rapid diagnosis of AHF is necessary to initiate appropriate treatment, but signs and symptoms often overlap with other conditions, such as chronic obstructive pulmonary disease. Signs and symptoms of AHF can include severe breathlessness, rapid weight gain, and fluid build-up in the lungs (often gives the sensation of drowning) and around the body. Patients suspected of AHF will be physically examined for elevated jugular venous pressure, peripheral edema or ascites, rales, hypoxia or tachypnea, tachycardia, arrhythmia, diffuse point of maximal intensity, ventricular filling gallop, atrial gallop, cool extremities above the hands and feet, and poor urine output.

Treatment. The treatment paradigm for AHF has not changed significantly in the past several decades, and is limited to angiotensin receptor blockers (ARB's), intravenous nitrates, inotropes, and diuretics/loop diuretics. Furthermore, none of the currently approved therapies improve long-term outcomes, and some, in fact, have been associated with poorer outcomes.

Angiotensin II receptor antagonists, or angiotensin receptor blockers (ARBs) are a class of compounds used to treat hypertension, diabetic nephropathy, and heart failure, particularly when the patient is intolerant to ACE inhibitor therapy. Common ARBs include losartan and valsartan. ARBs directly block both the GPCR and β-arrestin at the AT1R.

Diuretics in general can help relieve congestion. Loop diuretics were introduced in the 1960's which act on the ascending loop of Henle in the kidney and block channels and vasodilators, which relax the blood vessels. Loop diuretics are used over typical diuretics because they produce significantly more natriuresis (excretion of sodium in the urine). While successful at offloading fluid, loop diuretics further activate RAS, countering the diuretic effect and negatively affecting kidney function. There is an increasing prevalence of diuretic-resistant patients, so there is interest in alternative approaches to diuresis. If all diuretic strategies prove unsuccessful at reducing volume overload, the physician may consider ultrafiltration.

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Vasodilators are used in the treatment of AHF by reducing congestion. The difficulty with vasodilators is that they must be titrated slowly to reduce risk of unexpected hypotension, because reversibility is slow. Natrecor (nesiritide) was approved in 2001 for AHF but recently its benefit in dyspnea has been put into question (ASCEND-HF), and meta-analyses and other trials have suggested that Natrecor may worsen renal function (Teerlink, J. R. et al., *Circulation*, 2005, 111, 1459-1461) and decrease survival at 30 d versus other typical therapies (Sackner-Bernstein, J. D. et al., *JAMA*, 2005, 293, 1900-1905). Other vasodilators include nitroglycerin and Nitropress (nitroprusside). Morphine may also act as a venodilator and mild arterial dilator, but no studies in AHF have been performed to demonstrate its benefit.

Intravenous nitrates and inotropes were approved for AHF patients during the 1970's and 1980's and are still part of current treatment. These agents work by relaxing the blood vessels, thereby increasing the number of contractions in the heart. Inotropes, however, have been associated with increased mortality (ALARM-HF registry and OPTIME-CHF study).

Exhibit 15: Initial Therapeutic Management of AHF

Target	Therapeutic Example	Mechanism of Action	Side Effects
Alleviate congestion	IV furosemide	Water and sodium excretion	Electrolyte abnormalities
Reduce elevated LV filling pressures	IV nitriates	Direct relaxation of vascular smooth muscle cells	Hypotension, decreased coronary perfusion pressure
Poor cardiac performance	Inotropes	Activate camp or calcium sensitization resulting in improved contractility; vasodilators, inodilators	Hypotension, arrhythmias, myocardial damage, association with increased morbid events
Tachycardia and increased systemic BP	Beta-blockers: IV esmolol may be used when HF is related to AF with RVR and/or severe hypertension	Blockade of beta-1 and beta-2 receptors	Bradycardia, hypotension, negative inotropy; but side effects are short-lived given short half-life of esmolol

Source: Pang, P. S. et al., *European Heart Journal*, 2010, 31, 784-793; Khan, S. S. et al., *Am J Manag Care*, 2008, 14 (Suppl. 12 Managed): S273-S286 (adapted).

TRV130

Post-Operative Pain

TRV130 is Early-Stage, But Could be a Potential Game-Changer in Post-Operative Pain Management

Trevena is developing TRV130 as a first-line treatment for patients experiencing moderate to severe acute post-operative pain. As a "biased ligand," Trevena hopes that TRV130's mechanism will allow for more effective analgesia while reducing these adverse events as respiratory suppression and constipation commonly associated with opioids. Such a therapeutic profile would offer clear advantages over standard-of-care, which could help expedite recovery and hospital discharge, and ultimately reduce hospital costs. Early Phase I and preclinical data have been supportive, where TRV130 showed superior analgesia compared to high-dose morphine, while reducing the risk of respiratory depression, and observing lower rates of nausea and vomiting.

The next steps for TRV130 include starting a Phase II study to confirm earlier findings, which we expect in Q2 2014. Although the design of the trial remains to be finalized, Trevena has disclosed it intends to use a bunionectomy pain model for the Phase II that will be a comparative study with morphine. TRVN also may explore another pain model as well in a separate trial in H2 2014. Assuming positive data in the Phase II bunionectomy

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study expected H1 2015 and in the subsequent pivotal Phase III trial, we estimate TRV130 approval in 2019 and total risk-adjusted peak net sales (65% risk discount) for in- and out-patient surgery patients of $205 million by 2031. TRV130 is unpartnered and Trevena has retained all development and commercialization rights worldwide. At this time, Trevena intends to retain full commercialization rights in the U.S. but may consider partnership with collaborators to commercialize outside the U.S.

U.S. Market Opportunity

Market Opportunity in Post-Operative Pain. The initial market opportunity for TRV130 is likely to be in the acute care hospital setting with a focus on postoperative pain. We estimate the number of in-patient procedures in the U.S. with intravenous (IV) opioids at ~14 million in 2015. We estimate ~75% of those patients (10.5 million) have surgery, and the remaining ~25% do not (3.5 million). Assuming positive data from a pivotal Phase III trial, we estimate TRV130 approval in 2019. We assume a net price per day of $63.75 (after a 15% gross-to-net adjustment from $75/day). For inpatients, we assume 1.8 days of therapy. For outpatients, we assume 0.25 days of therapy. Under these assumptions, we estimate total peak net sales for in- and out-patient surgical patients at $585 million in 2031 on an unadjusted-basis ($562 million for in-patient and $22 million for out-patient). Applying a 65% discount rate to reflect the risk associated with this early stage asset, we estimate risk-adjusted peak sales of $205 million by 2031.

TRV130 - Potential for Potent Analgesia and Fewer Adverse Events

TRV130 is a small-molecule biased ligand that has G-protein coupling efficacy at the μ-opioid receptor but also reduced efficacy for β-arrestin2 coupling. Trevena hopes that TRV130's mechanism will allow for more effective analgesia while reducing adverse events as respiratory suppression and constipation commonly associated with opioids. Trevena has an active IND for TRV130 moderate to severe acute with the FDA since January 2012. TRV130 has shown supportive data in three Phase I clinical trials in 110 healthy patients and in preclinical studies, and Trevena intends to move forward with a Phase II trial.

Next Steps – Designing a Phase II. Trevena is currently considering how to design the Phase II development program for TRV130, and expects to initiate a Phase II trial in Q2 2014 for post-operative pain. It also expects to initiate two additional Phase II trials to compare TRV130's safety and tolerability profile with unbiased μ-opioid agonists.

When evaluating a drug for acute surgical pain, the company must decide on the type of surgery to be used, and can include: dental extraction, bunionectomy, joint replacement (JRS), and soft tissue surgery (STS). Trevena has decided on a bunionectomy (bony) pain model for the Phase II, a commonly used and validated model. The model relies on surgical pain generated by the correction of hallux valgus deformities of the first metatarsal, and the pain tends to be severe and of sufficient duration to measure multiple-day efficacy. Various Phase II trials within the past 5-6 years and their study designs are outlined in Exhibit 16. Many of the Phase II trials were randomized, double-blind, placebo-controlled trials recruiting approximately fifty to several hundred patients, but Trevena has disclosed that the trial will be a comparative (head-to-head) trial with morphine. If TRV130 can demonstrate non-inferiority to morphine with respect to efficacy but have improved tolerability, we believe Trevena may have a convincing data package to submit to the FDA. It is also possible that TRV130 could demonstrate greater efficacy if more TRV130 could be titrated without side effects, since morphine is frequently stopped due to nausea and constipation. Furthermore, a non-inferiority study may avoid the complication of a placebo-controlled pain trial, where placebo response rates can be very high which translates to a more difficult hurdle for the active group. The primary endpoint for many of the Phase II bunionectomy trials was commonly sum of pain

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intensity differences (SPID) at various time points such as at 24 hours or 48 hours (i.e. SPID24 or SPID48, respectively).

