TREVENA INC
Form 10-K
March 18, 2015

Use these links to rapidly review the document
TABLE OF CONTENTS

Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2014

or

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

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

Trevena, Inc.

(Exact Name of Registrant as Specified in Its Charter)

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

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

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

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

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

(Title of Class)

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

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

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

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

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

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

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

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

The aggregate market value of the voting stock held by non-affiliates of the registrant, as of June 30, 2014, the last business day of the registrant's most recently completed second fiscal quarter, was approximately $47.4 million. Such aggregate market value was computed by reference to the closing price of the Common Stock as reported on the NASDAQ Global Select Market on June 30, 2014. For purposes of making this calculation only, the registrant has defined affiliates as including only directors and executive officers and shareholders holding greater than 10% of the voting stock of the registrant as of June 30, 2014.

The number of shares of the registrant's Common Stock outstanding as of March 10, 2015 was 39,241,173.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2015 annual meeting of stockholders to be filed pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2014 are incorporated by reference into Part III of this Form 10-K.

Table of Contents

TABLE OF CONTENTS

Table of Contents

Cautionary Note Regarding Forward-Looking Statements

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

- our plans to develop and potentially commercialize our product candidates;
- the exercise by Actavis, Inc. (formerly Forest Laboratories Holdings Limited) 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 Annual Report for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Annual Report will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Table of Contents

PART I

ITEM 1. BUSINESS

Overview

Trevena, Inc. is a clinical stage biopharmaceutical company that discovers, develops and intends to commercialize therapeutics that use a novel approach to target G protein coupled receptors, or GPCRs. Unless the context otherwise requires, we use the terms "Trevena," "company," "we," "us" and "our" to refer to Trevena, Inc.

Using our proprietary product platform, we have identified and are developing the following three differentiated product candidates:

TRV130: We are developing TRV130 as a first-line treatment for patients experiencing moderate to severe pain where IV administration is preferred. We are currently conducting a second Phase 2 trial of TRV130 with the goal of evaluating analgesic efficacy following soft-tissue surgery and exploring TRV130's safety and tolerability profile benchmarked to morphine. We expect to report top-line data from this trial in mid-2015. In November 2014, we announced top-line data from our Phase 2a/b clinical trial of TRV130 in postoperative pain following bunionectomy surgery. 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. There were no serious adverse events reported in the trial, which we believe suggests that these levels of pain relief can be achieved safely. Based on the data from the recently completed Phase 2a/b study, we plan to move into Phase 3 preparations, which we expect to occur in parallel with the second Phase 2 soft tissue trial for TRV130 that we commenced in December 2014. We also anticipate that we will initiate a Phase 3 clinical trial for TRV130 in the first quarter of 2016. 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 for use in acute care settings such as hospitals and ambulatory surgery centers if it receives regulatory approval.

TRV734: We are developing TRV734 as a first-line, orally administered compound for the treatment of moderate to severe acute and chronic pain. We have completed both a Phase 1 single ascending dose clinical trial and a Phase 1 multiple ascending dose clinical study and reported positive results from these studies in June 2014 and February 2015, respectively. We are commencing a pharmacokinetic study with various formulations of TRV734 to prepare for phase 2 development. We have retained all worldwide development and commercialization rights to TRV734.

TRV027: We are developing TRV027 for the treatment of acute heart failure, or AHF. In early 2014 we initiated a Phase 2b clinical trial of TRV027 (BLAST-AHF) for the treatment of AHF. In January 2015, we conducted a planned interim analysis, evaluating data from approximately 250 patients. Upon reviewing the data, the data safety monitoring board (DSMB) and the BLAST-AHF Steering Committee recommended that future enrollment be weighted to the most promising dose of 5 mg/hr. We announced in March 2015 that remaining enrollment will be weighted 2:1:2:1 for placebo, 1 mg/hr, 5 mg/hr, and 25 mg/hr, respectively, and that we have increased target enrollment in the study from 500 patients to 620 patients. In addition, the DSMB and Steering Committee determined that patients with lower baseline systolic blood pressure could safely enroll in the study; inclusion criteria have been modified accordingly. Actavis plc, or Actavis, which holds an exclusive option to license TRV027, has fully funded this

Table of Contents

expansion of the study via a $10 million payment to us to defray the external and internal costs of increasing the study sample size. As a result of the increased target enrollment, we now expect to release top-line data in the first half of 2016.

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 that would support our submission of an investigational new drug application, or IND, to the U.S. Food and Drug Administration, or FDA.

Our Pipeline

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 IV administration is preferred. TRV130 activates the μ-opioid receptor G protein pathway, which in preclinical studies was associated with analgesia, and inhibits the β-arrestin pathway at the same receptor, which in preclinical studies was associated with limiting opioid analgesia and with promoting opioid-induced respiratory depression and constipation.

Disease and treatment options

According to 2013 data from IMS Health, 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. In terms of the total potential market opportunity, the World Health Organization estimates that over 230 million major surgical procedures are performed each year worldwide. According to Life Science Intelligence, a market research firm, over 30 million inpatient surgical procedures and 42 million outpatient or ambulatory surgical procedures were performed in the United States in 2013. According to the European Commission, about 30 million hospital inpatient surgeries are performed collectively in France, Germany, the United Kingdom, Italy and Spain each year. Accordingly, we believe that there is a large potential commercial opportunity for TRV130 in the treatment of both surgical and medical pain, if approved.

Table of Contents

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

Opioid analgesics like morphine, fentanyl and hydromorphone are mainstays of pain treatment in the immediate postoperative period. Despite the development and adoption of guidelines for the management of postoperative pain and the extensive use of current treatments, significant unmet need remains. In a 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 this pain was reported to be moderate or severe. The effectiveness of currently available μ-opioid agonists is limited in part because their doses are limited by severe side effects such as respiratory depression, nausea and vomiting, and constipation. Injectable non-opioid analgesics are often used to supplement IV opioids for post-surgical pain management. These drugs, such as IV non-steroidal anti-inflammatory drugs, or NSAIDs, IV acetaminophen or local anesthetics such as bupivacaine, have their own potential side effects in the cardiovascular and gastrointestinal, or GI, systems as well as the liver. We estimate that recently introduced branded versions of these drugs can add $50 to $300 per patient per day to the cost of managing patients with moderate to severe postoperative pain in the United States.

None of these non-opioid analgesic approaches has displaced the use of opioid analgesics as the cornerstone of IV therapy for acute moderate to severe pain. We believe that there remains significant unmet need for a more effective analgesic agent for postoperative and other types of acute pain.

