

TREVENA INC
Form 424B1
December 05, 2014

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Filed Pursuant to Rule 424(B)1
Registration No. 333-200386

PROSPECTUS

11,250,000 Shares

Trevena, Inc.
Common Stock

This is an offering 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 December 4, 2014, the last reported trading price of our stock was \$4.07 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	\$ 4.00	\$ 45,000,000
Underwriting discounts and commissions ¹	\$ 0.24	\$ 2,700,000
Proceeds to Trevena (before expenses)	\$ 3.76	\$ 42,300,000

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

Some of our existing investors and their affiliated entities, including Alta Partners VIII, L.P., New Enterprise Associates 12, Limited Partnership and some of our directors and executive officers, have agreed to purchase an aggregate of 1,556,500 shares of our common stock in this offering at the public offering price. The underwriters will receive the same underwriting discount on any shares purchased by these entities or individuals as they will on any other shares sold to the public in this offering.

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We have granted the underwriters the option to purchase up to 1,687,500 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 December 10, 2014.

Barclays

**Cowen and
Company**

Jefferies

JMP Securities

Needham & Company

Prospectus dated December 4, 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 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 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 tranching 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:

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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	11,250,000 shares of common stock.
Total common stock to be outstanding after this offering	37,626,626 shares (39,314,126 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 1,687,500 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 \$41.7 million, or approximately \$48.0 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.	

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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.

Some of our existing investors and their affiliated entities, including Alta Partners VIII, L.P., New Enterprise Associates 12, Limited Partnership and some of our directors and executive officers, have agreed to purchase an aggregate of 1,556,500 shares of our common stock in this offering at the public offering price. The underwriters will receive the same underwriting discount on any shares purchased by these entities or individuals as they will on any other shares sold to the public in this offering.

Table of Contents**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)

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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 11,250,000 shares of common stock in this offering, after deducting 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	\$ 113,925
Total assets	73,956	115,656
Total liabilities	9,696	9,696
Total stockholders' equity	64,259	105,959

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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.

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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

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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.

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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;

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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

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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 AcclRx, 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

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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

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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;

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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

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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

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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;

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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

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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

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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* review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, render unenforceable, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner.

The issuance of a patent does not foreclose challenges to its inventorship, scope, validity or enforceability. Therefore, our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our issued patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated, rendered unenforceable, or interpreted narrowly.

We may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

A third party may hold intellectual property, including patent rights, that are important or necessary to the development of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be

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required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including interference or derivation proceedings before the U.S. Patent and Trademark Office. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future.

If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, we could lose rights that are important to our business.

We are currently party to license agreements for technologies that we use in conducting our drug discovery activities. In the future, we may become party to licenses that are important for product development and commercialization. If we fail to comply with our obligations under current or future license and funding agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product or utilize any technology that is covered by these agreements or may face other penalties under the agreements. Such an occurrence could materially and adversely affect the value of a product candidate being developed under any such agreement or could restrict our drug discovery activities. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these employees or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Litigation may be necessary to defend against these claims.

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In addition, while it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patent protection for our product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We limit disclosure of such trade secrets where possible but we also seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who do have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

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Risks Related to Regulatory Approval of Our Product Candidates and Other Legal Compliance Matters

If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to timely commercialize, or to commercialize at all, our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and similar regulatory authorities outside the United States. Failure to obtain marketing approval for our product candidates will prevent us from commercializing these product candidates and will significantly limit our ability to generate revenue in the future. To date, we have not received approvals to market any of our product candidates from regulatory authorities in any jurisdiction and we may never be successful in obtaining any such approvals.

We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party contract research organizations to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug in this way, which could limit sales of the product.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical studies or clinical trials. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval, the commercial prospects for our product candidates may be harmed and our ability to generate revenue may be materially impaired. Furthermore, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may not approve the price we intend to charge for our products, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of these scenarios could compromise the commercial prospects for our product candidates.

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We anticipate that our μ -opioid receptor targeted product candidates, including TRV130 and TRV734, will require Risk Evaluation and Mitigation Strategies, which could delay the approval of these product candidates and increase the cost, burden and liability associated with the commercialization of these product candidates.