A potentially close proxy is the Phase II trial (CLIN2003) that investigated CR845 by Cara Therapeutics (private company) that recently reported positive data in October 2013. The trial was a randomized, double-blind, placebo-controlled trial and enrolled 51 patients at one clinical site in Salt Lake City, Utah. The primary endpoint of the trial was 24-hour summed pain intensity differences (SPID24), and secondary endpoints included use of rescue opioid analgesics during the post-operative period. The patients were enrolled if they achieved a certain VAS baseline score on the following morning after surgery and after the local nerve block had worn off. Fentanyl was available as "rescue" medication for any patient not reporting adequate pain relief vs morphine because fentanyl is shorter-acting. TRV130's Phase II could have a similar design, although a key difference is that TRV130's trial will be a comparative non-inferiority trial with morphine and not placebo-controlled. Given the Phase I data, we expect Trevena to test doses at 3.0-4.0 mg/hr IV (4.0 mg/hr was MTD), which appeared to have better therapeutic indices over high-dose morphine (10 mg).

TRV130 is unpartnered and Trevena has retained all development and commercialization rights worldwide. At this time, Trevena intends to retain full commercialization rights in the U.S. but may consider partnership with collaborators to commercialize outside the U.S.

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Exhibit 16: Designs of recent Phase II trials investigating agents in post-operative pain following bunionectomy.

Drug	Company	MoA	Trial Design	Patient	*n*=	Tx Arms	Primary Endpoint	Secondary Endpoints	Status
CR845	Cara Therapeutics	Peripheral kappa receptor agonist	Single-center, randomized, double-blind, placebo-controlled	Postoperative pain following bunionectomy	51	CR845 v. pbo	24-hr summed pain intensity differences (SPID24)	Efficacy in reducing pain following bunionectomy, use of rescue opioid analgesics	**Positive data reported in Oct '13**
Sufentanil NanoTab	AcelRx Pharmaceuticals, Inc.	Sufentanil, sublingual administration	Dose-finding, randomized, double-blind, parallel assessment	Acute pain following bunionectomy	101	Sufentanil NanoTab 20 µg, 30 µg, pbo NanoTab	Time Weighted Summed Pain Intensity Difference (SPID)	-	Completed (Feb 2013)
Tapentadol IV	Grunenthal GmbH (Germany)	Centrally acting analgesic	Randomized, double-blind, parallel assignment	Acute pain following bunionectomy	177	Tapentadol IV v. pbo	Sum of Pain Intensity Differences (SPID 24)	Mean Pain Intensity Scores at Fixed Time Points, Global Impression of Change, no. of pts with 30%/50% response after 24 hrs, time to first rescure medication, meaningful pain relief	Completed (Feb 2012)
Vicodin ER	Abbott	Opioid/acetaminophen combination, ER formulation	Randomized, double-blind, parallel assessment	Acute pain following bunionectomy	99	Vicodin ER v. pbo	Time-interval weighted Sum of Pain Intensity Difference (SPID)	Time-interval weighted sum of pain relief (TOTPAR), time-interval weighted sum of pain relief and pain intensity (SPRID), perceptible and meaningful pain relief	Completed (Jun 2011)
			Randomized, single-blind, parallel assessment	Acute pain following bunionectomy	250	Hydrocodone/ acetominophen ER (v. single component comparators) v. morphine v. pbo	Time-interval weighted Sum of Pain Intensity Difference (SPID)	Time-interval weighted sum of pain relief (TOTPAR), time-interval weighted sum of pain relief and pain intensity (SPRID), perceptible and meaningful pain relief, adverse events	Completed (May 2010)
GRT6005	Grunenthal GmbH (Germany)	Centrally acting analgesic	Randomized, double-blind	Moderate to severe pain following following bunionectomy	258	GRT6005 (Dose 1-3) v. morphine v. pbo	Sum of pain intensity 2-10 hrs after drug intake	Rescue medication, adverse events, time to first rescue, patient global impression of change	Completed (Oct 2009)
Q8003	QRxPharma, Inc.	Oxycodone/ morphine combination	Randomized, double-blind, multicenter, fixed dose factorial	Acute moderate to severe postoperative pain following bunionectomy surgery	197	Q8003 12mg/8mg (v. single component comparator) Q8003 6mg/4mg (v. single component comparator)	Difference in pain intensity scores from baseline (48 hrs)	Adverse events	Completed (Feb 2009)
SKY0402	Pacira Pharmaceuticals	Nerve block	Randomized, double-blind, parallel assessment	Postoperative pain following bunionectomy	58	SKY0402 (various doses) v. bupivacaine HCl	Time to first use of supplemental pain medication	Adverse events	Completed (Dec 2006)

Source: ClinicalTrials.gov.

Early Data Supports Proof-of-Concept

TRV130 Shows Analgesic Effect, and May Have Faster Onset of Action Than Morphine. TRV130 delivered subcutaneously shows rapid analgesia in humans and mice similar to morphine (Exhibit 17). In the Phase Ib trial, TRV130 showed superior efficacy in analgesia at the 3.0 and 4.5 mg doses compared to 10 mg of morphine (high dose) and was statistically significant at 10 and 30 minute time points after dosing. Furthermore, there were a higher proportion of responders (subject who experienced a doubling of latency versus pre-dose baseline) to TRV130 at the 3.0 mg and 4.5 mg doses (~65-70% analgesia responders) compared to morphine (~38%) and placebo (~5%). The durability of the analgesic effect by TRV130 appeared similar to morphine and it may also have a faster onset of action than morphine. Full analgesic effect in the Phase Ib evoked-pain model was observed ~10 minutes after dosing (first practical data collection point), compared to morphine which typically takes ~30 minutes to reach maximal efficacy. A

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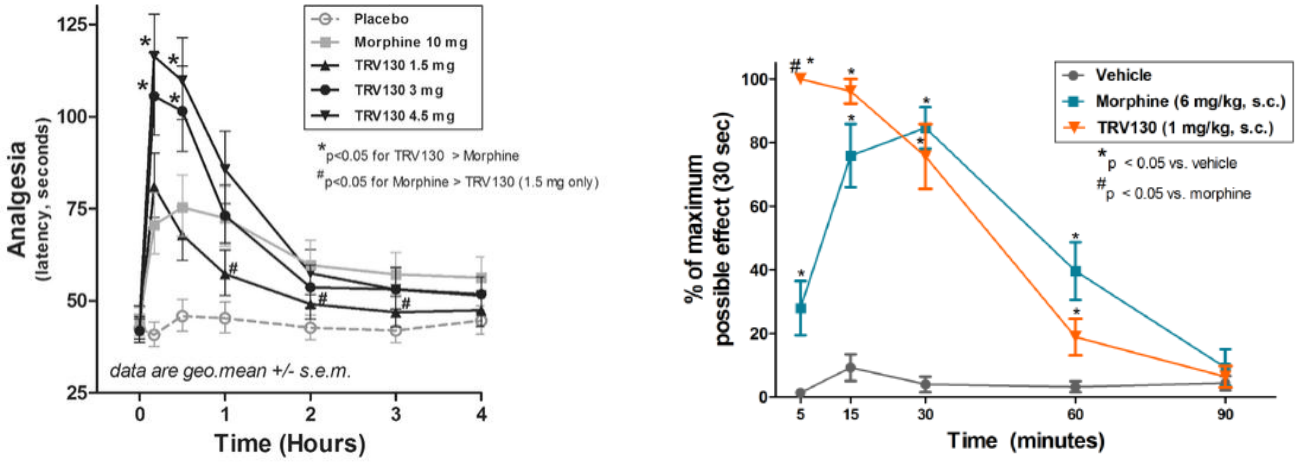
similar trend was observed in preclinical studies in mice, where TRV130 showed maximal efficacy at ~5 minutes after dosing versus morphine ($p<0.05$) (Exhibit 17; right), consistent with human data.

Exhibit 17: TRV130 analgesic effect versus morphine in humans (left) and mice (right).

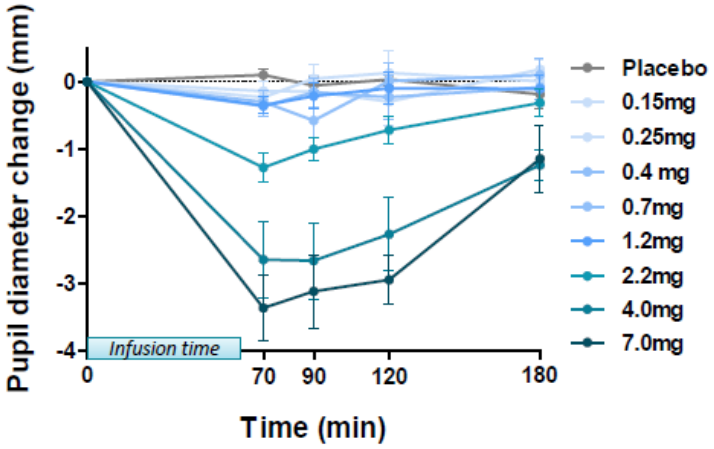


Source: Company slides.

