TREVENA INC
Form 10-K
March 20, 2014

Use these links to rapidly review the document
TABLE OF CONTENTS

Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ý **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2013

or

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to
Commission File Number 000-19119

Trevena, Inc.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**26-1469215**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
1018 West 8th Avenue, Suite A King of Prussia, PA	**19406**
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code: **(610) 354-8840**

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Name of each exchange on which registered**
Common Stock, par value $0.001 per share	NASDAQ Global Select Market

Securities registered pursuant to Section 12(g) of the Act: **None**

(Title of Class)

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes o No ý

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes o No ý

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes o No ý

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes o No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ý

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer," and "smaller reporting company" in Rule 12b-2 of the Exchange Act.:

Large accelerated filer o	Accelerated filer o	Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company ý

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes o No ý

The aggregate market value of the voting stock held by non-affiliates of the registrant, as of March 17, 2014, was approximately $72.0 million. Such aggregate market value was computed by reference to the closing price of the Common Stock as reported on the NASDAQ Global Select Market on March 17, 2014. The registrant has elected to use March 17, 2014 as the calculation date, as on June 30, 2013 the registrant was a privately held concern. For purposes of making this calculation only, the registrant has defined affiliates as including only directors and executive officers and shareholders holding greater than 10% of the voting stock of the registrant as of March 17, 2014.

The number of shares of the registrant's Common Stock outstanding as of March 17, 2014 was 26,208,754.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2014 annual meeting of stockholders to be filed pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2013 are incorporated by reference into Part III of this Form 10-K.

Table of Contents

TABLE OF CONTENTS

		Page
Cautionary Note Regarding Forward-Looking Statements		2
	PART I	
Item 1.	Business	3
Item 1A.	Risk Factors	46
Item 1B.	Unresolved Staff Comments	79
Item 2.	Properties	79
Item 3.	Legal Proceedings	79
Item 4.	Mine Safety Disclosures	79
	PART II	
Item 5.	Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	80
Item 6.	Selected Financial Data	82
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	83
Item 7A.	Quantitative and Qualitative Disclosures About Market Risk	96
Item 8.	Financial Statements and Supplementary Data	97
Item 9.	Changes in and Disagreements With Accountants on Accounting and Financial Disclosure	130
Item 9A.	Controls and Procedures	130
Item 9B.	Other Information	130
	PART III	
Item 10.	Directors, Executive Officers and Corporate Governance	131
Item 11.	Executive Compensation	131
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	131
Item 13.	Certain Relationships and Related Transactions, and Director Independence	131
Item 14.	Principal Accountant Fees and Services	131
	PART IV	
Item 15.	Exhibits and Financial Statement Schedules	132
SIGNATURES		136

Table of Contents

Cautionary Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K (this "Annual Report") contains forward-looking statements that involve substantial risks and uncertainties. The forward-looking statements are contained principally in the sections entitled "Business," "Risk Factors," and "Management's Discussion and Analysis of Financial Condition and Results of Operations," but are also contained elsewhere in this Annual Report. In some cases, you can identify forward-looking statements by the words "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "project," "potential," "continue" and "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Annual Report, we caution you that these statements are based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain. Forward-looking statements include statements about:

- our plans to develop and potentially commercialize our product candidates;
- the exercise by Forest of its option to license TRV027 and, if it does, our ability to achieve milestones under the license;
- our planned clinical trials and preclinical studies for our product candidates;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;
- the extent of clinical trials potentially required by the FDA for our product candidates;
- the clinical utility and market acceptance of our product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position; and
- our ability to identify additional product candidates with significant commercial potential that are consistent with our commercial objectives.

You should refer to the "Risk Factors" section of this Annual Report for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Annual Report will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Table of Contents

PART I

ITEM 1. BUSINESS

Overview

Trevena, Inc. is a clinical stage biopharmaceutical company that discovers, develops and intends to commercialize therapeutics that use a novel approach to target G protein coupled receptors, or GPCRs. Unless the context otherwise requires, we use the terms "Trevena," "company," "we," "us" and "our" to refer to Trevena, Inc. Using our proprietary product platform, we have identified and advanced three differentiated product candidates into the clinic. We have completed a Phase 2a clinical trial and initiated a Phase 2b clinical trial of TRV027 for acute heart failure, or AHF. Forest Laboratories Holdings Limited, or Forest, has the exclusive option to license TRV027 from us. TRV130 has completed a Phase 1b clinical trial to evaluate its potential to treat moderate to severe acute pain intravenously and we plan to complete an additional Phase 1 clinical trial and initiate a Phase 2a/b trial in the first half of 2014. We expect to have Phase 2a/b data for TRV130 by the end of the first quarter of 2015 and Phase 2b data for TRV027 by the end of the fourth quarter of 2015. We have retained all worldwide development and commercialization rights to TRV130. We are currently running a Phase 1 trial for our other product candidate, TRV734. We plan to develop and commercialize TRV027 and TRV130 initially in the acute care hospital market. We plan to advance TRV734 and our most advanced preclinical program focused on central nervous system, or CNS, indications.

GPCRs are a large family of cell surface receptors that trigger two signaling pathways, G protein and β-arrestin, and are implicated in cellular function and disease processes. More than 30% of all therapeutics currently marketed target GPCRs. Currently available therapeutics that target GPCRs, or GPCR ligands, are typically not signal specific, and therefore either inhibit both the G protein and β-arrestin pathways (an antagonist ligand) or activate both pathways (an agonist ligand). This lack of signal specificity often results in a suboptimal therapeutic profile for these drugs because in many cases one of the pathways is associated with a beneficial therapeutic effect and the other is associated with an undesirable side effect (see Figure 1). We use our proprietary Advanced Biased Ligand Explorer, or ABLE, product platform to identify "biased" ligands, which are compounds that activate one of the two signaling pathways of the GPCR and inhibit the other (see Figure 2). This signaling specificity is the basis for our drug discovery and development approach, which is to identify and develop therapeutics targeting established GPCRs while offering a differentiated and superior therapeutic profile compared to currently available GPCR-targeted drugs.