Key differentiating attributes of TRV130

We believe that TRV130 may offer several potential advantages over existing opioid treatments for postoperative pain, any of which may contribute to higher levels of pain relief for TRV130 compared to these drugs. Phase 2 data in post-surgical pain, Phase 1 data in experimental pain, and preclinical data all suggest that TRV130 may be able to rapidly and safely achieve superior pain relief with similar tolerability compared to standard intravenous morphine use. If this profile is confirmed in further clinical trials, we believe that TRV130 may offer best-in-class analgesic efficacy, which could position TRV130 for use in the most severe pain states. The predictable dose-related efficacy observed in our Phase 2 a/b study suggests that TRV130 also may be used broadly at different dose levels to control varying types of pain. In addition, preclinical and clinical evidence suggest that lower doses of TRV130, or alternative routes of administration, may be able to provide morphine-level pain relief with an improved profile for respiratory depression, nausea and vomiting, and constipation.

Clinical development strategy and experience

In December 2014, we initiated a second Phase 2 clinical trial of TRV130 with the goal of evaluating analgesic efficacy following a soft tissue surgery and exploring TRV130's safety and tolerability profile benchmarked to morphine. We expect to report top-line data from this trial in mid-2015. This trial employs as-needed dosing to broaden dosing information beyond the fixed-interval dosing used in the bunionectomy trial. In this trial, TRV130, morphine or placebo are administered as an initial loading dose followed by delivery of on-demand doses via a patient-controlled analgesia device. Approximately 200 patients who have undergone uncomplicated, elective abdominoplasty surgery will be enrolled in the trial, with approximately 40 receiving placebo, 80 receiving TRV130 and 80 receiving morphine. The primary endpoint of the trial is the efficacy of TRV130 compared to placebo over 24 hours, which may serve as a registration endpoint in Phase 3 development. In parallel with the Phase 2 abdominoplasty clinical trial, we have commenced Phase 3 preparations for TRV130, with the goal of initiating our first of two Phase 3 clinical trials in the first quarter of 2016. We expect that the Phase 2 abdominoplasty trial, if the data are promising, along with data from the Phase 2a/b

Table of Contents

clinical trial of treatment of postoperative pain following bunionectomy, would support Phase 3 development in soft and hard tissue pain, which we believe would be required by the FDA for approval of TRV130 for broad use in moderate to severe pain. In addition, we plan to complete other clinical trials that would support Phase 3 clinical development. Core pivotal studies in the Phase 3 program could closely resemble the Phase 2 trials, with additional trials exploring the therapeutic potential more broadly. This approach may enable an NDA for a broad acute moderate to severe pain label and may also guide commercial positioning.

We also are conducting additional Phase 1 trials in healthy subjects to evaluate the pharmacokinetics and the potential effects of TRV130 on cardiac conduction. This additional Phase 1 work is ongoing and is expected to conclude by 4Q 2015.

We plan to initially target TRV130 for the treatment of moderate to severe, acute pain where IV administration is preferred. If our trials for this indication are successful, we believe there may be additional opportunities to expand the target indications in subsequent trials. Other potential patient populations for the eventual use of TRV130 include perioperative use (including sustained dosing for the most painful surgery types); non-surgical hospitalized patients such as burn victims (including debridement); end-of-life palliative care; emergency service trauma care; renal stones; sickle cell crises and military applications. We also may explore other dosage forms, such as transmucosal or transdermal administration for breakthrough or chronic pain, respectively, in additional separate trials.

Phase 2a/b trial of TRV130 in acute postoperative pain following bunionectomy.

The aim of our Phase 2a/b clinical trial was to evaluate TRV130's efficacy and tolerability in the management of postoperative pain using morphine as a benchmark. The trial was a multicenter, randomized, double-blind, placebo- and active-controlled, multiple dose, adaptive trial in 333 women and men undergoing a primary unilateral first-metatarsal bunionectomy surgery at four sites in the United States. Patients were randomized after surgery to receive TRV130, morphine or placebo to manage their pain. Pain intensity was measured using validated numeric rating scales ranging from ten (most severe pain) to zero (no pain) at multiple time points up to 48 hours. Based on these scales, analgesic efficacy was assessed with a time-weighted average change in pain score over 48 hours a well-established measure of changes in the intensity of pain over time and an FDA-recommended endpoint for pain studies. The trial was conducted in two parts, with the goal of providing information on efficacy and dose- and interval-ranging and furthering the differentiation of TRV130 compared to morphine. In the first part, a pilot phase, patients were randomized to receive one of four doses of TRV130 (1 mg, 2 mg, 3 mg or 4 mg), morphine or placebo, all given at four hour intervals. In the second part of the trial, an adaptive phase, eight cohorts of approximately 25 patients each were randomized successively to one of two adaptive doses of TRV130 given every three hours, morphine given every four hours, and placebo given every three or four hours in a double-blind, double-dummy fashion. In this adaptive phase, doses of 0.5 mg, 1 mg, 2 mg and 3 mg of TRV130 were evaluated. Rescue medication consisting of acetaminophen or ketorolac was used in all groups. In total, 141 patients were treated in the pilot phase and 192 patients were treated in the adaptive phase. The second part of the trial was originally planned to include ten cohorts of 25 patients each, but after progressing through the pilot phase and eight of the ten planned cohorts in the second phase, we elected to close enrollment in the trial following a pre-specified interim analysis because the trial had met its objectives.

In November 2014, we announced top-line data from this trial. 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. Over the 48-hour trial period, the 3 mg dose of TRV130 administered every three hours also showed statistically superior analgesic efficacy compared to the 4 mg dose 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

Table of Contents

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 the 4 mg dose of morphine.

There were no serious adverse events reported in the trial. Both the 2 mg and 3 mg doses of TRV130 showed overall tolerability over the 48-hour trial period similar to that of the 4 mg dose of morphine administered every four hours. Adverse events attributable to TRV130 were largely opioid-related, with the most frequently reported events being dizziness, headache, somnolence, nausea, vomiting, flushing and itching. Adverse effects were generally dose-related.

Phase 1b clinical studies of TRV130

We have completed a number of Phase 1 clinical studies of TRV130 in more than 170 healthy subjects. These included two single ascending dose studies of TRV130 given as a 60 minute continuous infusion or a 2 minute bolus infusion that studies showed dose-related increases in plasma exposure and pupil constriction, a biomarker for CNS opioid activity across a range of doses that were generally well tolerated. Because in vitro data suggest that TRV130 is metabolized by at least two liver enzymes, CYP2D6 and CYP3A4, we assessed TRV130 pharmacokinetics, pharmacodynamics, safety and tolerability in CYP2D6 "poor metabolizer" healthy volunteers with little to no CYP2D6 activity. This study showed that TRV130 clearance was reduced by approximately 50% in the poor metabolizers suggesting that a lower frequency of dosing may be required to offer effective pain relief.

