TREVENA INC
Form S-1/A
November 28, 2014

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As filed with the Securities and Exchange Commission on November 28, 2014

Registration No. 333-200386

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

AMENDMENT NO. 1
TO

FORM S-1

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

TREVENA, INC.

(Exact name of registrant as specified in its charter)

Delaware	**2834**	**26-1469215**
(State or other jurisdiction of incorporation or organization)	(Primary Standard Industrial Classification Code Number)	(I.R.S. Employer Identification Number)

1018 West 8th Avenue, Suite A
King of Prussia, PA 19406
(610) 354-8840

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

John M. Limongelli, Esq.
Senior Vice President, General Counsel and Secretary
Trevena, Inc.
1018 West 8th Avenue, Suite A
King of Prussia, PA 19406
(610) 354-8840

(Name, address, including zip code,
and telephone number, including area code, of agent for service)

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Approximate date of commencement of proposed sale to the public:
As soon as practicable after the effective date of this registration statement.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, check the following box. o

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration number of the earlier effective registration statement for the same offering. o

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 under the Securities Exchange Act of 1934. (Check one):

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

The registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment that specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

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Subject to Completion, dated November 28, 2014

The information in this preliminary prospectus is not complete and may be changed. These securities may not be sold until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell nor does it seek an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

PROSPECTUS

$40,000,000

Trevena, Inc.

Common Stock

This is an offering of $40,000,000 of shares of the common stock of Trevena, Inc. All of the shares of common stock are being sold by us.

Our common stock trades on the NASDAQ Global Select Market under the symbol "TRVN." On November 28, 2014, the last reported trading price of our stock was $5.22 per share.

We are an "emerging growth company" as that term is used in the Jumpstart Our Business Startups Act of 2012 and, as such, have elected to comply with certain reduced public company reporting requirements.

Investing in our common stock involves risks. See "Risk Factors" beginning on page 14 of this prospectus.

	Per Share	Total
Price to the public	$	$
Underwriting discounts and commissions[1]	$	$
Proceeds to Trevena (before expenses)	$	$

[1] We refer you to "Underwriting" beginning on page 165 of this prospectus for additional information regarding underwriter compensation.

We have granted the underwriters the option to purchase up to $6,000,000 of additional shares of common stock on the same terms and conditions set forth above.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares on or about , 2014.

Barclays	Cowen and Company	Jefferies

JMP Securities	Needham & Company

Prospectus dated , 2014.

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We have not authorized anyone to provide any information or to make any representations other than those contained in this prospectus or in any free writing prospectuses we have prepared. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus is an offer to sell only the shares offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information contained in this prospectus is current only as of its date.

For investors outside the United States: We have not and the underwriters have not done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons who come into possession of this prospectus and any applicable free writing prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus and any such free writing prospectus applicable to that jurisdiction.

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PROSPECTUS SUMMARY

This summary highlights information contained elsewhere in this prospectus and does not contain all of the information that you should consider in making your investment decision. Before investing in our common stock, you should carefully read this entire prospectus, including our financial statements and the related notes thereto and the information set forth under the sections "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations," in each case included in this prospectus. Unless the context otherwise requires, we use the terms "Trevena," "company," "we," "us" and "our" in this prospectus to refer to Trevena, Inc.

Company Overview

We are 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. Using our proprietary product platform, we have identified and advanced three differentiated product candidates into the clinic as follows:

TRV130: We recently announced top-line data from our Phase 2a/b clinical trial of TRV130 in postoperative pain. At doses of 2 mg and 3 mg of TRV130 administered every three hours, the trial achieved its primary endpoint of statistically greater pain reduction than placebo for 48 hours, which we believe demonstrates proof of concept for TRV130. The 3 mg dose of TRV130 also showed statistically superior analgesic efficacy over the 48-hour trial period compared to 4 mg of morphine administered every four hours. Additionally, in the first three hours of dosing, when pain was most severe, the 1 mg, 2 mg and 3 mg doses of TRV130 demonstrated superior analgesic efficacy in the trial compared to placebo, and the 2 mg and 3 mg doses of TRV130 demonstrated superior analgesic efficacy compared to 4 mg of morphine. There were no serious adverse events reported in the trial, which we believe suggests that these levels of pain relief can be achieved safely. Over the 48-hour trial period, the tolerability of TRV130 at doses of 2 mg and 3 mg administered every three hours was similar to that of 4 mg of morphine administered every four hours. Based on these data, we plan to move into Phase 3 preparations, which we expect to occur in parallel with a second Phase 2 trial for TRV130 that we plan to commence in December 2014. We also anticipate that we will initiate a Phase 3 clinical trial for TRV130 in the first quarter of 2016. These data complement the data generated in our Phase 1b trial, in which TRV130 showed superior efficacy with an improved tolerability profile following a single dose of TRV130 relative to a 10 mg dose of morphine in a human evoked-pain model. We hold a U.S. patent covering the composition of matter and methods of use for TRV130. We have retained all worldwide development and commercialization rights to TRV130, and plan to commercialize it in acute care markets such as hospitals and ambulatory surgery centers if it receives regulatory approval.

TRV734: We have completed a first Phase 1 single ascending dose clinical trial for TRV734, an oral follow-on to TRV130 for the treatment of moderate to severe acute and chronic pain. We have completed enrollment in a second Phase 1 multiple ascending dose clinical trial and expect to report data from this trial early in the first quarter of 2015. We have retained all worldwide development and commercialization rights to TRV734.

TRV027: We have completed a Phase 2a clinical trial and in early 2014 we initiated a Phase 2b clinical trial of TRV027 for acute heart failure, or AHF. Enrollment in this trial is ongoing, with over 250 patients recruited out of planned enrollment of approximately 500 patients. More than 65 sites in 12 countries are now open and recruiting, and we expect patient enrollment will conclude in the third quarter of 2015. We expect to report top-line data from this trial in the fourth quarter of 2015. Actavis plc, or Actavis, has the exclusive option to license TRV027 from

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us. We plan for TRV027 to be commercialized in the acute care hospital market if it receives regulatory approval.

We also have identified a new product candidate, TRV250, from our preclinical δ-opioid receptor program focused on central nervous system, or CNS, indications and plan to advance TRV250 to preclinical studies in 2015 designed to support our submission of an investigational new drug application, or IND, to the U.S. Food and Drug Administration, or FDA.