We were founded in late 2007 to discover and develop product candidates based on biased ligands, a concept discovered by our scientific founder, Dr. Robert Lefkowitz, who was awarded the 2012 Nobel Prize in Chemistry in part for his elucidation of the multiple pathways that a GPCR engages. We believe that we are the first company to progress a GPCR biased ligand into clinical trials. The members of our executive management team have held senior positions at leading pharmaceutical and biotechnology companies and possess substantial experience across the spectrum of drug discovery, development and commercialization.

Table of Contents

Figure 1: Mechanism of current GPCR-targeted drugs

Figure 2: Mechanism of our biased ligands the next generation of GPCR-targeted drugs

Our Clinical Stage Programs

TRV027 for the treatment of AHF

We are developing TRV027 as a first-line, intravenous, or IV, treatment in combination with standard diuretic therapy for AHF patients. There are over 20 million people living with heart failure in the United States and Europe, according to the American Heart Association, or AHA, and the European Society of Cardiology, or ESC. AHF is heart failure requiring hospitalization. The National Hospital Discharge Survey, or NHDS, reported over 5 million hospital discharges in the United States in 2010 where heart failure was listed as a component of the diagnosis, over 1 million of which listed

Table of Contents

heart failure as the primary diagnosis. In 2009, the AHA estimated the cost of heart failure hospitalization in the United States to be $20.1 billion. AHF represents a serious unmet need for patients, physicians and healthcare systems.

TRV027 is a peptide β-arrestin biased ligand that targets the angiotensin II type 1 receptor, or AT1R, which is a GPCR expressed on cells within the cardiovascular system. The native ligand that activates the AT1R is angiotensin II, which is a key mediator of the renin angiotensin system, or RAS. In many individuals with heart failure, RAS is activated and angiotensin II levels are elevated. Angiotensin II stimulates cardiac contractility, which is the ability of the heart to produce force during contraction, through β-arrestin signaling, but also increases blood pressure and causes fluid retention through G protein signaling. Increased blood pressure and fluid retention strain the heart and damage the kidneys, resulting in multi-organ pathophysiology. Current AT1R-targeted therapies for chronic heart failure antagonize the receptor and are called angiotensin receptor blockers, or ARBs. These unbiased drugs fully block the effects of angiotensin II, decreasing blood pressure and preserving kidney function, but preventing the stimulation of cardiac contractility. We believe that the resulting risk of acutely impairing cardiac function has limited the development of ARBs for the treatment of AHF. In contrast, TRV027 selectively blocks G protein signaling at the AT1R, reducing blood pressure and preserving kidney performance, while activating β-arrestin signaling, and thereby has the potential to promote contractility, preserve cardiac performance and increase cardio-protective signaling.

In our preclinical studies and our Phase 1b and Phase 2a clinical trials, TRV027 demonstrated beneficial effects on the kidneys, heart and blood vessels. We believe that there are no therapies currently approved for AHF that benefit all three of these key organ systems. We have started enrolling patients in a Phase 2b dose-ranging clinical trial of TRV027 in AHF patients with the primary endpoint consisting of a composite of clinically important outcomes. If Forest exercises its option to license TRV027, they will be responsible for all the costs associated with any further development and commercialization of TRV027 and will have exclusive commercialization rights worldwide, subject to the obligation to consider in good faith whether to grant us the right to co-promote TRV027 in the United States on terms to be agreed.

TRV130 for the treatment of moderate to severe acute pain

We are developing TRV130 as a first-line treatment for patients experiencing moderate to severe acute pain where IV administration is preferred. According to data from IMS Health, a healthcare information firm, there were approximately 30 million reimbursement claims made for IV opioids by hospitals in the United States in 2010, of which 14 million were inpatient and 16 million were outpatient claims. We anticipate that the initial market opportunity for TRV130 will be in this acute care hospital setting, with a focus on postoperative pain. The IMS Health reimbursement data also show that 75% of inpatient claims and 50% of outpatient claims for IV opioids were surgery-related in 2010. Opioid analgesics such as morphine and fentanyl, which are unbiased μ-opioid agonists, are currently the most effective IV analgesics for moderate to severe acute postoperative pain, but their use is limited by well-known side effects such as respiratory depression, nausea and vomiting, constipation and postoperative ileus. Based on our analysis of a series of published clinical and health economic studies, we believe that the side effects of currently available intravenously administered μ-opioid agonists in the postoperative care setting result in additional annual costs of approximately $5 billion in the United States alone, predominantly due to the need for lengthier hospital stays.

TRV130 is a small molecule G protein biased ligand that targets the μ -opioid receptor, which is a GPCR expressed on cells within the central nervous and intestinal systems. TRV130 activates the μ-opioid G protein pathway, which has been associated with analgesia, or pain relief, while inhibiting the β-arrestin pathway, which in preclinical studies has been associated with constipation and respiratory depression. If further testing confirms that TRV130 avoids the side effects typically associated with the activation of the μ-opioid receptor, we believe that TRV130, if approved, could be a

Table of Contents

more effective treatment for postoperative pain than currently available μ-opioid therapies and could thereby expedite postoperative recovery and hospital discharge.

In a Phase 1b trial in healthy subjects using an evoked-pain model, TRV130 showed superior analgesia compared to a high dose of morphine, while causing less respiratory depression, nausea and vomiting. These data are consistent with our preclinical and Phase 1 data, and are the basis for our belief that TRV130 may have an improved therapeutic profile with respect to respiratory depression, nausea and vomiting compared to currently approved unbiased opioids. In preclinical studies, TRV130 also demonstrated less constipation as compared to morphine.

We expect to initiate a Phase 2a/b clinical trial of TRV130 in the first half of 2014 in postoperative patients with the goal of demonstrating analgesic efficacy and evaluating the relationship between its efficacy and tolerability compared to morphine. In the second half of 2014, we expect to initiate additional clinical work to evaluate TRV130's safety and tolerability profile compared to unbiased μ-opioid agonists. We have retained all development and commercialization rights to TRV130 worldwide. We intend to retain full commercialization rights in the United States for TRV130. After the availability of Phase 2 clinical data for TRV130, we may seek collaborators for commercializing TRV130 outside of the United States to offset risk and preserve capital.