In 2013, we completed a Phase 1b proof of concept exploratory trial in healthy male subjects. The aims of this trial were to characterize the analgesic efficacy and safety and tolerability of a single dose of TRV130 as compared to a single 10 mg dose of morphine. We used a well-established evoked-pain model, the cold pain test, to evaluate the analgesic effects of TRV130 by measuring the time to hand removal, or latency, from a temperature-controlled cold water bath. At both the 3.0 mg and 4.5 mg doses, TRV130 showed superior efficacy as compared to a 10 mg morphine dose that was statistically significant with a p-value of less than 0.05 at the ten and 30 minute time points after dosing. The durability of the analgesic effect was similar to morphine. In addition, the time to peak effect was more rapid than that for morphine. Overall, TRV130 was well tolerated in the trial. Subjects receiving TRV130 showed less severe nausea and less frequent vomiting at the 1.5 mg and 3.0 mg doses as compared to a 10 mg dose of morphine. TRV130 also showed less respiratory depression compared to morphine over 4 hours.

In October 2014, we completed an adaptive, multiple ascending dose study of TRV130 in more than 50 healthy subjects. The safety, tolerability, pharmacokinetics and pharmacodynamics results of this study were consistent with the earlier Phase 1 studies described above. We also have two ongoing Phase 1 studies of TRV130, an absorption, distribution, metabolism, and excretion study and a QTc interval study.

Commercialization

We plan to develop and, if approved, commercialize TRV130 for IV administration ourselves. We intend to build acute care commercial capabilities, initially in the United States, and to retain full U.S. rights. In the United States, sales of injectable analgesics have increased by more than 70% between 2011 and 2013 to approximately $660 million, according to data from IMS Health. We may seek collaborators for commercializing TRV130 outside the United States after the availability of full Phase 2 data to offset risk and preserve capital.

Manufacturing

We have carried out TRV130 drug substance synthesis, performed by a third party, at a scale up to 2 kg per batch. Phase 3 synthetic process development and regulatory compliance studies are in

Table of Contents

progress. Currently we manufacture drug substance and drug product, both with third parties, at single sites, but we plan to qualify additional sites in connection with any Phase 3 trials.

Competition

If TRV130 is approved for IV treatment of moderate to severe acute pain, it will compete with widely used, currently marketed generic opioid analgesics, such as morphine, hydromorphone and fentanyl. The analgesic effectiveness of these agents is limited by well-known adverse side effects, such as respiratory depression, nausea and vomiting, constipation and POI. TRV130 also may compete against, or be used in combination with, Ofirmev, marketed by Mallinckrodt plc, with Exparel, marketed by Pacira Pharmaceuticals, Inc., and with Dyloject, approved for marketing by Hospira, Inc., which are all reformulations of existing products. Together with generic versions of NSAIDs such as ketorolac and diclofenac, and generic versions of local anesthetics such as bupivacaine, these non-opioid analgesics are currently used in combination with opioids in the multimodal management of moderate to severe acute pain.

We are aware of a number of products in development that are aimed at improving the treatment of moderate to severe, acute pain. The most advanced product candidates are reformulations of existing opioids, in patient-activated delivery devices, such as a fentanyl ionophoresis patch, in development by The Medicines Company, and a sufentanil oral nanotab with hand-held dispenser, in development by AcelRx. Durect Corporation also has a proprietary long-acting reformulation of bupivacaine in late stage development. In addition, Cara Therapeutics Inc. is developing an IV and oral peripherally restricted κ-opioid receptor agonist, which has been administered in combination with μ-opioids in clinical trials.

Intellectual property

Our TRV130 patent portfolio is wholly owned by us. The portfolio includes one issued U.S. patent, which claims among other things, TRV130, compositions comprising TRV130 and methods of using TRV130. The portfolio also includes one pending U.S. patent application claiming TRV130, other compounds and/or methods of making or using the same. If issued, the pending U.S. application is predicted to expire no earlier than 2032, subject to any disclaimers or extensions. A related Patent Cooperation Treaty, or PCT, application was filed and national patent applications have been filed in South Korea, the European Patent Office, the Eurasian Patent Office, Australia, Brazil, Canada, Israel, India, Japan, China, and New Zealand. Any patents resulting from these national patent applications, if issued, are expected to expire no earlier than 2032, subject to any disclaimers or extensions.

TRV734

TRV734 is a small molecule G protein biased ligand at the μ-opioid receptor that 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 side effects. Subject to successful preclinical and clinical development and regulatory approval, we believe TRV734 may have an improved efficacy and side effect profile as compared to current commonly prescribed oral analgesics, such as oxycodone. We have filed patent applications covering TRV734 and methods of using TRV734.

Data from IMS Health shows that μ-opioid drug sales across the United States, Europe and Japan were approximately $11 billion in 2013. Despite widespread use, there are significant limitations to existing therapies with respect to efficacy and side effects, including constipation, nausea and vomiting, and respiratory depression. Dose-limiting side-effects may translate into inadequate pain control. The

Table of Contents

constipating effects of chronic opioids are particularly problematic because they do not lessen over time, while efficacy does tend to reduce over time for a particular dose level. Numerous approaches have been attempted to mitigate constipation. Laxatives, peripherally restricted opioid antagonists, such as naloxegol, methylnaltrexone and alvimopan, and multimodal analgesia, such as the opioid/SNRI tapentadol, are only partially effective and can raise problematic new side effects in an attempt to mitigate the adverse effects of opioid analgesics. Based on the very large market and substantial limitations confronting current analgesics, we believe a new opioid with a more precisely targeted mechanism of action and an improved therapeutic profile could provide a significant product opportunity in the acute and chronic pain markets.

Clinical development strategy and experience

Following successful single ascending dose and multiple ascending dose Phase 1 studies of TRV734 in healthy volunteers, described below, we are continuing development of TRV734 to support Phase 2 clinical trials. A third Phase 1 pharmacokinetic study to evaluate TRV734 formulations for Phase 2 clinical trials is ongoing. To support later-stage development and commercialization we intend to seek a collaborator with experience in developing and commercializing controlled-substance therapeutics in chronic care pain markets. We aim to retain rights to commercialize TRV734 in acute care settings, including hospitals, in the United States.