The FDA Amendments Act of 2007 implemented safety-related changes to product labeling and provided the FDA with expanded authority to require the adoption of a Risk Evaluation and Mitigation Strategy, or REMS, to assure safe use of the product candidates, either as a condition of product candidate approval or on the basis of new safety information. We anticipate that our μ -opioid receptor product candidates, if approved, will require a REMS, and it is possible that our other product candidates may require a REMS. The REMS may include medication guides for patients, special communication plans to health care professionals or elements to assure safe uses such as restricted distribution methods, patient registries and/or other risk minimization tools. We cannot predict the specific REMS that will be required as part of the FDA's approval of our product candidates. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of our product candidates, if approved. Depending on the extent of the REMS requirements, these requirements may significantly increase our costs to commercialize these product candidates and could negatively affect sales. Furthermore, risks of our product candidates that are not adequately addressed through proposed REMS for such product candidates also may prevent or delay their approval for commercialization.

Our μ -opioid receptor targeted product candidates, including TRV130 and TRV734, may be classified as controlled substances, the making, use, sale, importation, exportation and distribution of which are subject to regulation by state, federal and foreign law enforcement and other regulatory agencies.

Our μ -opioid receptor targeted product candidates, including TRV130 and TRV734, may be classified as controlled substances, which are subject to state, federal and foreign laws and regulations regarding their manufacture, use, sale, importation, exportation and distribution. Controlled substances are regulated under the federal Controlled Substances Act of 1970, or CSA, and regulations of the DEA.

The DEA regulates controlled substances as Schedule I, II, III, IV or V substances. Schedule I substances by definition have no established medicinal use and may not be marketed or sold in the United States. A pharmaceutical product may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest risk of abuse and Schedule V substances the lowest relative risk of abuse among such substances. We expect TRV130 and TRV734 to be regulated by the DEA as Schedule II controlled substances.

Various states also independently regulate controlled substances. Though state controlled substances laws often mirror federal law, because the states are separate jurisdictions, they may separately schedule drugs as well. While some states automatically schedule a drug when the DEA does so, in other states there must be rulemaking or a legislative action. State scheduling may delay commercial sale of any controlled substance drug product for which we obtain federal regulatory approval and adverse scheduling could impair the commercial attractiveness of such product. We or our collaborators must also obtain separate state registrations in order to be able to obtain, handle and distribute controlled substances for clinical trials or commercial sale, and failure to meet applicable regulatory requirements could lead to enforcement and sanctions from the states in addition to those from the DEA or otherwise arising under federal law.

For any of our product candidates classified as controlled substances, we and our suppliers, manufacturers, contractors, customers and distributors are required to obtain and maintain applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation, exportation and distribution of controlled substances. There is a risk that DEA regulations may limit the supply of the compounds used in clinical trials for our product candidates, and, in the future, the

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ability to produce and distribute our products in the volume needed to both meet commercial demand and build inventory to mitigate possible supply disruptions.

Regulations associated with controlled substances govern manufacturing, labeling, packaging, testing, dispensing, production and procurement quotas, recordkeeping, reporting, handling, shipment and disposal. These regulations increase the personnel needs and the expense associated with development and commercialization of product candidates including controlled substances. The DEA, and some states, conduct periodic inspections of registered establishments that handle controlled substances. Failure to obtain and maintain required registrations or comply with any applicable regulations could delay or preclude us from developing and commercializing our product candidates containing controlled substances and subject us to enforcement action. The DEA may seek civil penalties, refuse to renew necessary registrations or initiate proceedings to revoke those registrations. In some circumstances, violations could lead to criminal proceedings. Because of their restrictive nature, these regulations could limit commercialization of any of our product candidates that are classified as controlled substances.

Failure to obtain marketing approval in international jurisdictions would prevent our product candidates from being marketed abroad.

To market and sell our products in the European Union and many other jurisdictions, we or our third-party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or our collaborators may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, the failure to obtain approval in one jurisdiction may compromise our ability to obtain approval elsewhere. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

Any product candidate for which we obtain marketing approval could be subject to post-marketing restrictions or withdrawal from the market and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to ongoing requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a REMS. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the product.