Left: Analgesic effect of TRV130 at 1.5 mg, 3 mg, and 4.5 mg versus morphine at 10 mg and placebo in human subjects.
Right: TRV130 1 mg/kg, morphine 6 mg/kg administered subcutaneously. Mice evaluated for anti-nociceptive efficacy ~5 min after dosing.

Analgesic effect was also assessed by pupil diameter change, a well-established surrogate for analgesic efficacy and a more objective measure of analgesic drug effect (versus pain sensation which can be subjective). In the Phase I study of human volunteers, TRV130 showed marked pupil constriction at 70 minutes at doses of 2.2 mg (-1.2 mm), 4 mg (-2.6 mm), and 7 mg (-3.3 mm) versus placebo that were statistically significant (Exhibit 18). These pupil diameter changes are consistent with those observed with opioid analgesics. For example, after 60 minutes following administration in human volunteers, intravenous morphine showed a mean pupil diameter change of ~1.7 mm and codeine showed a mean change of ~1.2 mm (Knaggs, R. D. et al., *Anesth Analg*, 2004, 99, 108-112). Thus, at the dose of TRV130 we believe will be investigated in Phase II (~4.0 mg/hr), we believe the analgesic effect will be comparable, if not favorable, to currently used opioid analgesics.

Exhibit 18: Pupil diameter change at various doses of TRV130. Marked changes observed at the 2.2 mg, 4.0 mg, and 7.0 mg doses.



Source: Company data.

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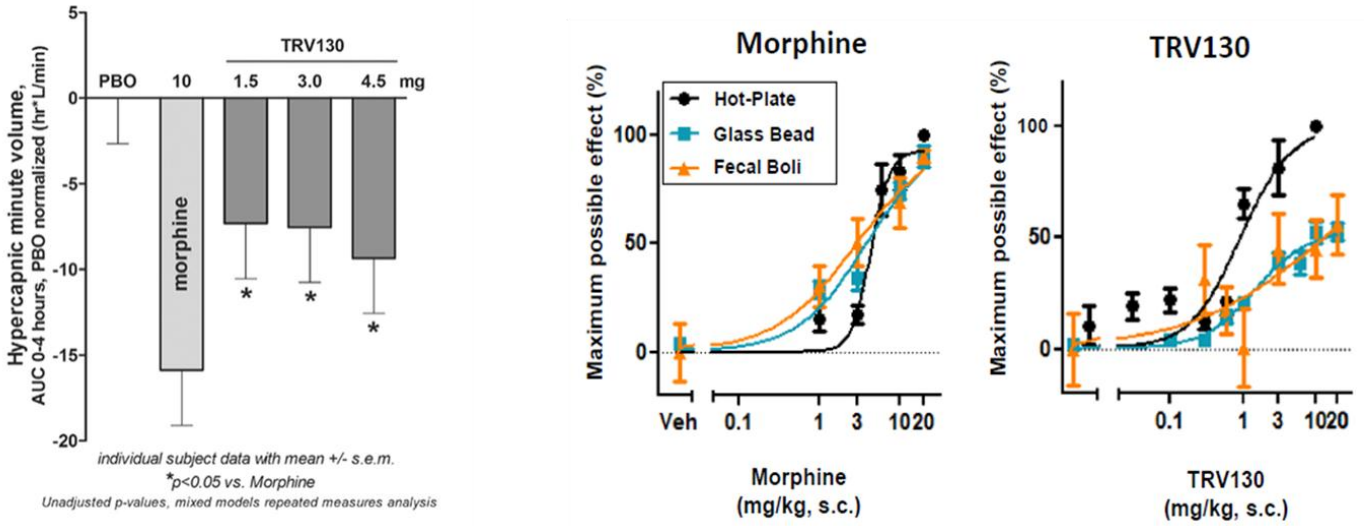
TRV130 May Have Less Respiratory Depression and Constipation Than Morphine. TRV130 may have less respiratory depression and constipation than morphine, consistent with the proposed mechanism of stimulating the GPCR with reduced β-arrestin coupling. In the Phase I study in human subjects, TRV130 showed less respiratory depression versus morphine, as measured by minute volume (MV), a product of the amount of air exhaled in a single breath thereby capturing the body's ability to expel CO_2. Furthermore, in preclinical studies in mice, respiratory depression was measured at pharmacologically equivalent doses by blood CO_2 levels at various timepoints after subcutaneous injection, and TRV130 consistently showed less respiratory depression than morphine. TRV130 also showed less constipation compared to morphine in mice (Exhibit 19), although this finding has yet to be confirmed in human subjects.

Exhibit 19: TRV130 demonstrated less respiratory depression in humans (left) and less constipation in mice (right).



Source: Company data.

Left: TRV130 v. morphine in hypercapnic minute volume. TRV130 consistently showed less respiratory depression compared to morphine at all doses investigated.

Right: TRV130 showed less constipation compared to morphine in mice by glass bead or fecal boli methods. Mice were administered TRV130 or morphine by SC bolus, followed by testing 30 min later. Maximum possible effect = 30 s latency in 56˚ hot plate, 240 min retention in glass bead assay, and zero fecal boli production.

TRV130 was Safe and Well-Tolerated – 4 mg/hr IV the MTD. In Phase I, TRV130 was well-tolerated up to the highest dose of 7 mg IV over 1 hour (investigated range: 0.15-7.0 mg/hr), where only moderate adverse events were reported. These events included vomiting, headache, dizziness, feeling hot, feeling of relaxation, and somnolence – all of which are similar to events associated with opioid analgesics. Dose-limiting events included nausea and vomiting, which were only observed at the 7 mg/hr dose, suggesting 4 mg/hr is the maximum-tolerated dose (MTD). One subject who was dosed 0.25 mg IV of TRV130 over 1 hour experienced a serious adverse event (severe vasovagal event) who was withdrawn from the study and replaced. One subject experienced increase amylase, lipase, and bilirubin following administration of TRV130 at 7 mg, although they were not considered adverse events. This subject showed higher baseline amylase and bilirubin concentrations than the reference range, and returned to the reference range within several hours following time of abnormal values. No other subjects experienced clinically significant laboratory changes.

PK Data. The dose-linear PK and exposure-related PD data suggest TRV130 will have a predictable dose-response relationship with respect to analgesia. The half-life ($t_{1/2}$) of TRV130 was determined to be ~1.6-2.7 hours, which appears similar to other opioid analgesics such as morphine (2.5-3.0 hours) and hydromorphone (2.6 hours). This

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similarity suggests that intravenous administration of TRV130 (by bolus, continuous infusions, or patient-controlled) could be similar to these commonly used opioid analgesics.

Patent Estate. U.S. and PCT applications were filed for TRV130 and TRV734 on March 23, 2012. TRVN will also file internationally in Australia, Canada, China, Europe, Hong Kong, India, Japan, New Zealand, Russia, Israel, and Brazil.

Background

The Limitations of Opioid Analgesics

Morphine, fentanyl, and hydromorphone are intravenous, unbiased μ-opioid receptor analgesics and are the mainstay of analgesic therapy for moderate to severe acute post-operative pain. They elicit analgesia by stimulating both G-protein coupled receptor (GPCR) and β-arrestin recruitment. The GPCR are highly expressed in the central nervous system (CNS) and gastrointestinal (GI) tract. Beyond effective analgesia, however, opioids can have serious adverse events including respiratory depression, sedation, nausea, vomiting, and constipation. Opioids cannot be dosed until pain is eliminated because the adverse events overlap with the opioids' range of efficacy. Respiratory depression, though rare, can be fatal in cases of overdose and associated with ~15,000 deaths per year (Manchikanti et al., *Ann Palliat Med*, 2012, 1(1), 2-3). Patients can also develop tolerance to opioid analgesia. Opioids also have significant abuse potential for patients taking them chronically.

It was hypothesized from early studies that analgesia and adverse events could be mediated by two distinct signaling pathways. In β-arrestin-2 knockout mice, it was found that analgesia from morphine was enhanced and prolonged compared to the wildtype mice (Bohn et al., 1999), while adverse events as constipation and respiratory suppression were lessened (Raehal et al., *J. Pharmacology and Experimental Therapeutics*, 2005, 314, 1195). Similarly, when β-arrestin2 was suppressed through interfering RNAs in certain brain regions (Li et al., 2009; Yang et al., 2011). β-arrestins may serve as negative modulators of analgesia and positive modulators of μ-opioid receptor-mediated adverse events, and suggests that a ligand that preferentially stimulates the GPCR and not the β-arrestin might exhibit a better therapeutic index and allow for better management of post-operative pain.