TRV734, oral agent for the treatment of moderate to severe acute and chronic pain

TRV734 is a small molecule G protein biased ligand targeting the μ-opioid receptor. We are developing TRV734 as a first-line, orally administered treatment of moderate to severe acute and chronic pain. Data from IMS Health shows that opioid drug sales across the United States, Europe and Japan were almost $11 billion in 2012. Despite widespread use, there are significant limitations to existing therapies with respect to constipation, nausea and vomiting and respiratory depression. The objective of TRV734 is to deliver the benefits we believe are characteristic of TRV130 in an orally bioavailable therapeutic. TRV734 exhibited similar effects as TRV130 in preclinical *in vitro* and *in vivo* studies, and has shown oral bioavailability in primates. We initiated a Phase 1 clinical trial of TRV734 in the first quarter of 2014 to evaluate safety, tolerability and oral bioavailability in humans. We intend to seek a collaborator with experience in developing and commercializing controlled-substance therapeutics in chronic care pain markets to assist in the development of TRV734, while retaining rights to commercialize TRV734 in hospital and specialist markets in the United States.

Our Additional Program

δ-*opioid receptor G protein biased ligand therapeutics*

We are also focused on the discovery of a novel, orally bioavailable, small molecule δ-opioid receptor G protein biased ligand with potential for the treatment of CNS disorders, of which we intend to initially focus on Parkinson's disease, pain or depression. We have identified potent, biased modulators of the δ-opioid receptor that show positive efficacy in animal models of each of these indications without the seizure risk characteristic of δ-opioid receptor agonists previously developed by others.

Our Strategy

Our goal is to build a leading biopharmaceutical company leveraging our expertise in biased ligands to develop and commercialize innovative, best-in-class drugs targeting established GPCRs. Key elements of our business strategy to achieve this goal are to:

Rapidly advance clinical development of our three lead product candidates to commercialization.

Table of Contents

We plan to complete the Phase 2b trial for TRV027 for the treatment of AHF by the end of 2015. If this trial is successful and Forest exercises its option, Forest will be responsible for all costs associated with further development and commercialization of TRV027. If the option is exercised, we will be entitled to an upfront option exercise fee and certain contingent milestone payments and royalties, which we intend to use to further develop and potentially commercialize our proprietary portfolio.

We plan to develop and commercialize TRV130 for the treatment of moderate to severe acute postoperative pain and other indications where IV therapy is preferred, such as end-of-life care. The efficacy of drugs targeting the μ-opioid receptor is well-established. We intend to conduct a Phase 2a/b trial to demonstrate efficacy and explore the relationship between efficacy and tolerability compared to morphine and to conduct additional clinical work in parallel to support the potential for an improved therapeutic profile compared to an unbiased μ-opioid analgesic. The Phase 2a/b is expected to be complete by the end of the first quarter of 2015 and the additional clinical work is expected to be complete by the end of the fourth quarter of 2015. We believe this parallel-track development plan will allow us to accelerate the transition into a Phase 3 program and, if approved, commercialization.

We plan to develop TRV734 for oral use in moderate to severe acute and chronic pain. We intend to seek a collaborator with experience in developing and commercializing controlled-substance therapeutics in chronic care pain markets while retaining rights to commercialize TRV734 in hospital and specialist markets in the United States. We are conducting a Phase 1 study of TRV734 to determine the oral bioavailability of the compound. The Phase 1 study is expected to be complete by the end of the third quarter of 2014.

Establish commercialization and marketing capabilities in the United States, initially in acute care markets, for any of our product candidates that are approved or that we anticipate may be approved.

If any of our products beyond TRV027 receive or are anticipated to receive regulatory approval, we intend to build a focused sales force and establish marketing capabilities to commercialize those products to specialists in the United States, initially in the acute care setting.

We intend to retain full commercialization rights in the United States for TRV130. After the availability of Phase 2 clinical data for TRV130, we may seek collaborators for commercializing TRV130 outside the United States to offset risk and preserve capital.

We intend to seek a collaborator with experience in developing and commercializing controlled-substance therapeutics in chronic care pain markets to assist in the development of TRV734, while retaining rights to commercialize TRV734 in hospital and specialist markets in the United States.

If Forest exercises its option to license TRV027, Forest will be responsible for commercialization of TRV027 worldwide. We have the option to negotiate with Forest for co-promotion rights in the United States, although Forest has no obligation to grant us any co-promotion rights. We expect that TRV027, if approved, would be used primarily in the acute care setting, thereby providing an opportunity to leverage the commercial infrastructure we plan to implement to market TRV130 if it is approved.

Expand our CNS product portfolio through the development of our preclinical program.

We plan to build a robust product portfolio in the CNS area, where we have identified potential for biased ligands, including TRV130, TRV734 and a product candidate from our δ-opioid receptor ligand program.

Our goal is to deliver the first δ-opioid receptor-targeted therapeutic for the treatment of CNS disorders, such as Parkinson's disease, pain and depression. We are currently optimizing our lead biased ligand product candidate. We intend to maintain flexibility on whether to develop and commercialize

Table of Contents

this product candidate in collaboration with a pharmaceutical company licensee depending on the clinical indications we ultimately decide to pursue, but we intend to retain meaningful commercial rights in any event.

Leverage our ABLE product platform to continue to discover and develop a pipeline of innovative biased ligand therapeutics and expand our product platform's impact through external collaborations.

We have used our ABLE product platform to identify three potential therapeutics targeting GPCRs. We are in lead optimization with a fourth product candidate discovery program, and have also identified additional high-value GPCR targets. As part of our longer term strategy, we plan to initiate internal drug discovery efforts in CNS indications and other areas of significant unmet medical need, and to continue to mitigate development risk by focusing on product candidates targeting GPCRs with well-established mechanisms of action. We also intend to selectively collaborate on discovery and development programs to leverage the potential of our ABLE product platform.

Our ABLE Product Platform

Our ABLE product platform is a collection of proprietary biological information, *in vitro* assays, know-how and expertise that we use to identify unique GPCR-targeted biased ligands with attractive pharmaceutical properties. These *in vitro* assays use cells that have the receptor of interest on the cell surface, where G protein and β-arrestin signaling from that receptor can be measured to determine if a particular ligand is biased, and if so whether it is a G protein or β-arrestin biased ligand. Our assays can also measure different cellular responses resulting from signaling through β-arrestin and can thereby help us to associate pharmacological responses with molecular signaling. Most components of our ABLE product platform are maintained as trade secrets, but the output of the product platform is reflected in the product candidates that we have advanced into clinical testing and the research we have published in numerous peer-reviewed journals. We believe the set of competencies reflected in our ABLE product platform provides us with an important competitive advantage in identifying further opportunities for efficient and high-impact biased ligand drug discovery, development and commercialization.