The FDA also may impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. The FDA closely regulates the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved

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indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if we do not market our products for only their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

restrictions on such products, manufacturers or manufacturing processes;

restrictions on the labeling or marketing of a product;

restrictions on product distribution or use;

requirements to conduct post-marketing studies or clinical trials;

warning letters;

withdrawal of the products from the market;

refusal to approve pending applications or supplements to approved applications that we submit;

recall of products;

fining, restitution or disgorgement of profits or revenue;

suspension or withdrawal of marketing approvals;

refusal to permit the import or export of our products;

product seizure; or

injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained.

Our current and future relationships with customers and third-party payors in the United States and elsewhere may be subject, directly or indirectly, to applicable anti-kickback, fraud and abuse, false claims, transparency, health information privacy and security and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens and diminished profits and future earnings.

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Healthcare providers, physicians and third-party payors in the United States and elsewhere will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations, including, without limitation, the federal Anti-Kickback Statute and the federal False Claims Act, which may constrain the business or financial arrangements and relationships through which we sell, market and distribute any drugs for which we obtain marketing approval. In addition, we may be subject to transparency laws and patient privacy regulation by U.S. federal and state governments and by governments in foreign

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jurisdictions in which we conduct our business. The applicable federal, state and foreign healthcare laws and regulations that may affect our ability to operate include:

the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs, such as Medicare and Medicaid;

federal civil and criminal false claims laws and civil monetary penalty laws, including the federal False Claims Act, which impose criminal and civil penalties, including civil whistleblower or *qui tam* actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government; the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, which impose obligations on covered healthcare providers, health plans, and healthcare clearinghouses, as well as their business associates that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

the federal Open Payments program, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to "payments or other transfers of value" made to physicians, which is defined to include doctors, dentists, optometrists, podiatrists and chiropractors, and teaching hospitals and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by the physicians and their immediate family members, requirements for manufacturers to submit reports to CMS by the 90th day of each calendar year, and subsequent disclosure of such information by CMS on a publicly available website; and

analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers; state and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations may involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties,

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including, without limitation, damages, fines, imprisonment, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations, which could have a material adverse effect on our business. If any of the physicians or other healthcare providers or entities with whom we expect to do business, including our collaborators, is found not to be in compliance with applicable laws, it may be subject to criminal, civil or administrative sanctions, including exclusions from participation in government healthcare programs, which could also materially affect our business.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the PPACA, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms.

Among the provisions of the PPACA of importance to our potential product candidates are:

an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;

an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively;

expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance;

a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;

extension of a manufacturer's Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;

expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the federal poverty level beginning in 2014, thereby potentially increasing a manufacturer's Medicaid rebate liability;

expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

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the new requirements under the federal Open Payments program and its implementing regulations;

a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and

a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. These changes include aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013, and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on customers for our drugs, if approved, and, accordingly, our financial operations.

We expect that the PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved drug. Any reduction in reimbursement from Medicare or other government healthcare programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our drugs.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenue, if any.

In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and

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any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Risks Related to Employee Matters and Managing Our Growth

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on the research, development, clinical, business development and financial expertise of our executive officers. Although we have entered into employment agreements with these individuals, each of them may terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees.

Recruiting and retaining qualified management, scientific and clinical personnel, and if any of our product candidates achieve regulatory approval, potentially manufacturing and sales and marketing personnel, will also be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific, clinical and commercial advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

We expect to expand our development and regulatory capabilities and potentially create sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs and, if any of our product candidates receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may

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lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could expose us to liability and hurt our reputation.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and financial results, including the imposition of significant fines or other sanctions.

Other Risks Related to our Business

We intend to conduct a substantial portion of the clinical trials for our product candidates outside of the United States and, if approved, we intend to market our product candidates abroad. Accordingly, we will be subject to the risks of doing business outside of the United States.