Biased ligands

β-arrestins may serve as negative modulators of analgesia and positive modulators of adverse events associated with opioids at the μ-opioid receptor. Trevena is developing TRV130, a "biased ligand" that has G-protein coupling efficacy at the μ-opioid receptor but also reduced efficacy for β-arrestin2 coupling (Exhibit 20). Trevena hopes that TRV130's mechanism will allow for more effective analgesia while reducing adverse events as respiratory suppression and constipation commonly associated with opioids. TRV130 has no structural relation to the other opioids of its class, such as morphine or fentanyl.

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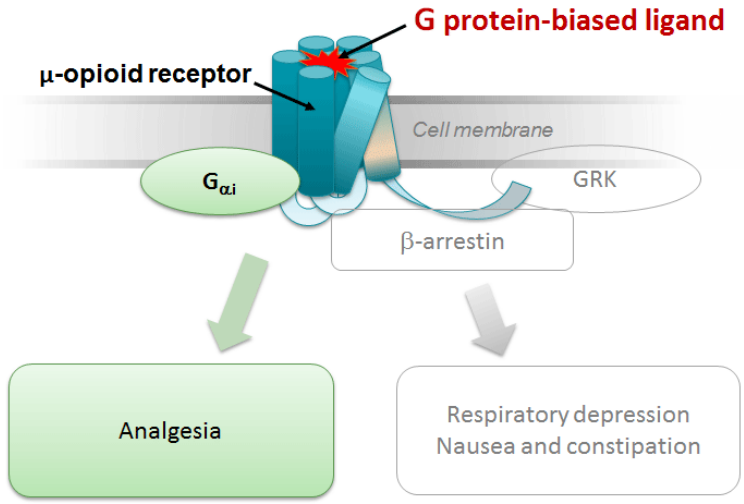
Exhibit 20: Mechanism of TRV130



Source: Company slides.

Competitive Landscape

To our knowledge, TRV130 is the only biased ligand targeting GPCR of the opioid receptor in clinical trials for post-operative pain. Other products in development for post-operative pain are reformulations of existing opioids, including MDCO's IONSYS (fentanyl patch), ACRX's Zalviso (sufentanil nanotab system), and QRX's MOXDUO IR (morphine + oxycodone). We believe the main challenge for products such as IONSYS and Zalviso which have their own delivery mechanisms, despite the clear advantages, is overturning IV PCA which has been well-entrenched in the hospital setting for decades.

- **IONSYS (MDCO)**. Through its acquisition of Incline Therapeutics (private company), The Medicine's Company (MDCO, $30.50, Hold) obtained full rights to IONSYS, a needle-free patient-controlled iontophoretic (electric charge-driven drug delivery) transdermal system providing on-demand systemic fentanyl delivery for short-term management of acute post-operative pain for adults in an in-patient setting. Essentially, IONSYS comprises two components, a drug (analgesic fentanyl) gel-based reservoir and a device providing an electric current for drug delivery through the skin at pre-set doses under a patient-controlled switch. It is approved in the U.S. and EU but is currently discontinued due to product stability issues. Currently, MDCO expects to submit filings for U.S. approval in 1Q14 and for EU in 3Q14. European filing was partly delayed because it requires a full MAA application. We therefore expect IONSYS to be available on the U.S. market in early 2015.

  IONSYS' value proposition over standard-of-care patient-controlled analgesia (PCA; mainly intravenous opioids) is largely related to potentially improved patient mobility (given its compact system without a complex set of equipment), and reduced requirement of logistics, caregiver technical expertise and venous access, and reduced risk for dosing error (with its pre-set dose). The current PCA process is complex, involving numerous steps before achieving the desired analgesic relief including obtaining/maintaining pumps, replacing supplies, analgesia, catheters, identifying adequate storage area, pump training, preparing pump for patient use, patient training, evaluating venous access, troubleshooting the alarm, addressing complications, and pump reprogramming. Additionally, PCA administration involves a bevy of equipment

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such as pumps, catheters, tubing, limiting patient mobility, and negatively impacting recovery times and rehabilitation. Given its technical complexities, PCA is also at risk for human errors on drug dose and administration, which could lead to safety issues and/or additional costs for medication, hospital services and lost revenue.

- **Zalviso (ACRX)**. AcelRx (ACRX, $12.08, Buy) is developing Zalviso (NanoTab delivery system), a unique handheld device that can deliver a very small tablet of sufentanil (3 mm disc-shaped tablets) sublingually. Sufentanil is a narcotic analgesic that is 5-10x the potency of fentanyl and 800-1,000x the potency of morphine. Due to sufentanil's highly lipophilic nature, it has an extremely short half-life (~6 minutes versus ~3 hours for morphine) resulting in rapid transmucosal uptake and onset of action. Sufentanil also does not have any active metabolites which limit adverse effects, giving it a very high therapeutic index versus other opioids. There are a number of security features including a 20-minute lockout period to prevent overdosing, and security card and RFID tag to ensure single-user identification. Each patient receives a new drug cartridge and tip that dispenses the tablet sublingually (under the tongue). Each drug cartridge comes with 40 nanotabs (~2-day supply). Because Zalviso is non-invasive, it eliminates many of the problems associated with IV PCA, as infection and restricted mobility. The PDUFA date for Zalviso is July 26, 2014.

- **CR845 (Cara Therapeutics).** Cara Therapeutics (CARA, $14.90, NC) is developing a peripherally-acting kappa opioid receptor agonist, CR845, which exhibits analgesic and anti-inflammatory properties. Because of its unique mechanism, CR845 is not expected to show typical opioid-related adverse events as respiratory depression or GI events. CR845 is also poor at penetrating the blood-brain barrier and showed no signs of addiction or euphoria in animal models. CR845 has demonstrated positive Phase II in both bunionectomy and hysterectomy pain models using SPID24 endpoint. Cara Therapeutics could begin a Phase III trial for CR845 shortly.

- **MOXDUO (QRxPharma)**. QRxPharma (ASX: QRX, $0.85, NC) is developing MOXDUO, a combination of morphine and oxycodone in various strengths, in both immediate release (IR) and controlled release (CR) formulations. MODXDUO IR is being targeted as first-line therapy for patients with acute moderate to severe pain. QRX believes that sub-analgesic doses of oxycodone may have synergy with sub-analgesic doses of morphine, and have thus prepared a "dual opioid" that could produce synergistic pain relief with fewer side effects. QRX received a complete response letter from the FDA in 2012 after the initial submission, and QRX will prepare an additional data package for re-submission.

TRV734

Moderate to Severe Pain

TRV734 – All of the Advantages of TRV130, and Making it Oral

TRV734 is follow-on program to TRV130 as a μ-opioid biased ligand that has G-protein coupling efficacy at the μ-opioid receptor but also reduced efficacy for β-arrestin2 coupling. Thus, like TRV130, TRVN believes TRV734 will show potent analgesia without the adverse events typically associated with opioids, such as constipation and respiratory depression. TRVN expects TRV734 will have pharmacokinetics that would make it amenable to chronic oral administration. TRVN intends to seek a collaborator in

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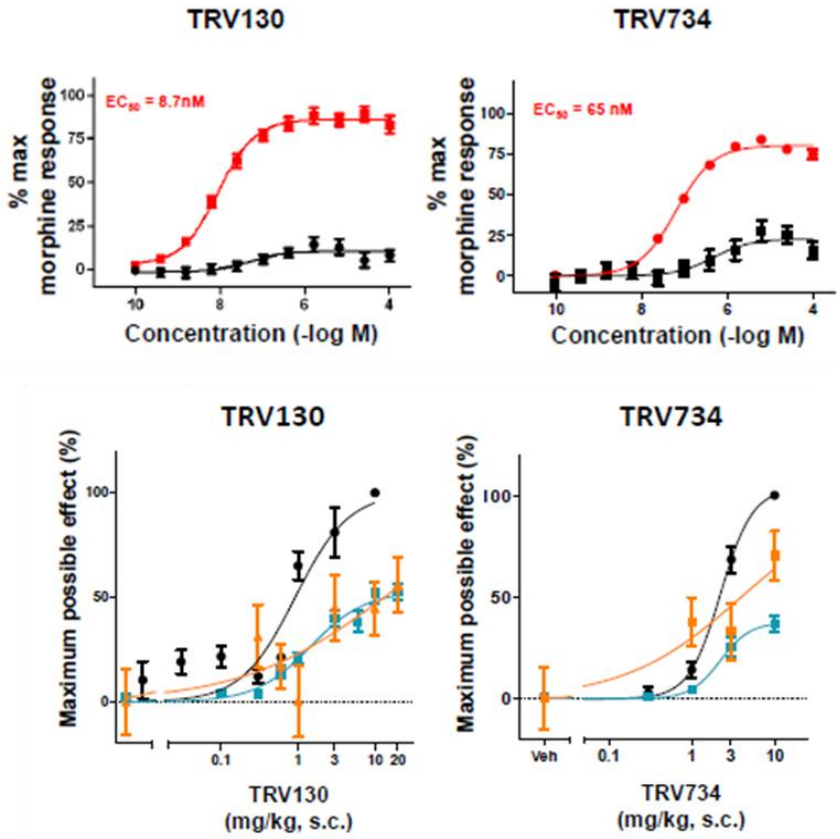
developing and commercializing TRV734 for the chronic care pain markets. We currently do not model TRV734, and represents upside to our valuation.