Our Pipeline

Table of Contents

TRV027

TRV027 is a peptide β-arrestin biased ligand that targets the AT1R, inhibiting G protein signaling and activating β-arrestin signaling. We are developing TRV027 for the treatment of AHF in combination with standard diuretic therapy. In our Phase 2a clinical trial, TRV027 rapidly reduced blood pressure and preserved renal, or kidney, function, while preserving cardiac performance. We have started enrolling patients in a Phase 2b clinical trial to evaluate the safety and efficacy of TRV027 in AHF. If subsequent Phase 3 development is successful and TRV027 is approved by regulatory authorities, we believe TRV027 would be used as a first-line in-hospital AHF treatment. We also believe TRV027 could improve AHF symptoms and shorten length of hospital stay and potentially lower readmission rates and mortality rates after hospital discharge.

Disease

Heart failure is the inability of the heart to supply adequate blood flow, and therefore oxygen, to peripheral tissues and organs. When the heart is failing, mechanisms are triggered by the body to maintain blood pressure and tissue perfusion. One such mechanism is the activation of RAS, of which angiotensin II is a key mediator. Through angiotensin II, RAS increases blood pressure and stimulates the kidneys to retain both sodium and water. These mechanisms maintain cardiac performance in the short term, but in the longer term, the heart must pump against higher pressure, referred to as afterload, and is overstretched when filled, referred to as preload. These effects make the failing heart pump less efficiently and lead to progressive damage to the muscular tissue of the heart.

There are over 20 million people living with heart failure in the United States and Europe, according to the AHA and ESC. AHF, also sometimes referred to as acute decompensated heart failure, is heart failure requiring hospitalization. AHF patients present with fluid overload and severe dyspnea, a serious shortness of breath sometimes described as "air hunger," leading to an inability to perform simple functions such as standing and walking short distances. AHF can also lead to organ dysfunction, such as in the kidneys and heart. Most patients experiencing an AHF event have a worsening of existing chronic heart failure, although an estimated 25% of AHF hospitalizations represent new diagnoses of heart failure.

According to NHDS data, in the United States there were over 5 million hospital discharges in 2010 where heart failure was listed as a component of the diagnosis, over 1 million of which listed heart failure as the primary diagnosis. Based on national hospital discharge statistics from 25 countries in Europe, we estimate that there were a total of 1.6 million hospitalizations with a primary heart failure diagnosis in 2010 in those countries. Despite long hospital stays, up to approximately 50% of AHF patients remain symptomatic on discharge according to data from ADHERE, a national U.S. registry of over 100,000 patients admitted to the hospital with AHF between 2000 and 2005. In addition, the risk of readmission is 25% after 30 days and the one-year mortality rate is approximately 30%. Combined, these poor outcomes result in a substantial burden to the healthcare system. In 2009, the AHA estimated the cost of heart failure hospitalization in the United States to be $20.1 billion. We believe there is a significant unmet medical need for improved treatments for AHF.

Current treatment options for AHF

None of the currently available therapeutic options, which are listed below, target all three of the key organ systems affected by AHF:

Loop diuretics, such as furosemide, target the kidneys and remove excess fluid, but can worsen renal function in the process.

Table of Contents

Vasodilators, like nitrates or nesiritide, target the blood vessels and reduce blood pressure, reducing load on the heart, but each of these agents has undesirable side effects that limit its use.

Inotropes, such as dobutamine, target the heart and directly stimulate cardiac contractility. However, current inotropes increase mortality through an increased risk of arrhythmia.

The mainstay of therapy for AHF is loop diuretics, such as furosemide. In AHF patients, fluid removal is important to relieve symptoms and to improve tissue oxygenation. Furosemide facilitates excretion of excess fluid, but aggressive diuresis can lead to renal dysfunction. Worsening renal function in AHF patients is associated with higher mortality and increased risk of hospital readmission. Diuretic therapy has also been shown to precipitate activation of RAS, further exacerbating the vicious cycle of heart failure.

After diuretics, IV vasodilators, such as nitroglycerin, nitroprusside and nesiritide, are the most common medications used for the treatment of AHF. These vasodilators effectively reduce blood pressure, but each is associated with undesirable side effects and other limitations. Hypotension, or low blood pressure, is the most common serious side effect of vasodilating agents. Nitroglycerin raises RAS and is also often hampered by rapid development of tolerance, such that the medication becomes less effective the longer that it is used. Nitroprusside is associated with possible cyanide toxicity and cannot be used without intensive monitoring, so its use is limited. Nesiritide was launched in 2001 and initially saw rapid adoption, reaching a peak in use of 16.6% of AHF hospital admissions in March 2005. Shortly thereafter, two independent publications reported associations between nesiritide and worsening renal function and an increase in mortality, after which sales of the drug declined significantly. In response, the drug's sponsor conducted a safety study of 7,000 patients, known as ASCEND. This study, while not confirming the safety risk for nesiritide, failed to demonstrate a benefit over background therapy, and subsequent use of the drug has continued to decline. Nesiritide lowers blood pressure, but if the blood pressure is lowered too far, the effect is difficult to reverse. This prolonged hypotension may produce end-organ dysfunction.

In severe cases, and those characterized by very low cardiac output, physicians sometimes resort to the use of inotropes, which work by increasing cardiac contractility by mobilizing calcium but at the expense of increased oxygen consumption and risk of arrhythmia. These agents can improve symptoms in the short term but have been shown to increase mortality.

There is an unmet need for better therapeutic approaches to treat AHF that can improve blood circulation through vasodilation, facilitate fluid excretion by the kidneys and enhance cardiac function through a novel mechanism not requiring calcium mobilization. Based on our preclinical studies and our clinical trials, we believe TRV027 has the potential to meet each of these critical criteria, and may prove to be more effective than currently available treatment options, reducing hospital readmission rates, mortality rates and length of hospital stay, while improving symptoms more rapidly and more completely.