Our Pipeline

Our Platform

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 currently marketed therapeutics 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 limiting that benefit or 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 while inhibiting the other (see Figure 2). This signaling specificity is the basis for our drug discovery and development approach, which is to identify selective GPCR biased ligands and develop them into differentiated clinical products. While some GPCRs trigger other signaling pathways in addition to G protein and β-arrestin, most GPCRs trigger those two pathways.

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. Our *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

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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 that 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.

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.

Figure 1: Mechanism of current GPCR-targeted drugs

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

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CNS Portfolio

TRV130

TRV130 is a small molecule G protein biased ligand at the μ-opioid receptor that we are developing as a first-line treatment for patients experiencing moderate to severe acute pain where intravenous, or IV, administration is preferred. The μ-opioid receptor is a well-established target for analgesics such as fentanyl and morphine, which are unbiased μ-opioid agonists. TRV130 activates the μ-opioid G protein pathway, associated with analgesia, and inhibits the β-arrestin pathway, which, in preclinical studies, was associated with limiting opioid analgesia, and with promoting opioid-induced respiratory depression and constipation. We believe that the management of moderate to severe, acute postoperative pain represents the largest opportunity for an intravenously administered μ-opioid therapy like TRV130. Accordingly, we have focused our initial clinical trials on the treatment of surgical patients. We believe that delivering better pain relief or mitigating dose limiting side effects typically associated with the activation of the μ-opioid receptor will position TRV130, if approved, to more effectively treat postoperative pain than currently available μ-opioid therapies.

According to data from IMS Health, a healthcare information firm, in 2013 there were approximately 47 million hospital inpatient stays and outpatient visits during which reimbursement claims for injectable opioids were made, 20 million of which involved a surgical procedure. Given its pharmacokinetic, tolerability and efficacy profile in our Phase 1 and Phase 2a/b clinical trials, we believe that both the inpatient and outpatient settings could be appropriate for TRV130 use. Despite the adoption of postoperative pain management guidelines, significant unmet need remains. In a 2012 survey of 300 surgical patients in the United States, over 80% of patients reported postoperative pain after the first analgesic medication had been administered, and 40% of those patients reported this pain to be moderate or severe. Currently available μ-opioid agonists, such as morphine and fentanyl, are the most effective class of analgesics for moderate to severe acute postoperative pain, but their effectiveness is limited in part because their doses are limited by severe side effects such as respiratory depression, nausea and vomiting, constipation and postoperative ileus, which is a condition that most commonly occurs after surgery involving interruption of movement of the intestines in which the bowel enters spasm and stops passing food and waste.

We have announced top-line data from our Phase 2a/b clinical trial of TRV130 in postoperative pain. At doses of 2 mg and 3 mg of TRV130 administered every three hours, the trial achieved its primary endpoint of statistically greater pain reduction than placebo for 48 hours, which we believe demonstrates proof of concept for TRV130. The 3 mg dose of TRV130 also showed statistically superior analgesic efficacy over the 48-hour trial period compared to 4 mg of morphine administered every four hours. Additionally, in the first three hours of dosing, when pain was most severe, the l mg, 2 mg and 3 mg doses of TRV130 demonstrated superior analgesic efficacy in the trial compared to placebo, and the 2 mg and 3 mg doses of TRV130 demonstrated superior analgesic efficacy compared to 4 mg of morphine. There were no serious adverse events reported in the trial, which we believe suggests that these levels of pain relief can be achieved safely. Over the 48-hour trial period, the tolerability of TRV130 at doses of 2 mg and 3 mg administered every three hours was similar to that of 4 mg of morphine administered every four hours. Based on these data, we plan to move into Phase 3 preparations, which we expect to occur in parallel with a second Phase 2 trial that we plan to commence in December 2014.

In our Phase 1b clinical trial in healthy subjects using an evoked-pain model, TRV130 showed superior analgesia compared to a high dose of morphine following a single dose administration, while causing less respiratory depression, less severe nausea and less vomiting. Together with our top-line Phase 2a/b data, we believe these results suggest that TRV130 may have an improved clinical profile in terms of efficacy, safety and tolerability compared to unbiased μ-opioid agonists, which are the current standard of care.

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We plan to initiate a second Phase 2 clinical trial in the fourth quarter of 2014 in soft tissue pain to inform Phase 3 development, since efficacy in both hard and soft tissue pain would be required by the FDA for a broad label in the treatment of acute moderate to severe pain. This trial will use flexible, as-needed dosing to allow patients to control the balance of efficacy and tolerability as their needs change over time. We expect to report top-line data from this second Phase 2 clinical trial in mid-2015. Prior to later-phase clinical development, we are also conducting or planning additional Phase 1 clinical testing in healthy subjects to add to our clinical understanding of TRV130.

We intend to retain full commercialization rights in the United States for TRV130. After the availability of the final Phase 2a/b clinical data for TRV130, we may seek collaborators for commercializing TRV130 outside of the United States to offset risk and preserve capital. We may also seek to collaborate with a third party to evaluate novel formulations of TRV130 for chronic pain and breakthrough pain. We have an issued U.S. patent that covers TRV130, compositions comprising TRV130 and methods of using TRV130, and this patent is expected to expire no earlier than 2032.

TRV734

TRV734 is a small molecule G protein biased ligand targeting the μ-opioid receptor, which we are developing as a first-line, orally administered compound for the treatment of moderate to severe acute and chronic pain. Like TRV130, TRV734 takes advantage of a well-established mechanism of pain relief by targeting the μ-opioid receptor, but does so with enhanced selectivity for the G protein signaling pathway, which in preclinical studies was linked to analgesia, as opposed to the β-arrestin signaling pathway, which in preclinical studies was associated with limiting analgesic efficacy and with promoting opioid-induced respiratory depression and constipation. Subject to successful non-clinical and clinical development and regulatory approval, we believe TRV734 may have an improved profile of efficacy relative to tolerability, or therapeutic profile, as compared to current commonly prescribed oral analgesics, such as oxycodone. We have filed patent applications covering TRV734 and methods of using TRV734.