Recently, TRVN has initiated a Phase I trial for TRV734. The main objective of the trial is to evaluate safety, tolerability, and PK/PD of single ascending doses of TRV734 in healthy subjects. The efficacy will be evaluated using pupilometry, a validated biomarker for mu-opioid receptor engagement. Phase II and III studies will evaluate the efficacy and tolerability of TRV734 in patients with acute and chronic pain.

Early preclinical data have shown that TRV734 has similar properties as TRV130 in its ability to show potent analgesia with reduced β-arrestin recruitment and less constipation in mice (Exhibit 21), particularly versus morphine. TRV734 has good oral pharmacokinetics in non-human primates.

Exhibit 21: Comparison of TRV130 and TRV734: ability to reduce β-arrestin recruitment (top), and constipation in mice (bottom)



Source: Violin, J. D. et al., *APS*, 2013; Company slides.

Delta Opioid Program

Trevena's delta opioid program involves developing a series of biased delta opioid receptor (DOR) ligands to treat pain, depression and Parkinson's disease. The delta opioid program is developed based on findings that seizures are reduced in β-arrestin2 knock-out mice being treated with delta opioid agonists, while maintaining the therapeutic benefit. TRVN's lead candidate in the biased delta opioid program is an oral selective DOR agonist TRV0110136 for treating depression. In preclinical models using mice

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TRV0110136 showed superior anti-depressant activity in tail suspension test while completely abolishing seizures when compared with unbiased DOR agonists. Earlier studies have also confirmed that delta opioid receptor activation reduces persistent pain and improves negative emotional states; clinical trials have been initiated to assess the effectiveness of delta opioid agonists in chronic pain and depression (Pradhan AA, et al, *Trends in Pharmcolo Sci*, 2011,32, 581-590, Mabrouk OS, et al, *J Neurochem*, 2008, 107, 1647-1659). TRVN will decide on the lead candidate for Parkinson's disease in 2014 and will file an IND in Q1 2015.

Capital Structure

After its IPO on January 31, 2014, in which Trevena raised net proceeds of $66.8 million from a public equity offering of 9.25 million shares of common stock (includes an underwriter option of 1.75 million) at $7/share, the company has cash of $107.8M, which is sufficient to fund operations to 2016. Lock-up expiration from the IPO occur 180 days post-IPO. Trevena plans to use the net proceeds to fund clinical trials of TRV027 and TRV130, pipeline development, and remainder for working capital and other general corporate purposes.

Management Team

Maxine Gowen, Ph.D. – President and Chief Executive Officer

Dr. Gowen is the founding President and CEO of Trevena. Prior to this Dr. Gowen held a variety of leadership roles at GlaxoSmithKline (GSK) over a period of fifteen years. As Senior Vice President for the Center of Excellence for External Drug Discovery (CEEDD), she developed an innovative new approach to externalizing drug discovery in big pharma. Dr. Gowen held a tenured academic position in the School of Pharmacology, University of Bath, UK from 1989-1992 and graduated with a B.Sc. in biochemistry from the University of Bristol, UK, a Ph.D. in cell biology from the University of Sheffield, UK, and received an MBA from the Wharton School of the University of Pennsylvania. Dr. Gowen is currently on the Board of Directors of the biotechnology industry association, BIO.

Michael W. Lark, Ph.D. – CSO and Senior Vice President, Research

Dr. Lark has served in a number of capacities with the company since February 2008, and currently serves as Chief Scientific Officer and Senior Vice President, Research, a position he has held since March 2011. Prior to joining Trevena, he was Vice President of Biology at Centocor Inc., a division of Johnson & Johnson, or Centocor, from 2004 until 2008 and the Senior Director of Cardiovascular and Metabolic Diseases at Centocor from 2002 to 2004. Prior to that, Dr. Lark was Director of Musculoskeletal Diseases at GSK, from 1999 until 2002. Dr. Lark received his Ph.D. in Molecular Biology and Microbiology from the Case Western Reserve University Medical School and his B.S. in Microbiology from the Pennsylvania State University.

Roberto Cuca - Chief Financial Officer

Mr. Cuca joined Trevena as Senior Vice President and Chief Financial Officer in September 2013. Prior to joining, he held various leadership positions in the finance organization of Endo Health Solutions Inc., a pharmaceutical company, from March 2010 to August 2013, including, most recently, Treasurer and Senior Vice President, Finance. Prior to that, he was Director, Corporate and Business Development, at moksha8 Pharmaceuticals, Inc., an emerging markets focused pharmaceutical company, from March 2008 until February 2010. From 2005 until 2008, he worked at JPMorgan Chase & Co. as an equity analyst covering U.S. pharmaceutical companies. Mr. Cuca received an M.B.A. from the Wharton School of The University of Pennsylvania, a J.D. from Cornell Law School, an A.B. from Princeton University and he is a CFA charterholder.

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David Soergel, M.D. – Senior Vice President, Clinical Development
Dr. Soergel joined Trevena in November 2009. Previously, he was Senior Director, Clinical Development at Concert Pharmaceuticals where he was responsible for clinical strategy and operations across diverse therapy areas, including infectious diseases and diabetic nephropathy. Prior to Concert, Dr. Soergel was Director of Discovery Medicine at GlaxoSmithKline for the Cardiovascular Urogenital Center of Excellence for Drug Discovery from 2005 to 2008. Dr. Soergel received an M.D. from Cornell University Medical College and a B.A. from The Johns Hopkins University. Dr. Soergel completed his clinical training in pediatric cardiology at Johns Hopkins Hospital and underwent additional training in heart failure and transplant at the Children's Hospital of Philadelphia.

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Exhibit 22: TRVN Income Statement

Trevena, Inc.

Quarterly Income Statement

(All values in $MM except EPS and average shares)