Key differentiating attributes of TRV027

We believe that TRV027 has the following potential advantages over currently available treatment options:

Efficacy

Benefits the three key organ systems. Unlike current therapies, in our preclinical studies and Phase 1b and 2a clinical trials, TRV027 has shown beneficial effects on the blood vessels, heart and kidneys. TRV027 rapidly and reversibly lowered blood pressure and pulmonary capillary wedge pressure, or PCWP, which is a measure of pressure buildup in the lungs. A drop in PCWP is correlated with an improvement in dyspnea. These beneficial

Table of Contents

effects on blood pressure and PCWP allow the heart to pump more effectively thereby preserving cardiac performance. TRV027 also preserved kidney function, which in the context of lowered blood pressure is an important characteristic of a vasodilator for AHF. In combination, we believe these effects may translate into improvements in symptoms and outcomes such as hospital readmission rates, length of hospital stay and mortality rates if TRV027 successfully completes Phase 3 development and is approved by regulatory authorities.

Enhances furosemide's effects on PCWP. Furosemide or other loop diuretics are used as the first-line treatment in approximately 90% of AHF patients in all major pharmaceutical markets. Loop diuretics, like furosemide, facilitate excretion of excess fluid, but also activate RAS, which may compromise their ability to fully resolve symptoms. Renal safety concerns limit dose escalation of furosemide. Approximately 50% of AHF patients remain symptomatic at hospital discharge. We believe that administering TRV027 in combination with furosemide may improve dyspnea directly by decreasing pressure on the heart and in the lungs and indirectly by allowing furosemide to work more effectively without the negative consequences of RAS activation. In a dog model of heart failure, TRV027 showed an additional decrease in PCWP when combined with furosemide compared to furosemide alone. TRV027's additive effect with furosemide is expected to more rapidly resolve dyspnea, reducing the length of hospital stay, and more fully resolve symptoms, reducing readmission.

Targets RAS, a mechanism that is central to the disease. None of the therapies currently approved for AHF improve long-term outcomes. RAS blockade has been shown to have morbidity and mortality benefits in chronic heart failure. We believe that TRV027, if approved, could be the first therapy to bring modulation of RAS to the acute hospital setting, allowing the physician to improve blood circulation while protecting the heart and kidneys.

Drug safety and tolerability

Favorable drug safety profile. We believe that TRV027's tolerability profile sets it apart from current therapies. In healthy subjects in our Phase 1 clinical trial, there were no significant adverse effects even at doses 20 times higher than the expected therapeutic dose. In addition, there were no TRV027-related serious adverse events in a Phase 2a trial in medically fragile, severe chronic heart failure patients and no clinically significant adverse events in subjects with heart failure and concomitant renal impairment. Finally, in preclinical toxicology studies, TRV027 had a favorable profile at doses up to 500 times the expected therapeutic dose.

Self-limiting blood pressure effect. In our Phase 2a clinical trial, there was a dose-dependent decrease in blood pressure up to doses of 1 μg/kg/min. No further reduction in blood pressure was seen at doses up to 3 μg/kg/min. We believe that this characteristic would offer a safety advantage over current vasodilators, which can cause dangerous hypotension.

Rapidly reversible effects on blood pressure. In our clinical trials, TRV027 had a very short half-life and its effects were rapidly reversible. In the acute care setting, this should allow the physician to alter the dose and avoid prolonged hypotension.

Action specific to target pathophysiology. In our clinical trials, TRV027 lowered blood pressure only in subjects with elevated measures of RAS activity, the target pathophysiology. This is important for any drug that is used in emergency rooms when the initial diagnosis may be uncertain.

Table of Contents

Clinical experience

We have had an active investigational new drug application, or IND, for TRV027 for AHF with the U.S. Food and Drug Administration, or FDA, since February 2010. Since then, we have completed three clinical trials of TRV027:

- A Phase 2a trial in medically fragile subjects with advanced stable heart failure, low ejection fraction and a clinical indication for right-heart catheterization. Ejection fraction is a measure of the volume of blood pumped by the heart. Right-heart catheterization is a procedure that allows measurement of intracardiac and intravascular pressures on the side of the heart leading to the lungs. This procedure is not commonly used for the treatment of AHF patients, so this trial enabled us to profile the hemodynamic effects of TRV027 in a comparatively stable chronic heart failure population, which could be considered an AHF forerunner population.

- A Phase 1b trial in subjects with moderate heart failure and concomitant renal dysfunction. Selecting a stable population allowed us to directly measure renal plasma flow, or RPF, and glomerular filtration rate, or GFR, two common measures used to evaluate renal safety.

- A Phase 1 clinical trial in healthy subjects to evaluate pharmacokinetics and tolerability prior to moving into chronic stable heart failure subjects.

Phase 2a hemodynamics trial in advanced stable heart failure subjects

The primary objectives of this trial were to characterize the safety and tolerability of TRV027 in subjects with advanced stable heart failure and to measure its effects on blood circulation, also known as hemodynamics. Due to the wide dose-range available following the Phase 1 clinical trial, we elected to employ a step-wise dose titration over five hours with the dose increased to a target dose 10-fold higher than the starting dose. This highest dose was continued for nine hours as a steady state infusion, for a total infusion time of 14 hours, to evaluate the stability of TRV027's hemodynamic effects. Reversibility of TRV027's effects was then studied for four hours after the infusion was discontinued. Three dosing regimens were evaluated in 24 subjects: 0.1 μg/kg/min titrated up to 1 μg/kg/min; 0.3 μg/kg/min titrated up to 3 μg/kg/min; and 1 μg/kg/min titrated up to 10 μg/kg/min. In total, 14 different doses were studied across the three different dosing regimens. Nine additional subjects received placebo in a double blind manner. Based on the preclinical and Phase 1 data, we were expecting the hemodynamic effects of TRV027 to depend on elevation of RAS activity. The data were therefore analyzed based on plasma renin activity, or PRA, elevation, with high PRA subjects defined as those with PRA levels greater than 5.82 ng/ml/hr, which is the upper limit of lab normal range. PRA is an enzyme in the RAS cascade and measures RAS activity. Eleven of the 24 treated subjects had high PRA.