In a Phase 1 single ascending dose clinical trial in healthy subjects, using pupil constriction as a surrogate for the analgesic efficacy of opioid drugs, orally administered TRV734 showed pharmacokinetics and pharmacodynamics across a dose range that was generally safe and well tolerated. These data supported further development, and we have completed enrollment in a second Phase 1 clinical trial, which is a multiple ascending dose trial evaluating the safety, tolerability, pharmacodynamics and pharmacokinetics of TRV734 given as a single dose and as multiple ascending doses in healthy volunteers. The aim of this trial is to support Phase 2 development, and top line data are expected early in the first quarter of 2015. We intend to seek a collaborator with experience in developing and commercializing controlled-substance therapeutics in acute and chronic care pain markets, thereby leveraging their expertise while retaining rights to commercialize TRV734 in treatment settings for which we can leverage our commercial strategy for TRV130.

TRV250

In November 2014, we identified a new product candidate, TRV250, a small molecule G protein biased ligand targeting the δ-opioid receptor. Based on the initial profile of TRV250, we anticipate focusing our initial development efforts on the treatment of treatment-refractory migraine headaches. According to Decision Resources, a healthcare consulting company, the acute episodic migraine market encompassed approximately 12 million drug-treated patients in 2013 in the United States, representing approximately $2.2 billion of sales. We estimate that approximately 20% to 30% of these patients either do not respond to or cannot tolerate the market-leading triptan drug class, and an additional 30% would benefit from improved efficacy compared to these drugs.

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We believe TRV250 also may have utility in other CNS areas such as depression, Parkinson's disease or neuropathic pain. We intend to conduct preclinical work beginning in 2015 designed to support the filing of an IND for TRV250. We also intend to seek a collaborator for TRV250 with CNS development and worldwide commercialization expertise, while potentially retaining commercialization rights in the United States.

Cardiovascular Program

TRV027

We are developing TRV027 as a first-line IV treatment in combination with standard diuretic therapy for AHF patients. 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 in the cardiovascular system. TRV027 inhibits G protein signaling and activates β-arrestin signaling. In our Phase 2a clinical trial, TRV027 rapidly reduced blood pressure and preserved renal, or kidney, function, while preserving cardiac performance. We are enrolling patients in a Phase 2b clinical trial to evaluate the safety and efficacy of TRV027 in AHF. Over 250 patients have been recruited out of planned enrollment of approximately 500 patients. More than 65 sites in 12 countries are open and recruiting, and we expect patient enrollment to conclude in the third quarter of 2015. We expect to report data from this trial by the end of the fourth quarter of 2015. 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, shorten length of hospital stay in the short term, and potentially lower readmission rates and mortality rates in the long term.

There are over 20 million people living with heart failure in the United States and Europe, according to the American Heart Association and the European Society of Cardiology. AHF, also sometimes referred to as acute decompensated heart failure, is heart failure requiring hospitalization. AHF patients present with severe dyspnea, a serious shortness of breath sometimes described as "air hunger," and fluid overload, leading to an inability to perform simple functions such as standing and walking short distances. This can also lead to organ dysfunction, including dysfunction in the kidneys and heart. The National Hospital Discharge Survey reported over five million hospital discharges in the United States in 2010 where heart failure was listed as a component of the diagnosis, over one million of which listed heart failure as the primary diagnosis. TRV027 has shown beneficial effects on the three key organ systems affected in heart failure, the blood vessels, heart and kidneys in our preclinical studies and Phase 1b and 2a clinical trials. In combination with standard diuretics, 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.

Safety and tolerability issues limit the effectiveness of currently available AHF treatments. We believe that TRV027's tolerability profile differentiates it from current therapies. In healthy subjects in our Phase 1 clinical trial, there were no serious adverse events, 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 clinical trial in medically fragile, advanced chronic heart failure subjects 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.

In May 2013, we entered into an option agreement and a license agreement with Forest Laboratories Holdings Limited, or Forest, under which we granted to Forest an exclusive option to license TRV027, which may be exercised at any time before we deliver our Phase 2b clinical trial results to Forest and during a specified period of time thereafter. In July 2014, Actavis plc, or Actavis, acquired Forest, including Forest's option to TRV027. If Actavis exercises its option, the license

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agreement between us and Actavis will become effective, and Actavis will have an exclusive worldwide license to develop and commercialize TRV027 and specified related compounds. Actavis will be responsible for subsequent development, regulatory approval and commercialization of TRV027 at Actavis's expense. If Actavis exercises the option, we would receive a $65 million option exercise fee and could potentially receive up to $365 million 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. We have three issued U.S. patents covering the composition of matter and method of use of TRV027 that are expected to expire no earlier than 2031 and 2029, respectively.

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 development of our three clinical-stage product candidates, TRV130, TRV734 and TRV027, to commercialization;
- 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;
- expand our CNS product portfolio by advancing TRV250, our preclinical δ-opioid receptor product candidate; and
- leverage our ABLE product platform to continue to discover innovative biased ligand therapeutics and expand our product platform's impact through external collaborations.

Financial Overview

Our revenue to date has been generated primarily through research grants and a research collaboration. We have not generated any commercial product revenue. As of September 30, 2014, we had $72.2 million of cash and cash equivalents and an accumulated deficit of $118.7 million.

In September 2014, we announced we had entered into a $35.0 million senior secured tranched term loan credit facility with Oxford Finance LLC and Square 1 Bank, of which we have drawn $2.0 million as of the date of this prospectus. The facility also provides for up to two additional term loan tranches of $16.5 million each. Based on the top-line results of the Phase 2a/b clinical trial of TRV130 announced in November 2014, we believe we have met the conditions to draw the second tranche of $16.5 million tranche from the credit facility. We may opt to draw the third term loan tranche if we receive positive data from the Phase 2 clinical trial of TRV027.

We believe that existing cash and the available borrowings under the second tranche of our credit facility, excluding any potential future draw from our credit facility if we receive positive data from the Phase 2 study of TRV027, plus the net proceeds from the offering will be sufficient to fund our operations through the fourth quarter of 2016.