We have had an active IND for TRV734 since January 2014, and we have completed two Phase 1 trials of TRV734 in healthy volunteers. The first study tested single ascending doses and the relative bioavailability of oral TRV734 in healthy subjects. In this trial, we observed that TRV734 was pharmacologically active at a range of safe and well-tolerated doses. TRV734 elicited dose-related increases in plasma concentrations, with peak plasma concentrations reached approximately one hour after dosing and a terminal half-life consistent with use for treating acute pain. Pupil constriction indicative of analgesia was observed at doses of 80 mg and higher, and mild-to-moderate adverse effects were reported at the maximum explored dose of 250 mg. We believe this suggests that the analgesic efficacy of TRV734 may be separable from opioid-related adverse effects. No clinically significant changes in vital signs, laboratory values or ECG parameters, and no severe or serious adverse events, were reported. We believe that the data from this trial suggest that TRV734 provides dose-related exposure, speed of onset, and duration of action suitable for treating moderate to severe acute pain.

We also have completed a multiple ascending dose trial of TRV734 in healthy volunteers. This two-part trial evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of oral TRV734 in healthy males and females. In part A of the study, 125 mg TRV734 was given to 13 males following a high fat meal, a standard meal, and in three split portions following a fast via randomized cross-over design. Results showed that dosing paradigm did not affect TRV734 bioavailability. TRV734 in each dosing paradigm was associated with pupil constriction, a marker of CNS opioid activity, lasting approximately 4-6 hours, consistent with previous data. This suggests that TRV734 should have an appropriate duration of action for the treatment of acute pain when taken with or without food. In part B of the study, 62 male and female subjects fed standard meals were given placebo, 10 mg immediate-release oxycodone, or 60, 80, 125, or 175 mg of TRV734 every 6 hours for 24 hours. Pharmacokinetics after the first and last dose were similar. Trends in pupil constriction and increased tolerability of cold-induced pain after the first and last dose were noted for all doses of TRV734, with duration of approximately 4-6 hours. These effects were similar to those seen with 10 mg oxycodone. TRV734 was generally well tolerated, and there were no serious or severe adverse events in either part of the study. Adverse events were generally opioid-related; the most common were somnolence, nausea, headache, dizziness, and vomiting, and were observed for both TRV734 and oxycodone. The Bowel Function Index (BFI), a validated tool to evaluate clinical constipation, was used to explore the

Table of Contents

potential for TRV734 to cause opioid-induced constipation and in this study showed encouraging trends compared to oxycodone.

Preclinical data

TRV734 has shown a similar profile to TRV130 in *in vitro* and *in vivo* studies. It is highly selective for the μ-opioid receptor where, like the most powerful opioid analgesics, it is a strong agonist of G protein coupling. TRV734 is distinct from those analgesics in its very weak recruitment of β-arrestins to the μ-opioid receptor. In our preclinical studies, TRV734 showed analgesic effects in preclinical pain models similar to oxycodone and morphine. In the same studies, TRV734 caused less constipation compared to equivalently analgesic doses of oxycodone and morphine. TRV734 is active after oral administration in mice and rats, has high oral bioavailability and has been well tolerated in non-human primates.

Based on these data and data for TRV130, we believe that TRV734 may offer an improved efficacy profile as compared to current opioid therapies or equivalent efficacy with an improved GI tolerability and respiratory safety profile.

Manufacturing

We have carried out TRV734 drug substance synthesis, performed by a third party, at a scale up to 2 kg per batch. A formulated tablet is being developed for Phase 2 clinical trials.

Intellectual property

Our TRV734 patent portfolio, which is wholly owned by us, includes one pending U.S. patent application claiming TRV734, other compounds and/or methods of making or using the same. If issued, we expect the pending U.S. application will expire no earlier than 2032, subject to any disclaimers or extensions. A related PCT application was filed and national patent applications have been filed in South Korea, the European Patent Office, the Eurasian Patent Office, Australia, Brazil, Canada, Israel, India, Japan, China, and New Zealand. Any patents resulting from these national patent applications, if issued, are predicted to expire no earlier than 2032, subject to any disclaimers or extensions.

TRV250

In the fourth quarter of 2014, we identified a new product candidate, TRV250, a small molecule G protein biased ligand of the δ-opioid receptor. Based on the profile of TRV250, we anticipate focusing our initial development efforts on addressing 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.

We believe our preclinical data support targeting the δ-opioid receptor for the treatment of CNS disorders. Prior approaches to modulate this receptor have been limited by a significant risk of seizure associated with this target. By contrast, TRV250 is a potent δ-opioid receptor ligand that displayed strong efficacy in animal models of migraine and other CNS disorders with reduced seizure liability through selectively activating G protein coupling without engaging β-arrestin. These *in vivo* data are further supported by data for δ-agonists in β-arrestin knockout mice suggesting that β-arrestin plays a role in seizures. We are progressing TRV250 into preclinical studies in 2015 designed to support our submission of an IND to the FDA. 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. Phase 1 clinical trials could include electroencephalogram studies to specifically assess seizure liability.

Table of Contents

We have two provisional patent applications directed to compounds that modulate the δ-opioid receptor. One of the applications is solely owned by us and the other is co-owned by us and Ligand Pharmaceuticals Incorporated, or Ligand. We have an exclusive worldwide, paid up, royalty-free license to any compound or method of use in the field of pharmaceuticals disclosed in the Ligand co-owned application. We expect that any compound that modulates the δ-opioid receptor we choose to pursue under our development program would be covered by the application solely owned by us. These applications are eligible for worldwide filing and may be used to establish non-provisional applications that, if issued, are predicted to expire no earlier than 2035.

Cardiovascular Program

TRV027

TRV027 is a peptide β-arrestin biased ligand that targets the angiotensin II type 1 receptor (AT1R), inhibiting G protein signaling and activating β-arrestin signaling. We are developing TRV027 for the treatment of AHF in combination with standard diuretic therapy. In our Phase 2a clinical trial TRV027 rapidly reduced blood pressure and preserved renal, or kidney, function while preserving cardiac performance in advanced chronic heart failure patients. We are currently enrolling patients in a Phase 2b clinical trial to evaluate the safety and efficacy of TRV027 in AHF. If our clinical development of TRV027 is successful and the product ultimately 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 and potentially lower readmission rates and mortality rates after hospital discharge. U.S. patents covering the composition of matter and method of use of TRV027 have issued and are expected to expire no earlier than 2031 and 2029, respectively.

Disease and treatment options

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 fluid overload and severe dyspnea, a serious shortness of breath sometimes described as "air hunger," leading to an inability to perform simple functions such as standing and walking short distances. AHF can also lead to organ dysfunction, including in the kidneys and heart. Most patients experiencing an AHF event have a worsening of existing chronic heart failure, although an estimated 25% of AHF hospitalizations represent new diagnoses of heart failure.