We intend to conduct a substantial portion of our clinical trials outside of the United States and, if approved, we intend to market our product candidates outside of the United States. We are thus subject to risks associated with doing business outside of the United States. With respect to our product candidates, we may choose to partner with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems outside of the United States or in lieu of our own sales force and distribution systems, which would indirectly expose us to these risks. Our business and financial results in the future could be adversely affected due to a variety of factors associated with conducting development and marketing of our product candidates, if approved, outside of the United States, including:

efforts to develop an international sales, marketing and distribution organization may increase our expenses, divert our management's attention from the development of product candidates or cause us to forgo profitable licensing opportunities in these geographies;

changes in a specific country's or region's political and cultural climate or economic condition;

unexpected changes in foreign laws and regulatory requirements;

difficulty of effective enforcement of contractual provisions in local jurisdictions;

inadequate intellectual property protection in foreign countries;

trade-protection measures, import or export licensing requirements such as Export Administration Regulations promulgated by the U.S. Department of Commerce and fines, penalties or suspension or revocation of export privileges;

regulations under the U.S. Foreign Corrupt Practices Act and similar foreign anti-corruption laws;

the effects of applicable foreign tax structures and potentially adverse tax consequences; and

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significant adverse changes in foreign currency exchange rates which could make the cost of our clinical trials, to the extent conducted outside of the United States, more expensive.

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Our business and operations would suffer in the event of system failures.

Despite our implementation of security measures, our internal computer systems and those of our contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption to our product candidate development programs. For example, the loss of clinical trial data from completed, ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of personal, confidential or proprietary information, we could incur liability and the further development of any of our product candidates could be delayed or abandoned.

Risks Related to this Offering and Ownership of Our Common Stock

An active trading market for our common stock may not continue to develop or be sustained.

Although our common stock is listed on the NASDAQ Global Select Market, or NASDAQ, we cannot assure you that an active, liquid trading market for our shares will continue to develop or be sustained. If an active market for our common stock does not continue to develop or is not sustained, it may be difficult for you to sell shares quickly or without depressing the market price for the shares or to sell your shares at all.

The trading price of the shares of our common stock has been and may continue to be volatile, and purchasers of our common stock could incur substantial losses.

Since our common stock commenced trading in January 2014, our stock price has been volatile. The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors in our stock may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including:

actual or anticipated variations in our operating results;

changes in financial estimates by us or by any securities analysts who might cover our stock;

the timing and results of our clinical trials for any of our product candidates;

failure or discontinuation of any of our development programs;

conditions or trends in our industry;

stock market price and volume fluctuations of comparable companies and, in particular, those that operate in the biopharmaceutical industry;

announcements by us or our competitors of significant acquisitions, strategic partnerships or divestitures;

developments or disputes concerning patent applications, issued patents or other proprietary rights;

announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;

capital commitments;

investors' general perception of our company and our business;

recruitment or departure of key personnel;

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announcements and expectations of additional financing efforts; and

sales of our common stock, including sales by our directors and officers or specific stockholders.

In addition, in the past, stockholders have initiated class action lawsuits against pharmaceutical and biotechnology companies following periods of volatility in the market prices of these companies' stock. Such litigation, if instituted against us, could cause us to incur substantial costs and divert management's attention and resources from our business.

If equity research analysts do not continue to publish research or reports or publish unfavorable research or reports about us, our business or our market, our stock price and trading volume could decline.

The trading market for our common stock is influenced by the research and reports that equity research analysts publish about us and our business. As a newly public company, we have only limited research coverage by equity research analysts. Equity research analysts may elect not to initiate or continue to provide research coverage of our common stock, and such lack of research coverage may adversely affect the market price of our common stock. We have no control over the analysts or the content and opinions included in their reports. The price of our stock could decline if one or more equity research analysts downgrade our stock or issue other unfavorable commentary or research. If one or more equity research analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which in turn could cause our stock price or trading volume to decline.

If you purchase shares of our common stock in this offering, you will suffer immediate dilution of your investment.

The public offering price of our common stock is substantially higher than the net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay a price per share that substantially exceeds our as adjusted net tangible book value per share after this offering. You will experience immediate dilution of \$1.18 per share, representing the difference between our as adjusted net tangible book value per share after giving effect to this offering and the public offering price.

In addition, as of September 30, 2014, we had outstanding stock options to purchase an aggregate of 3,552,124 shares of common stock at a weighted average exercise price of \$3.72 per share and warrants to purchase an aggregate of 30,258 shares of common stock at a weighted average exercise price of \$5.62 per share. To the extent these outstanding options and warrants are exercised, there will be further dilution to investors in this offering.