In this trial, TRV027 produced a dose-related decrease in mean arterial pressure, or MAP, in subjects with elevated PRA, as shown in Figure 3, which was sustained during the steady state infusion. This decrease in MAP was reversed during the washout period following the end of the infusion. This reversal of effect was statistically significant compared to both placebo and normal PRA subjects with p-values of less than 0.01 and 0.001, respectively. P-value is a conventional statistical method for measuring the statistical significance of clinical results. A p-value of 0.05 or less represents statistical significance, meaning that there is less than a 1-in-20 likelihood that the observed results occurred by chance. The decrease in MAP in the high PRA subjects compared to subjects receiving placebo in the maintenance phase was also statistically significant, with a p-value of less than 0.05.

Table of Contents

Figure 3: Effect of TRV027 on mean arterial pressure in advanced stable heart failure subjects with elevated PRA

We also observed evidence of pharmacologic effects on PCWP in the subjects with elevated PRA. PCWP dropped in subjects with high PRA during the titration phase and this was sustained during the maintenance phase and reversed during the wash-out phase. The interpretation of the results in the titration and maintenance phases was complicated by a baseline drift in PCWP in the placebo group, however, the increase in PCWP when the TRV027 infusion was stopped was clear and statistically significant in high PRA compared to normal PRA subjects, with a p-value of less than 0.01.

Table of Contents

Figure 4: Reversal of effect of TRV027 on pulmonary capillary wedge pressure in advanced stable heart failure subjects

We defined a responder as a subject experiencing decreases in both MAP and PCWP during the continuous infusion. Of the high PRA subjects, 73% were responders compared to 38% for normal PRA subjects and 13% for placebo subjects.

In this trial, there was no apparent change in cardiac index or heart rate observed in subjects with normal or high PRA following administration of TRV027. Cardiac index is a well accepted measurement of how well the heart is functioning as a pump by directly correlating the volume of blood pumped by the heart with an individual's body surface area. This contrasts with the response of heart failure subjects to acute administration of the ARB, losartan, which has been shown to decrease cardiac index in some studies.

TRV027 was well tolerated in this medically fragile population. Despite the substantial reduction in MAP in TRV027-treated high-PRA subjects, there was no apparent increase in heart rate or in levels of cystatin-C or creatinine, which are biomarkers of renal function. This suggests that the blood pressure reduction was accompanied by preservation of kidney function. This result was consistent with our observations in preclinical studies. One subject in the lowest-dose cohort in this trial experienced hypotension necessitating dose reduction and then discontinuation of the TRV027 infusion. No other TRV027-related clinically significant adverse events were reported. In addition, while subjects receiving placebo and normal PRA subjects treated with TRV027 showed an increase in levels of brain natriuretic peptide, or BNP, which is a marker of cardiac stress, high-PRA subjects treated with TRV027 showed less of an increase in BNP, suggesting that TRV027's hemodynamic effects in high-PRA subjects may be protecting the heart from cardiac stress.

This trial was conducted in subjects who were taking standard medication for chronic heart failure. The subjects with high PRA tended to have higher BNP levels and a lower ejection fraction, suggesting that they represent a sicker, more relevant population for AHF. We anticipate that most patients with AHF will have high PRA levels and, accordingly, based on our clinical trial results, we believe that many of them will be responsive to TRV027 if it is approved. Based on these data from the Phase 2a clinical trial, we also believe that TRV027 may show positive effects in patients who are currently taking ACE inhibitors, or ACEis, which are a commonly prescribed therapeutic for patients with high blood pressure and heart failure. In our trial, 21 of 24 treated subjects were taking ACEis.

Table of Contents

Medications were withheld on the day of dosing, but this is insufficient to wash-out background ACEi levels, which means that TRV027 was effectively studied in combination with background ACEis.

Approximately 12% of congestive heart failure patients are prescribed ARBs. Subjects taking ARBs were excluded from the Phase 2a trial because TRV027 may need to be administered at a different dose to these patients, due to competition for the same receptor. We expect to study the effects of TRV027 on ARB patients in later stage development.

Phase 1b renal safety trial in stable chronic heart failure subjects

The primary objective of this trial was to explore the pharmacokinetics and renal safety of TRV027, co-administered with furosemide, in 17 subjects with a history of heart failure and concomitant renal dysfunction. Two cohorts of six subjects and one cohort of five subjects were enrolled in this two-period crossover trial. All of the subjects had moderate heart failure and concomitant renal dysfunction.

TRV027 was administered using a standard dosing paradigm, with doses of 1.25 mg/hr, 6.25 mg/hr and 31.25 mg/hr (equivalent to 0.35 µg/kg/min, 1.74 µg/kg/min and 8.68 µg/kg/min, respectively, for a 60 kg person), without weight correction. The plasma concentrations obtained were similar to those obtained when TRV027 was administered on a per-kg basis to subjects with normal kidney function, suggesting that a standard dosing approach with no adjustment for weight or renal impairment is appropriate, which would facilitate use in the emergency room where patients are not routinely weighed.

TRV027 was well tolerated in these renally impaired subjects. There were no TRV027-related clinically significant or serious adverse events reported. Previously published research has shown that oral furosemide administration produces a reduction in GFR that can be inhibited by blocking the effects of elevated angiotensin II. In our trial, however, there was no effect of the single dose of furosemide on GFR or RPF; therefore, it was not possible to show a renal protective effect of TRV027. The trial did, however, show that TRV027 itself preserved GFR and RPF, before and after furosemide administration. In this trial, co-administration of TRV027 did not impair furosemide's effect on diuresis or urinary sodium excretion.

Taken together, we believe the Phase 2a and Phase 1b trials in stable chronic heart failure subjects provide evidence for TRV027's beneficial effects on the heart, the blood vessels and kidney function, consistent with the data we had obtained in preclinical studies.