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Risks Associated with Our Business

Our business is subject to a number of risks of which you should be aware before making an investment decision. These risks are discussed more fully in the "Risk Factors" section of this prospectus. These risks include the following:

- We will need substantial additional funding to pursue our business objectives. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our drug development programs or potential commercialization efforts.
- We are early in our clinical development efforts and have only two product candidates, TRV027 and TRV130, in Phase 2, and one more, TRV734, in Phase 1. If we, or Actavis if it exercises its option to license TRV027, are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.
- Advancing TRV250, our preclinical δ-opioid receptor product candidate, may not lead to the filing of an IND or future clinical development.
- If Actavis exercises its option to license TRV027, that relationship will be significant to our business. If Actavis' development and commercialization of TRV027 is not successful, our business could be adversely affected.
- We have incurred significant losses since our inception. We expect to continue to incur losses over the next several years and may never achieve or maintain profitability.
- We face substantial competition, which may result in others discovering, developing or commercializing drugs before or more successfully than we do.
- Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

Corporate Information

We were incorporated under the laws of the State of Delaware in November 2007. Our principal executive office is located at 1018 West 8th Avenue, Suite A, King of Prussia, Pennsylvania 19406. Our telephone number is (610) 354-8840. Our website address is *www.trevenainc.com*. The information contained on our website is not incorporated by reference into this prospectus, and you should not consider any information contained on, or that can be accessed through, our website as part of this prospectus or in deciding whether to purchase our common stock.

"Trevena", the Trevena logo and other trademarks or service marks of Trevena, Inc. appearing in this prospectus are the property of Trevena, Inc. This prospectus contains additional trade names, trademarks and service marks of others, which are the property of their respective owners.

Implications of Being an Emerging Growth Company

As a company with less than $1 billion in revenue during our last fiscal year, we qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from specified disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

Being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;

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Not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;

Not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;

Reduced disclosure obligations regarding executive compensation; and

Exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We may take advantage of these provisions through 2019 or such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company if we have more than $1 billion in annual revenue, have more than $700 million in market value of our capital stock held by non-affiliates or issue more than $1 billion of non-convertible debt over a three-year period. We may choose to take advantage of some, but not all, of the available exemptions. We have taken advantage of some reduced reporting burdens in this prospectus. Accordingly, the information contained herein may be different than the information you receive from other public companies in which you hold stock.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This provision allows an emerging growth company to delay the adoption of some accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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The Offering

Common stock offered by Trevena	$40,000,000 of shares of common stock.
Total common stock to be outstanding after this offering	34,039,461 shares (35,188,886 shares if the underwriters elect to exercise their option to purchase additional shares from us in full).
Option to purchase additional shares of common stock	The underwriters have an option to purchase a maximum of $6,000,000 of additional shares from us. The underwriters can exercise this option at any time within 30 days from the date of this prospectus.
Use of proceeds	We expect the net proceeds to us from this offering, after expenses, to be approximately $37.0 million, or approximately $42.6 million if the underwriters exercise their option to purchase additional shares from us in full. We intend to use the net proceeds from this offering, together with our existing cash and cash equivalents and the $16.5 million we believe we are entitled to draw from the second tranche of our credit facility, as follows: to fund clinical development expenses, including the completion of our ongoing Phase 2b clinical trial for TRV027, the initiation and completion of the next Phase 2 clinical trial and up to two Phase 3 clinical trials for TRV130 and the completion of a multiple ascending dose trial and other activities to support Phase 2 development for TRV734; to fund preclinical research and development activities, including work to support the filing of an IND for TRV250; and for working capital and general corporate purposes. See "Use of Proceeds" on page 51 for additional information.
Risk factors	See the section titled "Risk Factors" beginning on page 14 and the other information included in this prospectus for a discussion of factors you should carefully consider before deciding to invest in our common stock.
NASDAQ Global Select Market symbol	TRVN

The number of shares of our common stock that will be outstanding after this offering is based on 26,376,626 shares of common stock outstanding as of September 30, 2014 and assumes the sale of $40,000,000 of shares of common stock at an assumed public offering price of $5.22 per share, which was the last reported sale price of our common stock on the NASDAQ Global Select Market on November 28, 2014. A 5% increase or decrease in the assumed public offering price of $5.22 per share would decrease or increase the number of shares of our common stock issued in this offering by approximately 5%.

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The number of shares of our common stock that will be outstanding after this offering set forth above excludes:

- 3,552,124 shares of our common stock issuable upon the exercise of stock options outstanding under our 2008 Equity Incentive Plan and 2013 Equity Incentive Plan as of September 30, 2014, at a weighted average exercise price of $3.72 per share;
- 30,258 shares of our common stock issuable upon exercise of warrants outstanding as of September 30, 2014, at a weighted average exercise price of $5.62 per share;
- 33,000 shares of our common stock issuable upon the exercise of stock options granted after September 30, 2014, at a weighted average exercise price of $5.18 per share; and
- 868,235 shares of our common stock reserved for future issuance as of September 30, 2014 under our 2013 Equity Incentive Plan and our employee stock purchase plan.

Except as otherwise indicated herein, all information in this prospectus, including the number of shares that will be outstanding after this offering, assumes or gives effect to:

- no exercise of options or warrants outstanding as of September 30, 2014; and
- no exercise of the underwriters' option to purchase additional shares in this offering.

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Summary Financial Data

The following tables set forth our summary financial data for the periods indicated. The following summary financial data for the years ended December 31, 2012 and 2013 are derived from our audited financial statements, which have been audited by Ernst & Young LLP, our independent registered public accounting firm, appearing elsewhere in this prospectus. We have derived the following summary of our statement of operations data for the nine months ended September 30, 2013 and 2014 and the balance sheet data as of September 30, 2014 from our unaudited condensed financial statements appearing elsewhere in this prospectus.

The financial data for the nine months ended September 30, 2013 and 2014 and as of September 30, 2014 includes, in the opinion of our management, all adjustments, consisting only of normal recurring adjustments that are necessary for a fair presentation of our financial position and results of operations for these periods. Our historical results are not necessarily indicative of the results to be expected in the future, and our operating results for the nine months ended September 30, 2014 are not necessarily indicative of the results that may be expected for the entire year ending December 31, 2014.

This summary financial data should be read together with the historical financial statements and related notes to those statements, as well as "Management's Discussion and Analysis of Financial Condition and Results of Operations," which are included elsewhere in this prospectus.