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future. This could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. If our stockholders sell, or the market perceives that our stockholders intend to sell, substantial amounts of our common stock in the public market following this offering, the market price of our common stock could decline significantly.

Upon completion of this offering, based on the number of shares outstanding at September 30, 2014, we will have outstanding 37,626,626 shares of common stock, assuming no exercise of outstanding options or warrants. Substantially all of these shares are, and the shares sold in this offering will be, freely tradable in the public market, other than shares of common stock that are subject to lock-up agreements entered into by our directors, executive officers and stockholders associated with some of our affiliates and the underwriters, which will become eligible for sale in the public market beginning 90 days after the date of this prospectus. Barclays Capital Inc. may release these stockholders from

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their lock-up agreements with the underwriters at any time and without notice, which would allow for earlier sales of shares in the public market.

In addition, we have filed registration statements on Form S-8 registering the issuance of approximately 4.8 million shares of common stock subject to options or other equity awards issued or reserved for future issuance under our equity incentive plans. Shares registered under these registration statements on Form S-8 are available for sale in the public market subject to vesting arrangements and exercise of existing options, the grant of new options in the future, the lock-up agreements described above and the restrictions of Rule 144 in the case of our affiliates.

Additionally, the holders of an aggregate of approximately 15.2 million shares of our common stock and 22,580 shares of our common stock issuable upon the exercise of outstanding warrants, or their transferees, will have rights, subject to some conditions, to require us to file one or more registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. If we were to register the resale of these shares, they could be freely sold in the public market. If these additional shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

The issuance of additional stock in connection with financings, acquisitions, investments, our stock incentive plans or otherwise will dilute all other stockholders.

Our amended and restated certificate of incorporation authorizes us to issue up to 100,000,000 shares of common stock and up to 5,000,000 shares of preferred stock with such rights and preferences as may be determined by our board of directors. Subject to compliance with applicable rules and regulations, we may issue our shares of common stock or securities convertible into our common stock from time to time in connection with a financing, acquisition, investment, our stock incentive plans or otherwise. Any such issuance could result in substantial dilution to our existing stockholders and cause the trading price of our common stock to decline.

Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited.

We have incurred substantial losses during our history. We do not anticipate generating revenue from sales of products for the foreseeable future, if ever, and we may never achieve profitability. To the extent that we continue to generate tax losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire. Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50% change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income may be limited. We have not completed our analysis to determine what, if any, impact any prior ownership change has had on our ability to utilize our net operating loss carryforwards. In addition, we may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, including this offering. As of December 31, 2013, we had federal net operating loss carryforwards of approximately \$12.7 million that could be limited if we have experienced, or if in the future we experience, an ownership change.

Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management and hinder efforts to acquire a controlling interest in us, and the market price of our common stock may be lower as a result.

There are provisions in our amended and restated certificate of incorporation and amended and restated bylaws that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change in control was considered favorable by you and other stockholders. For example, our board of directors has the authority to issue up to 5,000,000 shares of preferred stock. The board of directors can fix the price, rights, preferences, privileges, and restrictions of the preferred

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stock without any further vote or action by our stockholders. The issuance of shares of preferred stock may delay or prevent a change in control transaction. As a result, the market price of our common stock and the voting and other rights of our stockholders may be adversely affected. An issuance of shares of preferred stock may result in the loss of voting control to other stockholders.

Our charter documents also contain other provisions that could have an anti-takeover effect, including:

only one of our three classes of directors will be elected each year;

stockholders are not entitled to remove directors other than by a 66²/₃% vote and only for cause;

stockholders are not permitted to take actions by written consent;

stockholders cannot call a special meeting of stockholders; and

stockholders must give advance notice to nominate directors or submit proposals for consideration at stockholder meetings.

In addition, we are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, which regulates corporate acquisitions by prohibiting Delaware corporations from engaging in specified business combinations with particular stockholders of those companies. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions.

Upon completion of this offering, our executive officers, directors and current beneficial owners of 5% or more of our common stock and their respective affiliates will, in the aggregate, beneficially own 53.3% of our outstanding common stock, assuming they purchase all of the shares they have agreed to purchase in this offering. As a result, these persons, acting together, would be able to control all matters requiring stockholder approval, including the election and removal of directors, the approval of any merger, consolidation, sale of all or substantially all of our assets, or other significant corporate transactions.