Phase 1 clinical trial

The Phase 1 clinical trial was a single center, crossover trial evaluating four-hour infusions of TRV027 in 20 healthy subjects at doses ranging from 0.01 to 20 µg/kg/min. The primary objective of the trial was to evaluate the tolerability and pharmacokinetics of TRV027. TRV027 was well tolerated with no serious adverse events or clinically significant adverse events reported even at doses up to 20 times higher than the expected therapeutic dose. There was a linear increase in exposure with dose and TRV027 was rapidly cleared when the infusion was stopped, suggesting that it will potentially be easy to reverse any unexpected hypotensive effects. There was no urinary excretion of TRV027 so we do not expect any dose adjustments to be required for renal insufficiency. We believe this characteristic may make TRV027 easy to use in the emergency room. We also employed a brief sodium restriction paradigm to attempt to physiologically activate RAS and thereby elicit the pharmacodynamic effects of TRV027. Based on this compressed sodium restriction paradigm, four of the 20 subjects experienced a measurable elevation in RAS, with elevated RAS defined as PRA greater than or equal to 3 ng/hr/mL. Modest decreases in MAP were evident in three of the four subjects with elevated RAS. No change in MAP was seen in subjects with normal PRA. These results are consistent with our belief that TRV027 reduces load on the heart but only in patients with elevated RAS, the target pathophysiology.

Table of Contents

Preclinical studies

In a paced dog animal model of heart failure, TRV027 decreased MAP and PCWP. TRV027 also increased renal blood flow and moderately increased cardiac output. TRV027 was also studied in combination with furosemide in another paced dog model study and showed additive effects on reducing PCWP, which would be consistent with beneficial effects on dyspnea in the clinic. In addition, combining the data in normal dogs, paced dogs and paced dogs treated with furosemide, we observed meaningful blood pressure decreases only in animals with elevated RAS, which is consistent with the data seen in the clinical trials and we believe provides further evidence supporting the premise that TRV027 only works in patients with the target pathophysiology. Furthermore, the dose response observed in paced dogs was consistent with that observed in subjects in the Phase 2a trial.

To examine the direct effects of TRV027 on cardiac contractility, we studied the hemodynamic effects of TRV027 compared to the unbiased ARB telmisartan in normal rats using a micromanometer conductance catheter. TRV027 treatment increased cardiac contractility independent of its effects on blood pressure, as measured by end systolic pressure volume relationship, or ESPVR, a common measure of cardiac output independent of blood pressure, and it also decreased MAP. This compared to telmisartan, which similarly decreased MAP but also decreased ESPVR (see Figure 5). Telmisartan is an unbiased ARB that inhibits both the G protein and β-arrestin AT1R pathways. In addition, in *in vitro* studies, TRV027 stimulated cardiomyocyte contractility through a β-arrestin dependent mechanism and selectively activated a subset of downstream signaling pathways seen with the full agonist, angiotensin II.

Figure 5: Effect of TRV027 on MAP and cardiac contractility in normal rats

The mechanism by which TRV027 increased cardiac contractility in *in vivo* studies does not appear to involve calcium mobilization seen in currently marketed inotropes. Calcium mobilization is linked to pro-arrhythmic effects. In a study we conducted in rats, a β-arrestin biased AT1R ligand closely related to TRV027 increased contractility through a myofilament calcium sensitization mechanism, a novel mechanism of cardiac contractility that does not involve calcium mobilization. In *in vivo* studies, this related ligand prevented hypertrophy and prevented cardiac apoptosis, suggesting a potential cardioprotective effect. Furthermore, cardiac stress in mice induces AT1R, β-arrestin-dependent cardioprotective signaling, suggesting that AT1R β-arrestin biased ligands could be potentially cardioprotective.

Table of Contents

Development strategy

We are enrolling a Phase 2b trial to evaluate the safety and efficacy of TRV027 in AHF. This is a randomized double-blind, placebo controlled trial comparing TRV027 plus standard of care to standard of care alone. The primary objective of this trial is to evaluate the effects of three doses of TRV027, 1.0 mg/hr, 5.0 mg/hr and 25 mg/hr, on a composite of clinically important outcomes. These outcomes are mortality, worsening heart failure, hospital readmission rate, dyspnea and length of hospital stay. Our trial design contemplates that at least 500 patients will be enrolled and randomized. We are targeting early administration of TRV027, ideally within six hours of arrival at the hospital. TRV027 will then continue to be administered for a minimum of 48 hours and up to 96 hours. We believe administration of TRV027 soon after hospital admission will improve in-hospital mortality rates and shorten length of hospital stay. We are enrolling patients with both low ejection fraction and preserved ejection fraction since RAS elevation is a key component of both conditions. We plan to conduct an interim analysis after 300 patients have been enrolled and, depending on the outcome of that analysis, enrollment into one or more of the active dose groups may be discontinued. We expect data from this trial to be available by the end of the fourth quarter of 2015.

We believe that an endpoint measuring dyspnea in Phase 3 trials could form the basis for FDA approval of TRV027. However, we believe the FDA may be open to other well-defined benefit parameters, such as a hospitalization benefit or a patient and caregiver quality of life benefit. The composite endpoint tested in Phase 2b will facilitate our evaluation of potential alternative proposals to be discussed with the FDA at an end-of-Phase 2 meeting.

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

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

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

TRV130

TRV130 is a small molecule G protein biased ligand at the μ-opioid receptor, which we are developing as a first-line treatment for patients experiencing moderate to severe acute pain where IV administration is preferred. TRV130 activates the μ-opioid G protein pathway, associated with

Table of Contents

analgesia, and inhibits the β-arrestin pathway, which, in preclinical studies, was associated with constipation and respiratory depression. We believe that the management of acute postoperative pain represents the largest opportunity for a μ-opioid therapy. Accordingly, the focus of our clinical trials will involve surgical patients. We believe avoiding the side effects typically associated with the activation of the μ-opioid receptor will position TRV130, if approved, to more effectively treat moderate to severe acute pain than currently available μ -opioid therapies and expedite postoperative recovery.

Disease

According to IMS Health, there were approximately 30 million reimbursement claims made for IV opioids by hospitals in the United States in 2010, of which 14 million were inpatient claims and 16 million were outpatient claims. We anticipate that the initial market opportunity for TRV130 will be in this acute care, hospital setting, with a focus on postoperative pain. The IMS Health reimbursement data also show that 75% of inpatient and 50% of outpatient claims for IV opioids were surgery-related in 2010.