According to National Hospital Discharge Survey data, in the United States there were over 5 million hospital discharges in 2010 where heart failure was listed as a component of the diagnosis, over 1 million of which listed heart failure as the primary diagnosis. Based on national hospital discharge statistics from 25 countries in Europe, we estimate that there were a total of 1.6 million hospitalizations with a primary heart failure diagnosis in 2010 in those countries. Despite long hospital stays, up to approximately 50% of AHF patients remain symptomatic on discharge according to data from ADHERE, a national U.S. registry of over 100,000 patients admitted to the hospital with AHF between 2000 and 2005. In addition, the risk of readmission is 25% after 30 days and the one-year mortality rate is approximately 30%. Combined, these poor outcomes result in a substantial burden to the healthcare system. In 2012, the American Heart Association estimated the annual direct medical cost of treating heart failure in the United States to be almost $21 billion.

The current approach to treating patients with AHF involves facilitating the excretion of accumulated fluid with loop diuretics like furosemide; improving hemodynamics by reducing preload and afterload blood pressure with vasodilators like nitroglycerin; and directly stimulating the heart to contract more forcefully with inotropes like dobutamine. None of these approaches has been robustly

Table of Contents

shown to improve patient outcomes in AHF, and each therapy has specific adverse effects that limit its clinical utility.

Key differentiating attributes of TRV027

We believe that TRV027, when used with current standard of care, particularly loop diuretics like furosemide, will have advantages in both efficacy and safety compared to alternative therapies. Renin-angiotensin system (RAS) blockade has been shown to have morbidity and mortality benefits in chronic heart failure, and RAS is a mechanism central to AHF. We believe that TRV027, if approved, could be the first therapy to bring modulation of RAS to the acute hospital setting, and could improve patient symptoms and outcomes by rapidly lowering afterload and preload, sustaining cardiac output, and preserving kidney performance. In addition, we believe that administering TRV027 in combination with furosemide may allow furosemide to work more effectively without the negative consequences of RAS activation that has been shown to occur with loop diuretics. In clinical trials to date, TRV027 has been well-tolerated in healthy subjects and in patients with advanced chronic congestive heart failure, in each case at doses up to 20-fold higher than the expected efficacious dose. In preclinical toxicology studies, TRV027 had a favorable profile at doses up to 500 times the expected therapeutic dose. We believe that the risk of hypotension, which has limited the use of other vasodilators in AHF, is reduced for TRV027 based on its self-limiting effects on blood pressure seen in our Phase 2a trial, as well as its rapidly reversible effects seen clinically and preclinically, and because in our three completed clinical trials, TRV027 lowered blood pressure only in subjects with elevated measures of RAS activity, the target pathophysiology. This is important for any drug that is used in emergency rooms when the initial diagnosis may be uncertain.

Clinical development strategy and experience

We are enrolling patients in a Phase 2b clinical trial to evaluate the safety and efficacy of TRV027 in AHF. This is a randomized double-blind, placebo controlled trial comparing TRV027 plus standard of care to standard of care alone. The primary objective of this trial is to evaluate the effects of three doses of TRV027, 1 mg/hr, 5 mg/hr and 25 mg/hr, on a composite of clinically important outcomes: mortality, worsening heart failure, hospital readmission rate, dyspnea and length of hospital stay. We are targeting early administration of TRV027, ideally within six hours of arrival at the hospital. TRV027 will then continue to be administered for a minimum of 48 hours and up to 96 hours. We believe administration of TRV027 soon after hospital admission will improve in-hospital mortality rates and shorten length of hospital stay. We are enrolling patients with both low ejection fraction and preserved ejection fraction since RAS elevation is a key component of both conditions.

We have conducted a planned interim analysis, evaluating data from approximately 250 patients. Upon reviewing the data, the data safety monitoring board (DSMB) and the BLAST-AHF Steering Committee recommended that future enrollment be weighted to the most promising dose of 5 mg/hr. We announced in March 2015 that remaining enrollment will be weighted 2:1:2:1 for placebo, 1 mg/hr, 5 mg/hr, and 25 mg/hr, respectively, and that we have increased target enrollment in the study from 500 patients to 620 patients. In addition, the DSMB and Steering Committee determined that patients with lower baseline systolic blood pressure could safely enroll in the study; inclusion criteria have been modified accordingly. Actavis plc, or Actavis, which holds an exclusive option to license TRV027, has fully funded the expansion of the study via a $10 million payment to Trevena to defray the external and internal costs of increasing the study sample size. As a result of the increased target enrollment, Trevena now expects to release top-line data in the first half of 2016.

We believe that an endpoint measuring dyspnea or worsening of heart failure during hospitalization in Phase 3 clinical trials could form the basis for FDA approval of TRV027. However, we believe the FDA may be open to other well-defined benefit parameters, such as a hospitalization benefit or a patient and caregiver quality of life benefit. The composite endpoint tested in Phase 2b will

Table of Contents

facilitate our evaluation of potential alternative proposals to be discussed with the FDA at an end-of-Phase 2 meeting.

We have had an active IND, for TRV027 for AHF with the FDA since February 2010. Since then, we have completed three clinical trials of TRV027:

- A Phase 2a clinical trial in medically fragile subjects with advanced stable heart failure, low ejection fraction and a clinical indication for right-heart catheterization. Ejection fraction is a measure of the volume of blood pumped by the heart. Right-heart catheterization is a procedure that allows measurement of intracardiac and intravascular pressures on the side of the heart leading to the lungs.

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

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

Phase 2a hemodynamics trial in advanced stable heart failure subjects

The primary objectives of this trial were to characterize the safety and tolerability of TRV027 in subjects with advanced stable heart failure and to measure its effects on blood circulation, also known as hemodynamics. Based on the preclinical and Phase 1 data, we were expecting the hemodynamic effects of TRV027 to depend on elevation of RAS activity. The data were therefore analyzed based on plasma renin activity, or PRA, elevation, with high PRA subjects defined as those with PRA levels greater than 5.82 ng/ml/hr, which is the upper limit of lab normal range. PRA is an enzyme in the RAS cascade and measures RAS activity. Eleven of the 24 treated subjects had high PRA. We believe that these high PRA subjects represent a sicker population more relevant to AHF, and we anticipate that most AHF patients will have high PRA.

In this trial TRV027 produced a dose-related decrease in mean arterial pressure, or MAP, in subjects with elevated PRA. The reduction in MAP was sustained during the steady state infusion period and reversed during the washout period following the end of the infusion.

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

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

TRV027 was well tolerated in this medically fragile population. Despite the substantial reduction in MAP in TRV027-treated high-PRA subjects, there was no apparent increase in heart rate or in levels of cystatin-C or creatinine, which are biomarkers of renal function. This suggests that the blood pressure reduction was accompanied by preservation of kidney function. This result was consistent with our observations in preclinical studies. One subject in the lowest-dose cohort in this trial experienced

Table of Contents

hypotension necessitating dose reduction and then discontinuation of the TRV027 infusion. No other TRV027-related clinically significant adverse events were reported.