	Year Ended December 31,		Nine Months Ended September 30,	
	2012	2013	2013	2014
	(in thousands, except share and per share data)			
Statement of Operations Data:				
Total revenue	$ 808	$ 135	$ 135	$
Operating expenses:				
General and administrative	3,123	4,718	2,843	7,034
Research and development	13,295	18,762	12,240	29,671
Total operating expenses	16,418	23,480	15,083	36,705
Loss from operations	(15,610)	(23,345)	(14,948)	(36,705)
Total other income (expense)	(26)	94	(1,398)	301
Net loss and comprehensive loss	(15,636)	(23,251)	(16,346)	(36,404)
Accretion of redeemable convertible preferred stock	(316)	(334)	(248)	(28)
Net loss attributable to common stockholders	$ (15,952)	$ (23,585)	$ (16,594)	$ (36,432)
Net loss per share basic and diluted	$ (23.70)	$ (29.71)	$ (22.23)	$ (1.58)

Weighted average shares of common stock outstanding used in computing net loss per share basic and diluted	673,191	793,806	746,587	23,036,366

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The following table presents our summary balance sheet data:

- on an actual basis as of September 30, 2014; and
- on an as adjusted basis to give effect to our sale of $40,000,000 of shares of common stock in this offering, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

	As of September 30, 2014	
	Actual	As adjusted
	(in thousands)	
Balance Sheet Data:		
Cash and cash equivalents	$ 72,225	$ 109,225
Total assets	73,956	110,956
Total liabilities	9,696	9,696
Total stockholders' equity	64,259	101,259

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RISK FACTORS

Investing in our common stock involves a high degree of risk. Before you invest in our common stock, you should carefully consider the following risks, as well as general economic and business risks, and all of the other information contained in this prospectus. Any of the following risks could have a material adverse effect on our business, operating results and financial condition and cause the trading price of our common stock to decline, which would cause you to lose all or part of your investment. When determining whether to invest, you should also refer to the other information contained in this prospectus, including our financial statements and the related notes thereto.

Risks Related to Our Financial Position and Capital Needs

We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net loss was $15.6 million and $23.3 million for the years ended December 31, 2012 and 2013, respectively, and $36.4 million for the nine months ended September 30, 2014. As of September 30, 2014, we had an accumulated deficit of $118.7 million. To date, we have financed our operations primarily through private placements and a public offering of our equity securities and through grant revenue. Virtually all of our revenue to date has been grant revenue. We have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and clinical trials. We are still in the early stages of development of our product candidates, and we have not completed development of any drugs. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially as we:

- continue to enroll our Phase 2b clinical trial of TRV027 and conduct Phase 2 and Phase 3 clinical trials of TRV130, our lead product candidates;
- complete Phase 1 clinical trials of TRV734 and initiate a Phase 2 trial of TRV734;
- initiate activities to support the filing of an IND for TRV250, our δ-opioid receptor product candidate;
- seek to discover additional product candidates;
- conduct late-stage clinical trials and seek regulatory approvals for any product candidates that successfully complete clinical trials;
- ultimately establish a sales, marketing and distribution infrastructure and scale up external manufacturing capabilities to commercialize any products that we choose not to license to a third party and for which we may obtain regulatory approval;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical and scientific personnel; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts.

To become and remain profitable, we must succeed in developing and eventually commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages

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of some of these activities and have not begun others. We may never succeed in these activities and, even if we do, may never achieve profitability.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. If we are required by the United States Food and Drug Administration, or FDA, or foreign regulatory authorities, to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates, our expenses could increase.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

We will need substantial additional funding, which may not be available to us on acceptable terms, or at all. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue to enroll the Phase 2b clinical trial for TRV027, complete the Phase 2 clinical program for TRV130 and then initiate and complete Phase 3 clinical trials, continue clinical development of TRV734, and continue research and development and initiate additional clinical trials of, and seek regulatory approval for, these and other product candidates. In addition, if we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we could be forced to:

- delay, reduce or eliminate our research and development programs or any future commercialization efforts;
- relinquish or license on unfavorable terms our rights to technologies or product candidates that we otherwise would seek to develop or commercialize ourselves;
- seek collaborators for one or more of our product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or
- cease operations altogether.

We estimate that the net proceeds from this offering, together with our existing cash and cash equivalents as of September 30, 2014 and our anticipated draw of $16.5 million from our credit facility based on the top-line results of the Phase 2a/b trial of TRV130 announced in November 2014, will enable us to fund our operating expenses and capital expenditure requirements through the fourth quarter of 2016, without giving effect to a potential option payment and, if the option is exercised, potential milestone payments we may receive under our option and license agreements with Actavis plc, or Actavis, and excluding any potential future drawdown from our credit facility if we receive positive data from the Phase 2 study of TRV027. We have based this estimate on assumptions that may prove to be wrong, and we could use up our capital resources sooner than we currently expect. We do not expect our existing capital resources, including the net proceeds from this offering, to enable us to complete Phase 3 development of TRV027 if Actavis chooses not to license the product candidate.

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Accordingly, we expect that we will need to raise substantial additional funds in the future. Our future capital requirements will depend on many factors, including:

- the progress and results of the Phase 2 clinical programs for TRV130 and TRV027;
- whether Actavis exercises its option to license TRV027;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for our other product candidates, including our ongoing Phase 1 clinical program for TRV734;
- our ability to enter into collaborative agreements for the development and commercialization of our product candidates, including TRV734;
- the number and development requirements of other product candidates that we pursue;
- the costs, timing and outcome of regulatory review of our product candidates or any future product candidates, both in the United States and in territories outside the United States;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;
- any product liability or other lawsuits related to our products;
- the expenses needed to attract and retain skilled personnel;
- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval; and
- the costs involved in preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims, both in the United States and in territories outside the United States.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenue, if any, will be derived from sales of products that we do not expect to be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans.

Raising additional capital may cause dilution to our stockholders, including purchasers of common stock in this offering, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, grants and license and development agreements in connection with any collaborations. We do not have any committed external source of funds other than the $65 million option payment from Actavis if it exercises the option and, in such case, possible milestone and royalty payments under the license agreement, the $16.5 million second tranche that we believe we have met the conditions to

draw under the credit facility with Oxford Finance and Square 1 Bank and the $16.5 million third tranche under that credit facility that we would be entitled to draw if we receive positive data from the Phase 2 clinical trial of TRV027. To

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the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Preferred equity financing and additional debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We commenced active operations in late 2007, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our ABLE product platform, identifying potential product candidates, undertaking preclinical studies and conducting clinical trials. Our three product candidates are early in development, and our preclinical program has not yet identified a product candidate. We have not yet demonstrated our ability to successfully complete later stage clinical trials, obtain regulatory approvals, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

In addition, as a young business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to expand our capabilities to support commercial activities. We may not be successful in adding such capabilities.