Some of these persons or entities may have interests different than yours. For example, because many of these stockholders purchased their shares at prices substantially below the price at which shares are being sold in this offering and have held their shares for a longer period, they may be more interested in selling our company to an acquirer than other investors, or they may want us to pursue strategies that deviate from the interests of other stockholders.

We are an "emerging growth company" and as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our common stock may be less attractive to investors.

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or JOBS Act, and we intend to take advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We cannot predict if investors will find our common stock less attractive because we will rely on these exemptions. If some investors find our common stock less

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attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. We may take advantage of these reporting exemptions until we are no longer an emerging growth company. We will remain an emerging growth company until the earliest of (a) December 31, 2019, (b) the last day of the fiscal year in which we have total annual gross revenue of at least \$1.0 billion, (c) the last day of the fiscal year in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds \$700 million as of the prior June 30th, and (d) any date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period.

Under Section 107(b) of the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards until such time as those standards 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.

If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired.

We are subject to the reporting requirements of the Securities Exchange Act of 1934, the Sarbanes-Oxley Act and the rules and regulations of NASDAQ. The Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal controls over financial reporting. For our fiscal year ending December 31, 2014, we are obligated to perform system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting in our Form 10-K filing for that year, as required by Section 404 of the Sarbanes-Oxley Act. We will continue to incur substantial additional professional fees and internal costs to expand our accounting and finance functions and expend significant management efforts. Prior to our initial public offering, or IPO, we were never required to test our internal controls within a specified period, and, as a result, we may experience difficulty in meeting these reporting requirements in a timely manner.

We may discover weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Our internal control over financial reporting will not prevent or detect all error and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act in a timely manner, or if we are unable to maintain proper and effective internal controls, we may not be able to produce timely and accurate financial statements. If that were to happen, the market price of our stock could decline and we could be subject to sanctions or investigations by the stock exchange on which our common stock is listed, the Securities and Exchange Commission, or SEC, or other regulatory authorities.

Our management might apply the net proceeds from this offering in ways with which you do not agree and in ways that may impair the value of your investment.

We intend to use the net proceeds from this offering for clinical development expenses, preclinical research and development efforts and for working capital and general corporate purposes. Our management has broad discretion as to the use of these proceeds and you will be relying on the judgment of our management regarding the application of these proceeds. We might apply these proceeds in ways with which you do not agree, or in ways that do not yield a favorable return. If our management applies these proceeds in a manner that does not yield a significant return, if any, on our

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investment of these net proceeds, it could compromise our ability to pursue our growth strategy and adversely affect the market price of our common stock.

Because we do not anticipate paying any cash dividends on our common stock in the foreseeable future, capital appreciation, if any, will be your sole source of gains and you may never receive a return on your investment.

You should not rely on an investment in our common stock to provide dividend income. We have not declared or paid cash dividends on our common stock to date and have no plans to pay cash dividends in the foreseeable future. We currently intend to retain our future earnings, if any, to fund the development and growth of our business. In addition, the terms of our term loan credit facility with Oxford Finance LLC and Square 1 Bank prohibits us from paying cash dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future. Investors seeking cash dividends should not purchase our common stock.

We incur costs and demands upon management as a result of being a public company.

As a newly public company listed in the United States, we are incurring, and will continue to incur, significant legal, accounting and other costs, particularly after we cease to be an "emerging growth company." These costs could negatively affect our financial results. In addition, changing laws, regulations and standards relating to corporate governance and public disclosure, including regulations implemented by the SEC and stock exchanges, may increase legal and financial compliance costs and make some activities more time consuming. These laws, regulations and standards are subject to varying interpretations and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. We intend to invest resources to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expenses and a diversion of management's time and attention from revenue-generating activities to compliance activities. If, notwithstanding our efforts to comply with new laws, regulations and standards, we fail to comply, regulatory authorities may initiate legal proceedings against us and our business may be harmed.