In terms of the total potential market opportunity, the World Health Organization estimates that over 230 million major surgical procedures are performed each year worldwide. The NHDS recorded over 30 million hospital inpatient surgical procedures in the United States in 2010. A similar number of hospital inpatient surgeries were performed in France, Germany, the United Kingdom, Italy and Spain, collectively. Data from the U.S. Centers for Disease Control and Prevention in 2006 estimated an additional 20 million outpatient surgical procedures in U.S. hospitals and an additional 14 million procedures in ambulatory surgical centers. Accordingly, we believe that there is a large potential commercial opportunity for TRV130, if approved.

Despite the development and adoption of guidelines for the management of postoperative pain and the extensive use of current treatments, significant unmet need remains. In a survey of 250 surgical patients in the United States, over 70% of the patients undergoing in-hospital procedures reported pain in the postoperative period before hospital discharge, of which almost 50% experienced severe or extreme pain. The dosing of the most effective class of analgesics currently available, μ-opioid agonists, is limited by severe side effects such as respiratory depression, nausea and vomiting, constipation, and postoperative ileus.

Treatment options for moderate to severe, acute postoperative pain

The typical treatment paradigm in developed markets for management of moderate to severe, acute postoperative pain is to initiate injectable or IV medication in the preoperative or immediate postoperative period to provide rapid and effective pain relief. As soon as it is safe and practical, a transition is typically made to oral pain medication, allowing patients to take medication home with them.

Opioid analgesics like morphine, fentanyl and hydromorphone are mainstays of pain treatment in the immediate postoperative period. Non-opioid analgesics are also often added for supplemental analgesia, and to keep opioid doses low to mitigate opioid-related adverse effects. A recent survey we conducted in a sample of 72 U.S. surgeons and anesthesiologists suggests that the most important attribute driving physicians' choice of an IV opioid is analgesic efficacy. In the same survey, respondents stated that injectable non-opioid analgesics are currently used to supplement IV opioids for post-surgical pain management in about 60% of hospital inpatient cases. These drugs, such as IV non-steroidal anti-inflammatory drugs, or NSAIDs, IV acetaminophen or local anesthetics such as bupivacaine, have their own potential side effects in the cardiovascular and GI systems as well as the liver. We estimate that recently introduced branded versions of these drugs can add $42 to $285 per patient per day to the cost of managing patients with moderate to severe postoperative pain in the

Table of Contents

United States. Anti-emetics, laxatives and peripherally restricted opioid antagonists are also employed to combat opioid-induced GI side effects in postoperative patients.

Morphine, fentanyl and hydromorphone are all associated with reduced respiratory rate and reduced tidal volume, which is the amount of air inhaled or exhaled in a single breath. Although serious complications or deaths from opioid-induced respiratory depression are rare, fear of respiratory depression represents a major barrier to the effective use of opioids in the management of postoperative pain because physicians are cautious about increasing dose. We estimate that about 80 thousand cases of opioid-induced respiratory depression occur each year in hospitalized patients in the United States. Risk is higher in some patient groups, such as the obese, patients with chronic obstructive pulmonary disease and patients who suffer sleep apnea. In our survey of U.S. surgeons and anesthesiologists, respiratory failure was cited as the most important opioid analgesic side effect they would like to see addressed.

In several published surveys, patients faced with surgery list the avoidance of postoperative nausea and vomiting, or PONV, as a leading concern. PONV occurs in approximately one third of surgical patients following treatment with IV opioids. We believe that there are over 5 million cases of opioid-induced PONV annually in U.S. hospitals for inpatients alone. We estimate that PONV results in $1.3 billion annually in additional costs for hospital inpatient management of postoperative pain in the United States. The major cost driver is increased length of hospital stay. We further estimate approximately $1.0 billion in cost for PONV in the outpatient setting.

The constipating effects of opioid drugs are also problematic and costly for surgical patients, who are typically not considered ready for discharge until they have had a meal or a bowel movement. Postoperative ileus, or POI, is a condition in which the bowel enters spasm and stops passing food and waste, which most commonly occurs after surgery involving interruption of movement of the intestines. POI is exacerbated by anesthetics and opioid analgesics, and occurs in at least 10% of patients following invasive abdominal procedures. We believe that opioid-induced constipation adds more than $2 billion to the cost of hospital inpatient post-surgical recovery in the United States annually and that POI adds another $1.5 billion.

Key differentiating attributes of TRV130

We believe that TRV130 has the following potential advantages over existing opioid treatments for postoperative pain:

Efficacy

Improved analgesia. In a Phase 1b trial in healthy subjects using an evoked-pain model, TRV130 showed superior analgesia compared to a high dose of morphine and produced less respiratory depression, less nausea and less vomiting compared to morphine. If TRV130 continues in clinical testing to demonstrate an improved therapeutic profile with respect to key safety and tolerability concerns, we believe that TRV130, if approved, may have an improved profile compared to unbiased μ-opioid agonists, which are the current standard of care in terms of efficacy, safety and tolerability.

Less time to peak effect. In preclinical studies, TRV130 delivered maximal efficacy at only five minutes after dosing, compared to morphine, which takes about 30 minutes to reach its maximum effect. In our Phase 1 trial, we also observed full pharmacodynamic response in the form of pupil constriction in humans at 10 minutes after dosing. Pupil constriction is a well-established surrogate for the analgesic efficacy of opioid drugs. We also observed full analgesic effect in the Phase 1b evoked-pain model at the first practical data collection point of 10 minutes after dosing. If our clinical trials continue to bear out this rapid time to peak effect, we believe TRV130, if approved, could provide benefit in the peri-operative

Table of Contents

pain market where fentanyl is commonly used today, thus allowing TRV130 to broaden its market potential.

Targets an established mechanism for the management of moderate to severe acute pain but in a novel way (ligand bias). TRV130 is a G protein biased ligand at the μ-opioid receptor and has shown equivalent or superior analgesic efficacy to morphine in multiple preclinical pain models and in an evoked-pain model in our clinical testing. Unbiased μ-opioid analgesics like morphine, fentanyl and hydromorphone are the mainstays of therapy in the postoperative period due to their strong analgesic efficacy. Different mechanisms of action are under evaluation by other companies for the management of postoperative pain, such as peripherally restricted modulation of the κ-opioid receptor, but we are not aware that any of these mechanisms has yet approached the level of analgesia achievable through a μ-op