We expect our financial condition and operating results to continue to fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any past quarterly or annual periods as indications of future operating performance.

Risks Related to the Discovery and Development of Our Product Candidates

Our research and development is focused on discovering and developing novel drugs based on biased ligands, and the approach we are taking to discover and develop drugs is not proven and may never lead to marketable products.

The discovery and development of drugs based on biased ligands is an emerging field, and the scientific discoveries that form the basis for our efforts to discover and develop product candidates are relatively new. The scientific evidence to support the feasibility of developing differentiated product candidates based on these discoveries is both preliminary and limited. We believe that we are the first company to conduct a clinical trial of a product candidate based on the concept of biased ligands. Therefore, we do not know if our approach will be successful.

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We are very early in our development efforts and have only two product candidates, TRV027 and TRV130, in Phase 2, and one more, TRV734, in Phase 1. If we are unable to successfully complete development and commercialization of our product candidates or experience significant delays in doing so, our business will be materially harmed.

We are very early in our development efforts and have only two product candidates, TRV027 and TRV130, in Phase 2 development, and one more, TRV734, in Phase 1 development. We have invested substantially all of our efforts and financial resources in the identification and development of biased ligands. Our ability to generate product revenue, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates. The success of our product candidates will depend on several factors, including the following:

- successful completion of preclinical studies and clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- obtaining, maintaining and protecting our intellectual property portfolio, including patents and trade secrets, and regulatory exclusivity for our product candidates;
- making arrangements with third-party manufacturers for, or establishing, commercial manufacturing capabilities;
- launching commercial sales of the products, if and when approved, whether alone or in collaboration with others;
- acceptance of our products, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- obtaining and maintaining healthcare coverage of our products and adequate reimbursement; and
- maintaining a continued acceptable safety profile of our products following approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business.

We may not be successful in our efforts to expand our pipeline of product candidates.

One element of our strategy is to expand our pipeline of therapeutics based on biased ligands and advance these product candidates through clinical development for the treatment of a variety of indications. Although our research and development efforts to date have resulted in a number of development programs based on biased ligands, we may not be able to develop product candidates that are safe and effective. Even if we are successful in continuing to expand our pipeline, the potential product candidates that we identify may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize product candidates based upon our technological approach, we will not be able to obtain product revenue in future periods, which would make it unlikely that we would ever achieve profitability.

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Preclinical and clinical drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

Clinical testing is expensive and can take many years to complete, and the risk of failure is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical studies and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or subsequently to commercialize our product candidates, including:

- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we may have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks;
- regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; and
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or institutional review boards to suspend or terminate the trials.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

be delayed in obtaining marketing approval for our product candidates;

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not obtain marketing approval at all;

obtain approval for indications or patient populations that are not as broad as intended or desired;

obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;

be subject to additional post-marketing testing requirements; or

have the product removed from the market after obtaining marketing approval.

Our product development costs also will increase if we experience delays in testing or in receiving marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical study or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside the United States. Some of our competitors have ongoing clinical trials for product candidates that treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. Patient enrollment is affected by other factors including:

the severity of the disease under investigation;

the eligibility criteria for the study in question;

the perceived risks and benefits of the product candidate under study;

the efforts to facilitate timely enrollment in clinical trials;

the patient referral practices of physicians;

the ability to monitor patients adequately during and after treatment; and

the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. For example, we face significant competition to recruit and enroll heart failure patients for our clinical trial of TRV027 due to a number of trials in heart failure currently being conducted by other sponsors. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

If serious adverse or unacceptable side effects are identified during the development of our product candidates, we may need to abandon or limit our development of some of our product candidates.

If our product candidates are associated with adverse side effects in clinical trials or have characteristics that are unexpected, we may need to abandon their development or limit development

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to more narrow uses or subpopulations in which the side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. In our industry, many compounds that initially showed promise in early stage testing have later been found to cause side effects that prevented further development of the compound. In the event that our clinical trials reveal a high and unacceptable severity and prevalence of side effects, our trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us to cease further development or deny approval of our product candidates for any or all targeted indications. Drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial and could result in potential product liability claims.

Additionally if one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of such product;
- regulatory authorities may require additional warnings on the label;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients, if one is not required before approval;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved.

TRV027 is a biased ligand targeted at the angiotensin II type 1 receptor, or AT1R, and has been shown to drop blood pressure in subjects with chronic heart failure. One subject in the Phase 2a clinical trial in advanced chronic heart failure was withdrawn from therapy after experiencing low blood pressure, or hypotension. If TRV027 drops blood pressure too much or causes prolonged low blood pressure, this could lead to adverse effects that could compromise the development, approval and market potential of TRV027.

TRV130 is predominantly metabolized by two liver enzymes, CYP2D6 and CYP3A4, that are common metabolic pathways for drugs. Because of competitive use of these pathways, we will need to conduct additional drug interaction studies and TRV130 may be limited in its co-administration with other drugs using these pathways as their safety and effectiveness, as well as TRV130's, may be adversely affected. This could limit our commercial opportunity due to the common co-administration of drugs in patients with moderate to severe acute pain requiring IV therapy. In addition, since CYP2D6 enzyme activity varies in the population, different dosing may be required in the product label for individuals that have low levels of CYP2D6 activity, which could limit the commercial opportunity of the drug, if approved. We are in discussion with the FDA on this question and cannot assure you that the FDA will not require us to utilize different dosing for this population and/or prospectively characterize individuals' CYP2D6 activity prior to administering TRV130.