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

The primary objective of this trial was to explore the pharmacokinetics and renal safety of TRV027, co-administered with furosemide, in 17 subjects with a history of heart failure and concomitant renal dysfunction. TRV027 was administered using a standard dosing paradigm, with doses of 1.25 mg/hr, 6.25 mg/hr and 31.25 mg/hr, without weight correction. The plasma concentrations obtained were similar to those obtained when TRV027 was administered on a per-kg basis to subjects with normal kidney function, suggesting that a standard dosing approach with no adjustment for weight or renal impairment is appropriate, which would facilitate use in the emergency room where patients are not routinely weighed. In this study, TRV027 was well tolerated in these renally impaired subjects. There were no TRV027-related clinically significant or serious adverse events reported. In this trial, co-administration of TRV027 did not impair furosemide's effect on diuresis or urinary sodium excretion.

Phase 1 clinical trial

The Phase 1 clinical trial was a single center, crossover trial evaluating four-hour infusions of TRV027 in 20 healthy subjects at doses ranging from 0.01 to 20 μg/kg/min. The primary objective of the trial was to evaluate the tolerability and pharmacokinetics of TRV027. TRV027 was well tolerated with no serious adverse events or clinically significant adverse events reported even at doses up to 20 times higher than the expected therapeutic dose.

Preclinical studies

In a paced dog animal model of heart failure, TRV027 decreased MAP and PCWP. TRV027 also increased renal blood flow and moderately increased cardiac output. In another paced dog model study, TRV027 was studied in combination with furosemide and showed additive effects on reducing PCWP, which would be consistent with beneficial effects on dyspnea in the clinic. In addition, combining the data in normal dogs, paced dogs and paced dogs treated with furosemide, we observed meaningful blood pressure decreases only in animals with elevated RAS.

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

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

Table of Contents

cardioprotective signaling, suggesting that AT1R β-arrestin biased ligands could be potentially cardioprotective.

Option and License Agreements with Actavis

On May 3, 2013, we entered into an option agreement and a license agreement with Actavis plc (formerly Forest Laboratories Holdings Limited), under which we granted to Actavis an exclusive option to license TRV027. If Actavis exercises this option, the license agreement will become effective and Actavis will have an exclusive worldwide license to develop and commercialize TRV027 and specified related compounds. At our request, Actavis will consider in good faith whether to grant us the right to co-promote the licensed products in the United States under terms to be agreed upon by the parties, but it has no obligation to provide co-promotion rights to us. Actavis will be responsible for subsequent development, regulatory approval and commercialization of TRV027 at Actavis' expense.

Under the option agreement, we will conduct, at our expense, a Phase 2b clinical trial of TRV027 in AHF. The Phase 2b clinical trial is being conducted pursuant to a mutually agreed upon development plan and under the oversight of a joint development committee, which has an equal number of representatives from us and from Actavis, with operational authority during the option period retained by us, subject to Actavis' right to assume control in certain circumstances if we fail to conduct the development activities adequately.

Actavis may exercise its option during the Phase 2b clinical trial or during a specified time period after we deliver the data from the Phase 2b clinical trial to Actavis. During the option period, we are not permitted to negotiate for or enter into any agreement with a third party for the development and commercialization of TRV027 and its related compounds. Under specified circumstances linked to adverse changes in the market or related to the results from the Phase 2b trial of TRV027, Actavis has the right to renegotiate the terms of the license agreement. If Actavis exercises such right, we will be obligated to negotiate in good faith with Actavis for a period of time the terms of any new arrangement. If we and Actavis are unable to agree on the terms of any new arrangement, then the option agreement will terminate and for a specified period of time thereafter we may not offer a license to any third party on terms better than those last proposed either by us or by Actavis during the negotiations. If Actavis does not exercise the option during the specified period, its option will expire and the license agreement will not become effective. In that case, we would be free to enter into a collaboration arrangement with another party for the development and commercialization of TRV027 or to pursue development and commercialization on our own.

We received no consideration upon the grant of the option to Actavis. In March 2015, Actavis and we signed a letter agreement wherein Actavis agreed to pay us $10 million to fund the expansion of the ongoing Phase 2b trial from 500 patients to 620 patients. The March 2015 letter agreement does not otherwise amend the terms of the May 2013 option agreement. If Actavis exercises the option, we would receive a $65 million option exercise fee and could potentially receive up to $365 million in additional payments depending upon the achievement of future development and commercial milestones. We also could 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. The term of the royalty on sales of TRV027 for a given country would extend until the latest to occur of (i) ten years from first commercial sale of TRV027 in that country, (ii) the expiration of the last to expire patent claiming TRV027 that is sufficient to block the entrance of a generic version of the product, or (iii) the expiration of any period of exclusivity granted by applicable law or any regulatory authority in such country that confers exclusive marketing rights on the product.

If the license agreement becomes effective, Actavis has the right to grant sublicenses under the license agreement to affiliates and third parties. Any sublicensing does not act to relieve Actavis of any

Table of Contents

of its obligations under the license agreement, including Actavis' obligation to make milestone payments to us with respect to TRV027 or pay royalties to us on sales of TRV027 by such sublicensee. Under the license, both Actavis and we have the right to terminate the agreement in the event of an uncured material breach or insolvency of the other party. In addition, Actavis is permitted to terminate the license agreement without cause at any time upon prior written notice or immediately for product safety reasons. Following a termination of the license agreement, all licenses granted to Actavis would terminate, and Actavis would grant to us an exclusive royalty bearing license under specified patents and know-how to develop and commercialize reverted licensed products. If not terminated, the license agreement would remain in effect until the expiration of the last royalty term for the last licensed product.

Manufacturing

TRV027 drug substance has been made by a third party at a scale up to 2 kg per batch. We are exploring potential process improvements, which we will implement as appropriate as development progresses. Currently drug substance and drug product are each manufactured at single sites, but additional sites are planned for qualification in connection with any Phase 3 clinical trials.

Commercialization

If Actavis exercises its option to license TRV027, Actavis will have the exclusive rights to commercialize TRV027 and will be responsible for all commercialization activities at Actavis's expense. At our request, Actavis will consider in good faith whether to grant us the right to co-promote TRV027 in the United States under terms to be agreed upon by the parties, but it has no obligation to provide co-promotion rights to us. If Actavis does not exercise its option to license TRV027 and we are successful in obtaining necessary regulatory approval, we might pursue commercialization on our own or seek to collaborate with a third party for commercialization, particularly outside the United States.