Failure to comply with these rules also might make it more difficult for us to obtain some types of insurance, including directors' and officers' liability insurance, and we might be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, on committees of our board of directors or as members of senior management.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

our plans to develop and potentially commercialize our product candidates;

the exercise by Actavis of its option to license TRV027 and, if exercised, our ability to achieve milestones under the license;

our planned clinical trials and preclinical studies for our product candidates;

the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;

the extent of clinical trials potentially required by the FDA for our product candidates;

the clinical utility and market acceptance of our product candidates;

our commercialization, marketing and manufacturing capabilities and strategy;

our intellectual property position; and

our ability to identify additional product candidates with significant commercial potential that are consistent with our commercial objectives.

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

You should read this prospectus and the documents that we reference in this prospectus and have filed as exhibits to the registration statement, of which this prospectus is a part, completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

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This prospectus includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information.

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USE OF PROCEEDS

We estimate that the net proceeds from our issuance and sale of shares of our common stock in this offering will be approximately \$41.7 million, or approximately \$48.0 million if the underwriters exercise their option to purchase additional shares in full, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

As of September 30, 2014, we had cash and cash equivalents of \$72.2 million. We currently estimate that we will 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.

Although it is difficult to predict future liquidity requirements, we believe that the net proceeds from this offering, our existing cash and cash equivalents and our expected draw of \$16.5 million from our credit facility, together with interest thereon, will be sufficient to fund our operations through the fourth quarter of 2016. However, the expected proceeds from this offering and our existing resources will not be sufficient to complete advanced clinical development of more than one of our product candidates, or if applicable, to prepare for commercializing any product candidate that achieves approval. Accordingly, we will continue to require substantial additional capital beyond the expected proceeds of this offering to continue our clinical development and potential commercialization activities. Because successful development of our product candidates is uncertain, we are unable to estimate the actual funds we will require to complete research and development and commercialize our products under development.

This expected use of net proceeds from this offering represents our intentions based upon our current plans and business conditions, and could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development, the status of and results from clinical trials, as well as any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. As a result, our management will have broad discretion in the application of the net proceeds from this offering, and investors will be relying on the judgment of our management regarding the application of the net proceeds of this offering.

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PRICE RANGE OF COMMON STOCK

Our common stock commenced trading on the NASDAQ Global Select Market under the symbol "TRVN" on January 31, 2014. The following table sets forth, for the periods indicated, the high and low reported sales prices of our common stock as reported on the NASDAQ Global Select Market:

	High	Low
2014		
First quarter (from January 31, 2014)	\$ 9.95	\$ 6.00
Second quarter	\$ 7.82	\$ 4.07
Third quarter	\$ 7.00	\$ 5.20
Fourth quarter (through December 4, 2014)	\$ 6.73	\$ 4.01

As of December 3, 2014, there were 40 holders of record of our common stock. The last reported sale price of the common stock on December 4, 2014 was \$4.07 per share.

DIVIDEND POLICY

We have never declared or paid any dividends on our common stock. We anticipate that we will retain all of our future earnings, if any, for use in the operation and expansion of our business and do not anticipate paying cash dividends in the foreseeable future. In addition, our ability to pay dividends, other than dividends payable solely in capital stock, is currently prohibited by the terms of our term loan credit facility with Oxford Finance LLC and Square 1 Bank.

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The following table sets forth our cash and cash equivalents and capitalization as of September 30, 2014:

on an actual basis; and

on an as adjusted basis to give effect to our sale of 11,250,000 shares of common stock in this offering, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

The information in this table is illustrative only and our capitalization following the completion of this offering will depend on the actual public offering price and other terms of this offering determined at pricing. You should read this table together with "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our financial statements and the related notes appearing elsewhere in this prospectus.

	As of September 30, 2014	
	Actual (in thousands, except share and per share data)	As adjusted
Cash and cash equivalents	\$ 72,225	\$ 113,925
Long-term loan	\$ 1,774	\$ 1,774
Stockholders' equity:		
Common stock, \$0.001 par value; 100,000,000 shares authorized, 26,376,626 shares issued and outstanding, actual; 100,000,000 shares authorized, 37,626,626 shares issued and outstanding, as adjusted	26	38
Preferred stock, \$0.001 par value; 5,000,000 shares authorized, no shares issued and outstanding, actual and as adjusted		
Additional paid-in capital	182,906	224,594
Accumulated deficit	(118,673)	(118,673)
Total stockholders' equity	64,259	105,959
Total capitalization	\$ 66,033	\$ 107,733