TRV130 and TRV734 are both biased ligands targeted at the μ-opioid receptor. Common adverse reactions for agonists of the μ-opioid receptor include respiratory depression, constipation, nausea, vomiting and addiction. In rare cases, μ-opioid receptor agonists can cause respiratory arrest requiring immediate medical intervention. Since TRV130 and TRV734 also modulate the μ-opioid receptor, these adverse reactions and risks could apply to the use of TRV130 and TRV734. One healthy subject in the 0.25 mg dosing cohort of our Phase 1 clinical trial of TRV130 experienced a severe episode of vasovagal syncope during which he fainted and his pulse stopped. These were considered severe adverse events. Although this individual recovered without medical intervention and experienced no known adverse consequences from this, certain potential triggers of vasovagal syncope were removed from the

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trial protocol, and dose escalation proceeded up to 7 mg/hr (28-fold higher than the 0.25 mg/hr dose at which the syncope occurred) without further incident, it is possible that serious adverse vasovagal events could occur in other patients dosed with TRV130. We have to date administered TRV130 to only 371 subjects at doses up to 7mg/dose.

Agonists at the δ-opioid receptor have been associated with a risk of seizures. TRV250, our δ-opioid receptor product candidate, targets the same receptor as other programs that have been associated with seizures and, accordingly, it is possible that it will be associated with similar side effects.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. In addition, under our option agreement with Actavis, we have agreed to conduct, at our expense, a Phase 2b clinical trial of TRV027 in AHF. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Risks Related to the Commercialization of Our Product Candidates

Even if any of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.

If any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenue and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy, safety and potential advantages compared to alternative treatments;
- the timing of market introduction of the product candidate as well as competitive products;
- our ability to offer the product for sale profitably and at competitive prices;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of sales, marketing and distribution support;
- the availability of third-party coverage and adequate reimbursement;
- the prevalence and severity of any side effects;

the clinical indications for which the product is approved; and

any restrictions on the use of our products together with other medications.

If we are unable to establish sales, marketing and distribution capabilities or to enter into agreements with third parties to market and sell our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We currently do not have a marketing or sales organization for the marketing, sales and distribution of pharmaceutical products and have no experience in this area. To commercialize any product candidates that receive marketing approval, we would need to build marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. If we successfully develop and obtain regulatory approval for any of our product candidates, we expect to build a targeted specialist sales force to market or co-promote the product in the United States. There are substantial risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

There are a number of factors that may inhibit our efforts to commercialize our products on our own, including:

our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;

the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;

the lack of complementary or other products to be offered by sales personnel, which may put us at a competitive disadvantage from the perspective of sales efficiency relative to companies with more extensive product lines; and

unforeseen costs and expenses associated with creating an independent sales and marketing organization.

As an alternative to establishing our own sales force, we may choose to partner with third parties that have well-established direct sales forces to sell, market and distribute our products. In the case of TRV027, should Actavis elect to license TRV027, it would thereafter have responsibility for further clinical development, regulatory approval and commercialization. If we are unable to enter into collaborations with third parties for the commercialization of approved products, if any, on acceptable terms or at all, or if any such partner, including Actavis if it exercises its option to license TRV027, does not devote sufficient resources to the commercialization of our product or otherwise fails in commercialization efforts, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies

worldwide. In addition to existing therapeutic treatments for the indications we are targeting with our product candidates, which our goal would be to displace if any of our product candidates achieves regulatory approval, we also face potential competition from other drug candidates in development by other companies. With respect to competition for TRV027, we are aware of three product candidates in mid-to late-stage clinical development for AHF. These are serelaxin, being developed by Novartis, which has completed a single Phase 3 clinical trial, omecamtiv mercarbil, being developed by Cytokinetics and Amgen, which has completed a Phase 2b clinical trial, and ularitide, being developed by Cardiorentis and currently in a Phase 3 clinical trial. With respect to competition for TRV130, the most advanced and directly competitive product candidates are reformulations of existing opioids, such as a fentanyl iontophoresis patch, in development by The Medicines Company, and sufentanil nanotab, in development by AcelRx, and a peripherally-restricted κ-opioid agonist (CR845) in development by Cara Therapeutics Inc. Some of these potential competitive compounds are being developed by large, well-financed and experienced pharmaceutical and biotechnology companies or have been partnered with such companies, which may give them development, regulatory and marketing advantages over us, or Actavis, if it exercises its option for TRV027.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. Generic products are currently on the market for the indications that we are pursuing. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competing generic products.

Some of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Even if we or our collaborators are able to commercialize any of our product candidates, the product candidates may become subject to unfavorable pricing regulations, third-party coverage and reimbursement policies or healthcare reform initiatives.

Both our and our collaborators' ability to commercialize any of our product candidates successfully will depend, in part, on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government payor programs at the federal and state level authorities, including Medicare and Medicaid, private health insurers, managed care plans and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices

charged for medical products. Coverage and reimbursement may not be available for any drug that we or our collaborators commercialize and, even if these are available, the level of reimbursement may not be satisfactory. Inadequate reimbursement levels may adversely affect the demand for, or the price of, any product candidate for which we or our collaborators obtain marketing approval. Obtaining and maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we or our collaborators may not be able to successfully commercialize any product candidates for which marketing approval is obtained.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or similar regulatory authorities outside the United States. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution expenses. Interim reimbursement levels for new drugs, if applicable, also may not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our or our collaborators' inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any approved drugs that we develop could adversely affect our operating results, our ability to raise capital needed to commercialize drugs and our overall financial condition.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drugs vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we or our collaborators might obtain marketing approval for a drug in a particular country, but then be subject to price regulations that delay commercial launch of the drug, possibly for lengthy time periods, and negatively impact our ability to generate revenue from the sale of the drug in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

There can be no assurance that our product candidates, if they are approved for sale in the United States or in other countries, will be considered medically reasonable and necessary for a specific indication, that they will be considered cost-effective by third-party payors, that coverage or an adequate level of reimbursement will be available, or that third-party payors' reimbursement policies will not adversely affect our ability to profitably sell our product candidates if they are approved for sale.

Product liability lawsuits against us could cause us to incur substantial liabilities and limit commercialization of any products that we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any products that we may develop. For example, we may be sued if any product we develop allegedly

causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- significant costs to defend the related litigation;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

We currently maintain $15 million in product liability insurance coverage, which may not be adequate to cover all liabilities that we may incur. We will likely need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

Risks Related to Our Dependence on Third Parties

If Actavis exercises its option to license TRV027, that relationship will become even more important to our business, and any future relationships or collaborations we may elect to pursue may also be important to us. If we are unable to maintain our relationship with Actavis or any of these collaborations, or if our relationship with Actavis or these collaborators is not successful, our business could be adversely affected.