Competition

If TRV027 is approved for the indication of AHF, it will be used with standard loop diuretic therapy and may result in reduced need for vasodilators and/or inotropes. We also are aware of three product candidates in mid- to late-stage clinical development for AHF, specifically serelaxin, which is being developed by Novartis and currently is in Phase 3 clinical trials in patients with AHF; omecamtiv mecarbil, which is being developed by Amgen in collaboration with Cytokinetics Incorporated, and currently is in Phase 2b clinical trials in patients with AHF and chronic heart failure; and ularitide, which is being developed by Cardiorentis and currently is in Phase 3 clinical trials for AHF. In addition, several product candidates are in mid- to late-stage clinical development for treating chronic heart failure which may, if approved, reduce the incidence of AHF. These product candidates include LCZ-696 from Novartis and Mydicar from Celladon.

Intellectual Property

Our TRV027 patent portfolio is wholly owned by us. The portfolio includes three issued U.S. patents that claim, among other things, TRV027, compositions comprising TRV027 and methods of using TRV027, and issued patents in Japan, New Zealand and China. The issued U.S. patents covering the composition of matter and methods of using TRV027 are expected to expire no earlier than 2031 and 2029, respectively, subject to any disclaimers or extensions available under the Hatch-Waxman Act. The TRV027 patent portfolio also includes two pending U.S. patent applications, which claim a genus of compounds that would encompass TRV027 and methods of using such compounds. If the two pending U.S. patent applications were to issue, they would be expected to expire no earlier than 2029, subject to any disclaimers or extensions. Outside of the United States, we have pending patent applications in Australia, Canada, the European Patent Office, Hong Kong and India that are directed

Table of Contents

to TRV027. The patents from these applications, if issued, are predicted to expire in 2029, subject to any disclaimers or extensions.

Additionally, the TRV027 patent portfolio includes two U.S. provisional applications directed to, among other things, synthesis of TRV027, crystalline and amorphous forms of TRV027, and methods of preparing crystalline and amorphous forms of TRV027. Any patents resulting from these patent applications, if issued are expected to expire no earlier than 2035. The TRV027 patent portfolio is subject to Actavis' option for an exclusive license.

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. 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. 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. *In vitro* assays are laboratory tests performed outside of a living organism. 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 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.

Intellectual Property

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to cover the composition of matter of our product candidates, their methods of use, related technology and other inventions that are important to our business. We also rely on trade secrets and careful monitoring of our proprietary information to

Table of Contents

protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, maintain our licenses to use intellectual property owned by third parties, preserve the confidentiality of our trade secrets and operate without infringing valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how, and continuing technological innovation to develop, strengthen and maintain our proprietary position in the field of modulating G protein coupled receptors with biased ligands.

One or more third parties may hold intellectual property, including patent rights, that is 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 required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially. If we were not able to obtain a license, or were not able to obtain a license on commercially reasonable terms, our business could be harmed, possibly materially.

We plan to continue to expand our intellectual property estate by filing patent applications directed to dosage forms, methods of treatment and additional biased modulators of G protein coupled receptors. We anticipate seeking patent protection in the United States and internationally for compositions of matter covering the compounds, the chemistries and processes for manufacturing these compounds and the use of these compounds in a variety of therapies.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and the patent's scope can be modified after issuance. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

Because many patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain that we will be able to obtain patent protection for the inventions disclosed and/or claimed in our pending patent applications. Moreover, we may have to participate in interference proceedings declared by the United States Patent and Trademark Office or a foreign patent office to determine priority of invention or in post-grant challenge proceedings, such as oppositions, *inter-partes* review, post grant review or a derivation proceeding, that challenge our entitlement to an invention or the patentability of one or more claims in our patent applications or issued patents. Such proceedings could result in substantial cost, even if the eventual outcome is favorable to us.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a PCT application or a non-provisional patent application, subject to any disclaimers or extensions. The term of a patent in the United States can be adjusted and extended due to the failure of the United States Patent and Trademark Office following certain statutory and regulation deadlines for issuing a patent.

In the United States, the patent term of a patent that covers an FDA- approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for a portion of the patent term lost during clinical development and the FDA regulatory review process. The Hatch-

Table of Contents

Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under clinical development and regulatory review. Patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other non-United States jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. Although, we intend to seek patent term extensions to any of our issued patents in any jurisdiction where these are available there is no guarantee that the applicable authorities, including the United States Patent and Trademark Office, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

We also rely on trade secret protection for our confidential and proprietary information. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property.

Manufacturing

We do not have any manufacturing facilities. We currently 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 our product candidates receive marketing approval. At this time, none of our contract manufacturing agreements limit where, or with whom we can contract for commercial manufacture or distribution. It is our intention that by the time of any regulatory approvals for commercialization, we will have negotiated long-term commitments with at least one primary and one secondary supplier for each manufacturing and distribution function.

Commercialization

We have not yet established a sales, marketing or product distribution infrastructure. Subject to successfully completing product development and receiving marketing approvals, we expect to commence commercialization activities for our products other than TRV027 by building a focused sales and marketing organization in the United States, initially in the acute care area. We believe that such an organization will be able to address the community of physicians who are the key specialists in treating the patient populations for which our product candidates are being developed. We further believe that this sales organization could be adapted and expanded to provide support for TRV027 in the acute care setting if Actavis does not exercise its option to license TRV027. Outside the United States, we expect to enter into distribution and other marketing arrangements with third parties for any of our product candidates that obtain marketing approval. We also intend to license out commercial rights for products that require a substantial primary care presence.

Table of Contents

We plan to build a marketing and sales management organization to create and implement marketing strategies for any products that we market through our own sales organization and oversee and support our sales force. In parallel with building this organization, we plan to develop educational initiatives with respect to approved products and relationships with thought leaders in relevant fields of medicine.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. Products in development by other companies may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain marketing approval.

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, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

The key competitive factors affecting the success of all of our therapeutic product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the level of generic competition and the availability of reimbursement from government and other third party payors.

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 that broadly address these indications are currently on the market for the indications that we are pursuing, and additional products are expected to become available on a generic basis over the coming years. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance

Table of Contents

with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

FDA Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implemented regulations. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending new drug applications, or NDAs, withdrawal of an approval, imposition of a clinical hold, issuance of warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;

submission to the FDA of an IND which must become effective before human clinical trials may begin;

approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;

performance of human clinical trials, including adequate and well-controlled clinical trials, in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;

submission to the FDA of an NDA;

completion of an FDA advisory committee review, if applicable;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity, as well as satisfactory completion of an FDA inspection of selected clinical sites to determine GCP compliance;

FDA review and approval of the NDA; and

Some of our potential products are anticipated to require DEA review and scheduling activities prior to launch.