	2012A	2013E					2014E					2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
	FY	1QA	2QA	3QA	4QE	FY	1QE	2QE	3QE	4QE	FY	FY	FY	FY	FY	FY	FY	FY	FY	FY	FY	FY
Revenue:																						
TRV027 US Royalties	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	0.0	0.0	3.6	6.3	12.5	17.3	23.9	26.6
TRV027 EU Royalties	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	0.0	0.0	2.6	4.5	7.2	9.2	11.5	12.6
TRV027 ROW Royalties	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	0.0	0.0	0.6	1.0	1.6	2.0	2.5	2.8
TRV130 US Sales	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	0.0	7.3	52.6	94.0	122.3	143.3	156.3	169.6
TRV130 EU/ROW Royalties	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	0.0	0.0	0.6	4.1	7.1	9.0	10.2	11.0
Grant and collaboration revenues	0.8	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	42.3	1.0	0.0	17.5	35.0	0.0	17.5	0.0	17.5	0.0
Total revenue, net	**0.8**	**0.0**	**0.1**	**0.0**	**0.0**	**0.1**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**42.3**	**1.0**	**0.0**	**24.8**	**95.0**	**109.8**	**168.2**	**180.8**	**221.9**	**222.5**
Costs and expenses:																						
Cost of goods sold	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	0.0	0.7	5.3	9.4	12.2	14.3	15.6	17.0
Research & development	13.3	2.3	3.2	6.6	6.7	18.8	7.5	8.0	8.4	8.8	32.7	38.0	35.0	35.0	20.0	15.0	15.8	16.5	17.4	18.2	19.1	20.1
Selling, general & administrative	3.1	0.7	0.9	1.2	1.0	3.8	0.9	1.1	1.2	1.0	4.2	4.5	3.4	3.7	4.0	14.7	16.0	17.4	18.6	19.5	20.5	21.5
Total operating expenses	**16.4**	**3.0**	**4.1**	**7.8**	**7.7**	**22.6**	**8.4**	**9.1**	**9.6**	**9.8**	**36.9**	**42.5**	**38.4**	**38.7**	**24.0**	**30.4**	**37.0**	**43.4**	**48.1**	**52.0**	**55.2**	**58.5**
Income (loss) from operations	**(15.6)**	**(3.0)**	**(4.0)**	**(7.8)**	**(7.7)**	**(22.5)**	**(8.4)**	**(9.1)**	**(9.6)**	**(9.8)**	**(36.9)**	**(42.5)**	**3.9**	**(37.7)**	**(24.0)**	**(5.6)**	**58.0**	**66.4**	**120.0**	**128.8**	**166.7**	**163.9**
Other income (expense):																						
Miscellaneous (expense) income	(0.0)	(0.2)	(0.2)	(0.9)	(0.3)	(1.7)	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	0.0	0.0
Interest 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	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Interest expense	-	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	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net profit (loss) before income taxes	**(15.6)**	**(3.2)**	**(4.2)**	**(8.8)**	**(7.7)**	**(24.2)**	**(8.4)**	**(9.1)**	**(9.6)**	**(9.8)**	**(36.9)**	**(42.5)**	**3.9**	**(37.7)**	**(24.0)**	**(5.6)**	**58.0**	**66.4**	**120.0**	**128.8**	**166.7**	**163.9**
Income tax expense (benefit)														0.0	0.0	0.0	5.8	6.6	12.0	45.1	58.3	57.4
Income tax (%)														*0.0%*	*0.0%*	*0.0%*	*10.0%*	*10.0%*	*10.0%*	*35.0%*	*35.0%*	*35.0%*
Net Income (GAAP)	**(15.6)**	**(3.2)**	**(4.2)**	**(8.8)**	**(7.7)**	**(24.2)**	**(8.4)**	**(9.1)**	**(9.6)**	**(9.8)**	**(36.9)**	**(42.5)**	**3.9**	**(37.7)**	**(24.0)**	**(5.6)**	**52.2**	**59.8**	**108.0**	**83.7**	**108.4**	**106.6**
Adjusted Items (Non-GAAP)																						
Stock options	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.4	0.5	0.5	0.5	0.5	0.5	0.7	0.7	0.7	1.0	1.0	1.0
Accretion of redeemable convertible preferred stock	(0.3)	(0.1)	(0.1)	(0.1)	(0.1)	(0.3)	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	0.0	0.0
Net Income (Non-GAAP)	**(16.0)**	**(3.3)**	**(4.3)**	**(8.9)**	**(7.8)**	**(24.5)**	**(8.3)**	**(9.0)**	**(9.5)**	**(9.7)**	**(36.5)**	**(42.0)**	**4.4**	**(37.2)**	**(23.5)**	**(5.1)**	**52.9**	**60.5**	**108.7**	**84.7**	**109.4**	**107.6**
EPS, GAAP																						
Basic	(1.50)	(0.23)	(0.30)	(0.64)	(0.56)	(1.76)	(0.33)	(0.35)	(0.37)	(0.38)	(1.44)	(1.64)	0.11	(1.03)	(0.65)	(0.15)	1.39	1.57	2.81	2.16	2.76	2.69
Diluted	**$ (1.50)**	**$ (0.23)**	**$ (0.30)**	**$ (0.64)**	**$ (0.56)**	**$ (1.76)**	**$ (0.33)**	**$ (0.35)**	**$ (0.37)**	**$ (0.38)**	**$ (1.44)**	**$ (1.64)**	**$ 0.11**	**$ (1.03)**	**$ (0.65)**	**$ (0.15)**	**$ 1.39**	**$ 1.57**	**$ 2.81**	**$ 2.16**	**$ 2.76**	**$ 2.69**
Weighted average share- Basic	10.4	13.8	13.8	13.8	13.8	13.8	25.7	25.7	25.7	25.7	25.7	26.0	36.2	36.6	36.9	37.3	37.7	38.1	38.4	38.8	39.2	39.6
Weighted average share- Diluted	10.4	13.8	13.8	13.8	13.8	13.8	25.7	25.7	25.7	25.7	25.7	26.0	36.2	36.6	36.9	37.3	37.7	38.1	38.4	38.8	39.2	39.6

Source: Jefferies estimates, company data

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 23: TRVN Balance Sheet

Trevena, Inc.

Balance Sheet

(All values in $MM)

	2012A FY	2013E FY	2014E FY	2015E FY	2016E FY	2017E FY	2018E FY	2019E FY	2020E FY	2021E FY	2022E FY	2023E FY
Current assets:												
Cash and cash equivalents	6.7	100.3	63.4	20.4	123.4	84.3	58.4	50.4	99.9	156.4	261.2	341.9
Cash and investments	**6.7**	**100.3**	**63.4**	**20.4**	**123.4**	**84.3**	**58.4**	**50.4**	**99.9**	**156.4**	**261.2**	**341.9**
Prepaid expenses	0.2	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Receivable	0.0	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Restricted cash	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Total current assets	**7.0**	**102.4**	**65.5**	**22.5**	**125.5**	**86.4**	**60.5**	**52.4**	**102.0**	**158.5**	**263.3**	**344.0**
Property and equipment	0.9	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Restricted cash, net current	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Other assets	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total assets	**8.1**	**103.0**	**66.0**	**23.1**	**126.0**	**87.0**	**61.0**	**53.0**	**102.5**	**159.0**	**263.8**	**344.6**
Current liabilities:												
Accounts payable	0.5	1.4	1.7	2.1	3.6	2.3	4.5	5.1	6.2	7.3	8.4	9.5
Accrued expenses	1.3	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Deferred rent	0.1	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Loans payable	2.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total current liabilities	**3.9**	**3.4**	**3.8**	**4.2**	**5.7**	**4.4**	**6.6**	**7.2**	**8.3**	**9.4**	**10.5**	**11.6**
Loans payable, net current	2.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Deferred rent, excluding current portion	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Preferred stock warrant liability	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Liabilitiy	**8.1**	**3.7**	**3.8**	**4.2**	**5.7**	**4.4**	**6.6**	**7.2**	**8.3**	**9.4**	**10.5**	**11.6**
Total stockholders' equity	**(0.0)**	**99.3**	**62.2**	**18.9**	**120.3**	**82.6**	**54.4**	**45.8**	**94.2**	**149.6**	**253.3**	**333.0**
Total liabilities and stockholders' equity	**8.1**	**103.0**	**66.0**	**23.1**	**126.0**	**87.0**	**61.0**	**53.0**	**102.5**	**159.0**	**263.8**	**344.6**

Source: Jefferies estimates, company data

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 24: TRVN Cash Flow Statement

Trevena, Inc.

Cash Flow Statement

(All values in $MM)

	2012A FY	2013E FY	2014E FY	2015E FY	2016E FY	2017E FY	2018E FY	2019E FY	2020E FY	2021E FY	2022E FY	2023E FY
Cash flows from operating activities:	(15.6)	(24.2)	(36.9)	(42.5)	3.9	(37.7)	(24.0)	(5.6)	52.2	59.8	108.0	83.7
Net income												
Adjustments to reconcile cash by operating activities:												
Depreciation and amortization expense	0.8	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Non-cash stock-based compensation expense	0.2	0.5	0.4	0.5	0.5	0.5	0.5	0.5	0.7	0.7	0.7	1.0
Non-cash interest expense on loans	0.0	0.1										
Loss on diposal of assets	0.0	0.0										
Revaluation of preferred stock warrant liability	(0.0)	1.2										
Changes in operating assets and liabilities:												
Prepaid expenses	0.1	(1.3)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Restricted cash	0.1	0.1	0.0	0.0	0.0	0.1	(0.1)	0.0	0.0	0.0	0.0	0.0
Accounts payable & accr expenses	(0.3)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Net cash provided by operating activities	**(14.8)**	**(21.5)**	**(34.5)**	**(40.0)**	**6.4**	**(35.1)**	**(21.5)**	**(3.1)**	**55.0**	**62.5**	**110.7**	**86.7**
Cash flows from investing activities:												
Purchase of property and equipment	(0.0)	(0.1)	(2.5)	(3.0)	(3.5)	(4.0)	(4.5)	(5.0)	(5.5)	(6.0)	(6.0)	(6.0)
Net cash (used in) provided by investing activities	**(0.0)**	**(0.1)**	**(2.5)**	**(3.0)**	**(3.5)**	**(4.0)**	**(4.5)**	**(5.0)**	**(5.5)**	**(6.0)**	**(6.0)**	**(6.0)**
Cash flows from financing activities:												
Issuance of common stock, net of offering costs	0.0	60.2	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Issuance of common stock from exercise of stock options	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Repurchase from preferred stock	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Proceeds from preferred stock	0.0	59.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Proceeds from notes payable	5.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Principal payments on debt	(0.8)	(4.9)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Payments under capital lease obligations	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net cash (used in) provided by financing activities	**4.5**	**115.2**	**0.0**	**0.0**	**100.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Effect if exchange rate changes on cash/equivalents												
Increase (decrease) in cash and cash equivalents	(10.3)	93.6	(36.9)	(42.9)	102.9	(39.0)	(26.0)	(8.0)	49.5	56.5	104.8	80.8
Cash and cash equivalents at beginning of period	17.0	6.7	100.3	63.4	20.4	123.4	84.3	58.4	50.4	99.9	156.4	261.2
Cash and cash equivalents at end of period	**6.7**	**100.3**	**63.4**	**20.4**	**123.4**	**84.3**	**58.4**	**50.4**	**99.9**	**156.4**	**261.2**	**341.9**

Source: Jefferies estimates, company data

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 25: TRVN DCF Analysis

Trevena, Inc.