We have limited capabilities for product development and do not yet have any capability for sales, marketing or distribution. We have an option agreement and a license agreement with Actavis, which provide Actavis with an option to license TRV027. If Actavis exercises this option, it will be responsible for subsequent development, regulatory approval and commercialization of TRV027 and we will be eligible to receive milestone payments and royalties on product sales. This relationship, any future collaboration with Actavis, and any future collaborations we might enter into with another third party, may pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;

collaborators may elect not to continue or renew development or commercialization programs or may not pursue commercialization of any product candidates that achieve regulatory approval based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;

collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;

collaborators could fail to make timely regulatory submissions for a product candidate;

collaborators may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements;

collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;

product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;

a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;

disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and

collaborations may be terminated at the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If our potential collaboration with Actavis, or any other collaborations we might enter into in the future, do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product platform and product candidates could be delayed and we may need additional resources to develop our product candidates and our product platform. All of the risks relating to our product development, regulatory approval and commercialization described in this prospectus also apply to the activities of our therapeutic program collaborators.

If Actavis exercises its option to license TRV027 from us, the license agreement will contain a restriction on our engaging in activities relating to certain product candidates that may compete with TRV027 for a specified period of time. This restriction may have the effect of preventing us from undertaking development and other efforts for TRV027 that we would otherwise prefer to pursue. Additionally, subject to its contractual obligations to us, if Actavis or a future collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate development or

commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our reputation in the business and financial communities could be adversely affected.

For our product candidates other than TRV027, we may in the future determine to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of these candidates. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our product platform and our business may be materially and adversely affected.

We rely, and expect to continue to rely, on third parties to conduct our preclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials or complying with applicable regulatory requirements.

We rely on third-party contract research organizations and clinical research organizations to conduct some of our preclinical studies and all of our clinical trials for TRV027, TRV130 and TRV734. We expect to continue to rely on third parties, such as contract research organizations, clinical research organizations, clinical data management organizations, medical institutions and clinical investigators, to conduct some of our preclinical studies and all of our clinical trials. The agreements with these third parties might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that could delay our product development activities.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our preclinical studies and clinical trials are conducted in accordance with the general investigational plan and protocols for the trial and for ensuring that our preclinical studies are conducted in accordance with good laboratory practice, or GLP, as appropriate. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, clinical investigators and trial sites. If we or any of our clinical research organizations fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product produced under current good manufacturing practice, or cGMP, regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register ongoing clinical trials and post the results

of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

The third parties with whom we have contracted to help perform our preclinical studies or clinical trials may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

If any of our relationships with these third-party contract research organizations or clinical research organizations terminate, we may not be able to enter into arrangements with alternative contract research organizations or clinical research organizations or to do so on commercially reasonable terms. Switching or adding additional contract research organizations or clinical research organizations involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new contract research organization or clinical research organization commences work. As a result, delays could occur, which could compromise our ability to meet our desired development timelines. Though we carefully manage our relationships with our contract research organizations or clinical research organizations, there can be no assurance that we will not encounter similar challenges or delays in the future.

We contract with third parties for the manufacture of our product candidates for preclinical and clinical testing and expect to continue to do so for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not have any manufacturing facilities or personnel. We rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture, if any, of our product candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts. For example, in March 2011, TRV027 was put on clinical hold by the FDA following an FDA audit at the company then manufacturing the TRV027 drug product. We replaced this drug product with new drug product manufactured by another company and the FDA lifted the clinical hold in June 2011.

We also expect to rely on third-party manufacturers or third-party collaborators for the manufacture of commercial supply of any product candidates for which our collaborators or we obtain marketing approval. We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

reliance on the third party for regulatory compliance and quality assurance;

the possible breach of the manufacturing agreement by the third party;

manufacturing delays if our third-party manufacturers give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreement between us;

the possible misappropriation of our proprietary information, including our trade secrets and know-how; and

the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

The facilities used by our contract manufacturers to manufacture our product candidates must be approved by the FDA pursuant to inspections that will be conducted after we submit an NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturers for compliance with cGMP regulations for manufacture of our product candidates. Third-party manufacturers may not be able to comply with the cGMP regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products.

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us. Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a second source for bulk drug substance. If our current contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers. We may incur added costs and delays in identifying and qualifying any replacement manufacturers.

The U.S. Drug Enforcement Administration, or DEA, restricts the importation of a controlled substance finished drug product when the same substance is commercially available in the United States, which could reduce the number of potential alternative manufacturers for our μ-opioid receptor targeted product candidates, including TRV130 and TRV734. In addition, a DEA quota system controls and limits the availability and production of controlled substances and the DEA also has authority to grant or deny requests for quota of controlled substances, which will likely include the active ingredients in TRV130 and TRV734. Supply disruptions could result from delays in obtaining DEA approvals for controlled substances or from the receipt of quota of controlled substances that are insufficient to meet future product demand. The quota system also may limit our ability to build inventory as a method for mitigating possible supply disruptions if TRV130 or TRV734 are approved for sale in the United States.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We rely on clinical data and results obtained by third parties that could ultimately prove to be inaccurate or unreliable.

As part of our strategy to mitigate development risk, we seek to develop product candidates with validated mechanisms of action and we utilize biomarkers to assess potential clinical efficacy early in the development process. This strategy necessarily relies upon clinical data and other results obtained by third parties that may ultimately prove to be inaccurate or unreliable. Further, such clinical data and

results may be based on products or product candidates that are significantly different from our product candidates. If the third-party data and results we rely upon prove to be inaccurate, unreliable or not applicable to our product candidates, we could make inaccurate assumptions and conclusions about our product candidates and our research and development efforts could be compromised.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for our technology and products or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our product candidates. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidates.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. If Actavis exercises its option to license TRV027, it will have the first right to prosecute, maintain and enforce TRV027 patents and these obligations may have an effect on our strategy regarding the preparation, filing and prosecution of patent applications, or maintenance of the patents, covering our product candidates. Moreover, should we enter into other collaborations we may be required to consult with or cede control to collaborators regarding the prosecution, maintenance and enforcement of our patents. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after a first filing, or in some cases at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The United States Patent Office recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective

on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

Moreover, we may be subject to a third-party preissuance submission of prior art to the U.S. Patent and Trademark Office, or become involved in opposition, derivation, reexamination, *inter partes*