Discounted Cash Flow Analysis

(All values in $MM)	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
Sales	0.1	0.0	0.0	42.3	1.0	0.0	24.8	95.0	109.8	168.2	180.8	221.9	222.5
Operating Expenses	22.6	36.9	42.5	38.4	38.7	24.0	30.4	37.0	43.4	48.1	52.0	55.2	58.5
EBIT	(22.5)	(36.9)	(42.5)	3.9	(37.7)	(24.0)	(5.6)	58.0	66.4	120.0	128.8	166.7	163.9
(-): Taxes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.8	6.6	12.0	45.1	58.3	57.4
EBIAT	(22.5)	(36.9)	(42.5)	3.9	(37.7)	(24.0)	(5.6)	52.2	59.8	108.0	83.7	108.4	106.6
(+):Depreciation	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.0	0.0
(+):FAS-123 Options	0.0	0.4	0.5	0.5	0.5	0.5	0.5	0.7	0.7	0.7	1.0	1.0	1.0
Unlevered free cash flow	***(22.0)***	***(36.0)***	***(41.5)***	***4.9***	***(36.6)***	***(22.9)***	***(4.5)***	***53.5***	***61.0***	***109.3***	***85.2***	***109.4***	***107.6***

Source: Jefferies estimates, company data

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 26: TRV027 U.S. Revenue Build

TRV027 Revenue Build	2020		2021		2022		2023		2024		2025		2026		2027	
U.S.																
Total Net Sales of TRV-027 in AHF ($M)	**$68.7**		**$119.1**	*73%*	**$223.0**	*87%*	**$309.3**	*39%*	**$402.2**	*30%*	**$446.2**	*11%*	**$493.2**	*11%*	**$543.3**	*10%*
Risk discount	*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*	
Total Net Sales of TRV-027 in AHF - risk adj. ($M)	**$24.0**		**$41.7**		**$78.0**		**$108.2**		**$140.8**		**$156.2**		**$172.6**		**$190.2**	
Total Net Sales of TRV-027 - risk adj. ($M)	**$24.0**		**$41.7**	*73%*	**$78.0**	*87%*	**$108.2**	*39%*	**$140.8**	*30%*	**$156.2**	*11%*	**$172.6**	*11%*	**$190.2**	*10%*
Royalty rate	*15%*		*15%*		*16%*		*16%*		*17%*		*17%*		*18%*		*18%*	
U.S. royalties to TRV-027 - risk adj. ($M)	**$3.61**		**$6.25**	*73%*	**$12.49**	*100%*	**$17.32**	*39%*	**$23.93**	*38%*	**$26.55**	*11%*	**$31.07**	*17%*	**$34.23**	*10%*
	2020		**2021**		**2022**		**2023**		**2024**		**2025**		**2026**		**2027**	
U.S. AHF Market Opportunity																
Total no. of AHF patients (000's)	1,156	*1%*	1,168	*1%*	1,179	*1%*	1,191	*1%*	1,203	*1%*	1,215	*1%*	1,227	*1%*	1,240	*1%*
Patients on TRV-027 (000's)	35		58	*68%*	106	*82%*	143	*35%*	180	*26%*	194	*8%*	209	*7%*	223	*7%*
% mkt share	*3.0%*		*5.0%*		*9.0%*		*12.0%*		*15.0%*		*16.0%*		*17.0%*		*18.0%*	
U.S. Net Sales of TRV027($M)	**$68.7**		**$119.1**	*73%*	**$223.0**	*87%*	**$309.3**	*39%*	**$402.2**	*30%*	**$446.2**	*11%*	**$493.2**	*11%*	**$543.3**	*10%*
Risk discount	*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*	
U.S. Net Sales of TRV027 - risk adj. ($M)	**$24.0**		**$41.7**		**$78.0**		**$108.2**		**$140.8**		**$156.2**		**$172.6**		**$190.2**	

Source: Jefferies estimates, company data

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Exhibit 27: TRV027 EU Revenue Build

TRV027 Revenue Build	2020		2021		2022		2023		2024		2025		2026		2027	
EU																
Total Net Sales of TRV-027 in AHF ($M)	**$50.4**		**$84.9**	*68%*	**$128.7**	*52%*	**$164.6**	*28%*	**$192.5**	*17%*	**$212.1**	*10%*	**$232.1**	*9%*	**$252.4**	*9%*
Risk discount	*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*	
Total Net Sales of TRV-027 in AHF - risk adj. ($M)	**$17.7**		**$29.7**		**$45.0**		**$57.6**		**$67.4**		**$74.2**		**$81.2**		**$88.3**	
Total Net Sales of TRV-027 - risk adj. ($M)	**$17.7**		**$29.7**	*68%*	**$45.0**	*52%*	**$57.6**	*28%*	**$67.4**	*17%*	**$74.2**	*10%*	**$81.2**	*9%*	**$88.3**	*9%*
Royalty rate	*15%*		*15%*		*16%*		*16%*		*17%*		*17%*		*18%*		*18%*	
EU. royalties to TRV-027 - risk adj. ($M)	**$2.65**		**$4.46**	*68%*	**$7.20**	*62%*	**$9.22**	*28%*	**$11.45**	*24%*	**$12.62**	*10%*	**$14.62**	*16%*	**$15.90**	*9%*

	2020		2021		2022		2023		2024		2025		2026		2027	
EU AHF Market Opportunity																
Total # of AHF	1,682	*1%*	1,698	*1%*	1,715	*1%*	1,733	*1%*	1,750	*1%*	1,767	*1%*	1,785	*1%*	1,803	*1%*
Patients on TRV-027 (000's)	50		85	*68%*	129	*52%*	165	*28%*	192	*17%*	212	*10%*	232	*9%*	252	*9%*
% mkt share	*3.0%*		*5.0%*		*7.5%*		*9.5%*		*11.0%*		*12.0%*		*13.0%*		*14.0%*	
EU Net Sales of TRV027 ($M)	**$50.4**		**$84.9**	*68%*	**$128.7**	*52%*	**$164.6**	*28%*	**$192.5**	*17%*	**$212.1**	*10%*	**$232.1**	*9%*	**$252.4**	*9%*
Risk discount	*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*	
EU Net Sales of TRV027 - risk adj. ($M)	**$17.7**		**$29.7**		**$45.0**		**$57.6**		**$67.4**		**$74.2**		**$81.2**		**$88.3**	

Source: Jefferies estimates, company data

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Exhibit 28: TRV027 ROW Revenue Build

TRV027 Revenue Build	**2020**		**2021**		**2022**		**2023**		**2024**		**2025**		**2026**		**2027**	
ROW																
Total Net Sales of TRV-027 in AHF ($M)	**$11.0**		**$18.6**	*68%*	**$28.1**	*52%*	**$36.0**	*28%*	**$42.1**	*17%*	**$46.4**	*10%*	**$50.8**	*9%*	**$55.2**	*9%*
Risk discount	*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*	
Total Net Sales of TRV-027 in AHF - risk adj. ($M)	**$3.9**		**$6.5**		**$9.9**		**$12.6**		**$14.7**		**$16.2**		**$17.8**		**$19.3**	
Total Net Sales of TRV-027 - risk adj. ($M)	**$3.9**		**$6.5**	*68%*	**$9.9**	*52%*	**$12.6**	*28%*	**$14.7**	*17%*	**$16.2**	*10%*	**$17.8**	*9%*	**$19.3**	*9%*
Royalty rate	*15%*		*15%*		*16%*		*16%*		*17%*		*17%*		*18%*		*18%*	
EU. royalties to TRV-027 - risk adj. ($M)	**$0.58**		**$0.98**	*68%*	**$1.58**	*62%*	**$2.02**	*28%*	**$2.51**	*24%*	**$2.76**	*10%*	**$3.20**	*16%*	**$3.48**	*9%*

	2020		**2021**		**2022**		**2023**		**2024**		**2025**		**2026**		**2027**	
ROW AHF Market Opportunity																
Total no. of AHF patients (000's)	736	*1%*	743	*1%*	750	*1%*	758	*1%*	766	*1%*	773	*1%*	781	*1%*	789	*1%*
Patients on TRV-027 (000's)	22		37	*68%*	56	*52%*	72	*28%*	84	*17%*	93	*10%*	102	*9%*	110	*9%*
% mkt share	*3.0%*		*5.0%*		*7.5%*		*9.5%*		*11.0%*		*12.0%*		*13.0%*		*14.0%*	
ROW Net Sales of TRV027 ($M)	**$11.0**		**$18.6**	*68%*	**$28.1**	*52%*	**$36.0**	*28%*	**$42.1**	*17%*	**$46.4**	*10%*	**$50.8**	*9%*	**$55.2**	*9%*
Risk discount	*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*	
ROW Net Sales of TRV027 - risk adj. ($M)	**$3.9**		**$6.5**		**$9.9**		**$12.6**		**$14.7**		**$16.2**		**$17.8**		**$19.3**	

Source: Jefferies estimates, company data

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Exhibit 29: TRV130 U.S. Revenue Build

TRV130 Revenue Build	2019	2020	2021	2022	2023	2024	2025	2026	2027
U.S.									
TRV130 Net Sales Inpatient Procedures ($M)	**$20.9**	**$150.4** 620%	**$265.0** 76%	**$340.4** 28%	**$396.5** 16%	**$431.3** 9%	**$467.7** 8%	**$493.1** 5%	**$506.4** 3%
TRV130 Net Sales Outpatient Procedures ($M)	**$0.0**	**$0.0**	**$3.5**	**$9.0** 157%	**$13.0** 44%	**$15.2** 17%	**$16.8** 10%	**$17.9** 6%	**$19.0** 6%
Total TRV130 Net Sales	**$20.9**	**$150.4**	**$268.5**	**$349.4**	**$409.4**	**$446.5**	**$484.5**	**$510.9**	**$525.3**
Risk discount	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*
Total Net Sales of TRV130 in Post-operative Pain - risk adj. ($M)	**$7.3**	**$52.6** 620%	**$94.0** 79%	**$122.3** 30%	**$143.3** 17%	**$156.3** 9%	**$169.6** 9%	**$178.8** 5%	**$183.9** 3%

	2019	2020	2021	2022	2023	2024	2025	2026	2027
U.S. Post-Operative Inpatient Pain Market Opportunity									
Total no. of inpatient procedures w/ IV opioids (000's)	14,568 1%	14,714 1%	14,861 1%	15,010 1%	15,160 1%	15,312 1%	15,465 1%	15,619 1%	15,776 1%
Inpatient surgical patients on IV opioids (000's)	10,926	11,036	11,146	11,257	11,370	11,484	11,599	11,715	11,832
% of inpatients on IV opioids w/ surgery	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
Patients on TRV130 - Inpatient surgery eligible (000's)	146	1,030 607%	1,783 73%	2,251 26%	2,577 14%	2,756 7%	2,938 7%	3,046 4%	3,076 1%
% of total no. of eligible patients	*1.0%*	*7.0%*	*12.0%*	*15.0%*	*17.0%*	*18.0%*	*19.0%*	*19.5%*	*19.5%*
Inpatient non-surgical patients on IV opioids (000's)	3,642	3,679	3,715	3,752	3,790	3,828	3,866	3,905	3,944
% of in inpatients on IV opioids w/out surgery	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
Patients on TRV130 - Inpatient non-surgery eligible (000's)	36	257	446	563 26%	644 14%	689 7%	735 7%	761 4%	769 1%
% of total no. of eligible patients	*1.0%*	*7.0%*	*12.0%*	*15.0%*	*17.0%*	*18.0%*	*19.0%*	*19.5%*	*19.5%*
Inpatients on TRV130 - In hospital (000's)	182	1,287	2,229	2,814	3,221	3,445	3,673	3,807	3,845
U.S. Net Sales of TRV130 in Post-operative In Hospital Pain ($M)	**$20.9**	**$150.4** 620%	**$265.0** 76%	**$340.4** 28%	**$396.5** 16%	**$431.3** 9%	**$467.7** 8%	**$493.1** 5%	**$506.4** 3%
U.S. Post-Operative Outpatient Pain Market Opportunity									
Total no. of outpatients on IV opioids (000's)	16,650 1%	16,816 1%	16,984 1%	17,154 1%	17,326 1%	17,499 1%	17,674 1%	17,851 1%	18,029 1%
Outpatient surgical patients on IV opioids (000's)	12,487	12,612	12,738	12,866	12,994	13,124	13,255	13,388	13,522
% of outpatients on IV opioids w/ surgery	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
Patients on TRV130 - Outpatient surgery eligible (000's)	0	0	170	429 153%	606 41%	700 15%	760 9%	794 5%	829 4%
% of total no. of eligible patients	*0.0%*	*0.0%*	*1.0%*	*2.5%*	*3.5%*	*4.0%*	*4.3%*	*4.5%*	*4.6%*
In hospital non-surgical patients on IV opioids (000's)	4,162	4,204	4,246	4,289	4,331	4,375	4,418	4,463	4,507
% of outpatients on IV opioids w/ surgery	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
Patients on TRV130 - Outpatient non-surgery eligible (000's)	0	0	42	107 153%	152 41%	175 15%	190 9%	199 5%	207 4%
% of total no. of eligible patients	*0.0%*	*0.0%*	*1.0%*	*2.5%*	*3.5%*	*4.0%*	*4.3%*	*4.5%*	*4.6%*
Patients on TRV130 - Outpatient hospital (000's)	0	0	212	536	758	875	950	993	1,037
U.S. Net Sales of TRV130 in Post-operative In Hospital Pain ($M)	**$0.0**	**$0.0**	**$3.5**	**$9.0** 157%	**$13.0** 44%	**$15.2** 17%	**$16.8** 10%	**$17.9** 6%	**$19.0** 6%

Source: Jefferies estimates, company data

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Exhibit 30: TRV130 EU-ROW Revenue Build

TRV130 Revenue Build	2020		2021		2022		2023		2024		2025		2026		2027	
EU/ROW																
Total Net Sales of TRV130 ($M)	**$11.0**		**$78.0**	607%	**$135.1**	73%	**$170.5**	26%	**$195.2**	14%	**$208.8**	7%	**$222.6**	7%	**$224.8**	1%
Risk discount	*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*	
Total Net Sales of TRV130 - risk adj. ($M)	**$3.9**		**$27.3**		**$47.3**		**$59.7**		**$68.3**		**$73.1**		**$77.9**		**$78.7**	
Total Net Sales of TRV130 - risk adj. ($M)	**$3.9**		**$27.3**	607%	**$47.3**	73%	**$59.7**	26%	**$68.3**	14%	**$73.1**	7%	**$77.9**	7%	**$78.7**	1%
Royalty rate	*15%*		*15%*		*15%*		*15%*		*15%*		*15%*		*15%*		*15%*	
Royalties to TRV130 - risk adj. ($M)	**$0.58**		**$4.10**	607%	**$7.09**	73%	**$8.95**	26%	**$10.25**	14%	**$10.96**	7%	**$11.69**	7%	**$11.80**	1%
	2020		**2021**		**2022**		**2023**		**2024**		**2025**		**2026**		**2027**	
EU/ROW Market Opportunity																
Patients on TRV130 - In hospital surgery eligible (000's)	14,714	1%	14,861	1%	15,010	1%	15,160	1%	15,312	1%	15,465	1%	15,619	1%	15,776	1%
Patients on TRV130 (000's)	147		1,040	607%	1,801	73%	2,274	26%	2,603	14%	2,784	7%	2,968	7%	2,997	1%
% mkt share	*1.0%*		*7.0%*		*12.0%*		*15.0%*		*17.0%*		*18.0%*		*19.0%*		*19.0%*	
Net Sales of TRV130 ($M)	**$11.0**		**$78.0**	607%	**$135.1**	73%	**$170.5**	26%	**$195.2**	14%	**$208.8**	7%	**$222.6**	7%	**$224.8**	1%
Risk discount	*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*		*65%*	
Net Sales of TRV130 - risk adj. ($M)	**$3.9**		**$27.3**		**$47.3**		**$59.7**		**$68.3**		**$73.1**		**$77.9**		**$78.7**	

Source: Jefferies estimates, company data

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Company Description

Trevena Inc. a clinical stage biopharmaceutical company, headquartered in King of Prussia, PA, and is the leader in the discovery and development of G-protein coupled receptors (GPCR) biased ligands. Trevena's lead pipeline program, TRV-027, is currently in Phase IIb trials in acute heart failure. Trevena is also developing novel therapeutics for pain with TRV-130 in Phase II trials in patients with post-surgical pain.

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- Novartis AG (NOVN VX: CHF74.85, HOLD)
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- Verastem Inc. (VSTM: $14.60, BUY)
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