Preclinical Studies

Preclinical studies include laboratory evaluation of drug substance chemistry, toxicity and drug product formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Manufacture of drug substance, drug product and the labeling and distribution of clinical supplies must all comply with cGMP standards. Some preclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and

Table of Contents

places the trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must continue to oversee the clinical trial while it is being conducted. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined. In Phase 1, the drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an initial indication of its effectiveness. In Phase 2, the drug typically is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. In Phase 3, the drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

Marketing Approval

Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has agreed to certain performance goals regarding the timing of its review of an application.

Table of Contents

In addition, under the Pediatric Research Equity Act an NDA or supplement to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements.

The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, to mitigate any identified or suspected serious risks and ensure safe use of the drug. The REMS plan could include medication guides, physician communication plans, assessment plans and elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools. We expect that the μ-opioid agonist products will be subject to a REMS, since currently marketed opioid products are subject to this requirement.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA typically refers a question regarding a novel drug to an external advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured, referred to as a Pre-Approval Inspection, or PAI. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with GCP.

The testing and approval process for an NDA requires substantial time, effort and financial resources, and each may take several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval of an NDA on a timely basis, or at all.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for the FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing

Table of Contents

information for specific indications. For some products, an additional step of DEA review and scheduling is required.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including Phase 4 clinical trials and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;

- fines, warning letters or holds on post-approval clinical trials;

Table of Contents

refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;

product seizure or detention, or refusal to permit the import or export of products; or

injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Although physicians, in the practice of medicine, may prescribe approved drugs for unapproved indications, pharmaceutical companies generally are required to promote their drug products only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

DEA Regulation

Both TRV130 and TRV734 will be regulated as a "controlled substance" as defined in the Controlled Substances Act of 1970, or CSA, which establishes registration, security, recordkeeping, reporting, storage, distribution and other requirements administered by the DEA. The DEA is concerned with the control of handlers of controlled substances, and with the equipment and raw materials used in their manufacture and packaging, in order to prevent loss and diversion into illicit channels of commerce.

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. TRV130 and TRV734, if approved, are expected to be listed by the DEA as Schedule II controlled substances under the CSA. Consequently, their manufacture, shipment, storage, sale and use will be subject to a high degree of regulation.

Annual registration is required for any facility that manufactures, distributes, dispenses, imports or exports any controlled substance. The registration is specific to the particular location, activity and controlled substance schedule. For example, separate registrations are needed for import and manufacturing, and each registration will specify which schedules of controlled substances are authorized.

The DEA typically inspects a facility to review its security measures prior to issuing a registration. Security requirements vary by controlled substance schedule, with the most stringent requirements applying to Schedule I and Schedule II substances. Required security measures include background checks on employees and physical control of inventory through measures such as cages, surveillance cameras and inventory reconciliations. Records must be maintained for the handling of all controlled substances, and periodic reports made to the DEA, for example distribution reports for Schedule I and II controlled substances, Schedule III substances that are narcotics, and other designated substances. Reports must also be made for thefts or losses of any controlled substance, and to obtain authorization to destroy any controlled substance. In addition, special authorization and notification requirements apply to imports and exports.

Table of Contents

In addition, a DEA quota system controls and limits the availability and production of controlled substances in Schedule I or II. Distributions of any Schedule I or II controlled substance must also be accompanied by special order forms, with copies provided to the DEA. The DEA may adjust aggregate production quotas and individual production and procurement quotas from time to time during the year, although the DEA has substantial discretion in whether or not to make such adjustments. Our, or our contract manufacturers', quota of an active ingredient may not be sufficient to meet commercial demand or complete clinical trials. Any delay or refusal by the DEA in establishing our, or our contract manufacturers', quota for controlled substances could delay or stop our clinical trials or product launches.

To meet its responsibilities, the DEA conducts periodic inspections of registered establishments that handle controlled substances. Individual states also regulate controlled substances, and we and our contract manufacturers will be subject to state regulation with respect to the distribution of these products.

Federal and State Fraud and Abuse and Data Privacy and Security Laws and Regulations

In addition to FDA restrictions on marketing of pharmaceutical products, federal and state fraud and abuse laws restrict business practices in the biopharmaceutical industry. These laws include anti-kickback and false claims laws and regulations as well as data privacy and security laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term "remuneration" has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting some common activities from prosecution, the exemptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated.

The reach of the Anti-Kickback Statute was also broadened by the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively PPACA, which, among other things, amended the intent requirement of the federal Anti-Kickback Statute such that a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, PPACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent. PPACA also created new federal requirements for reporting, by applicable manufacturers of covered drugs of payments and other transfers of value to physicians and teaching hospitals.

The federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal

Table of Contents

government. A claim includes "any request or demand" for money or property presented to the U.S. government. Several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new federal criminal statutes that prohibit knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the federal or state laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including criminal and significant civil monetary penalties, damages, fines, imprisonment, exclusion from participation in government healthcare programs, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

Coverage and Reimbursement

The commercial success of our product candidates and our ability to commercialize any approved product candidates successfully will depend in part on the extent to which governmental payor programs at the federal and state levels, including Medicare and Medicaid, private health insurers and other third-party payors provide coverage for and establish adequate reimbursement levels for our product candidates. Government health administration authorities, private health insurers and other organizations generally decide which drugs they will pay for and establish reimbursement levels for healthcare. In particular, in the United States, private health insurers and other third-party payors often

Table of Contents

provide reimbursement for products and services based on the level at which the government provides reimbursement through the Medicare or Medicaid programs for such treatments. In the United States, the European Union and other potentially significant markets for our product candidates, government authorities and third-party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which often has resulted in average selling prices lower than they would otherwise be. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the European Union will put additional pressure on product pricing, reimbursement and usage, which may adversely affect our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical coverage and reimbursement policies and pricing in general.

Third-party payors are increasingly imposing additional requirements and restrictions on coverage and limiting reimbursement levels for medical products. For example, federal and state governments reimburse covered prescription drugs at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of healthcare services and products. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drug products for a particular indication. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our products and product candidates or exclusion of our products and product candidates from coverage. The cost containment measures that healthcare payors and providers are instituting and any healthcare reform could significantly reduce our revenue from the sale of any approved product candidates. We cannot provide any assurances that we will be able to obtain and maintain third-party coverage or adequate reimbursement for our product candidates in whole or in part.

Impact of Healthcare Reform on Coverage, Reimbursement and Pricing

The United States and some foreign jurisdictions are considering enacting or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. 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. For example, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, imposed new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Part D plans include both standalone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not

Table of Contents

necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for any products for which we receive marketing approval. However, any negotiated prices for our future products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from Medicare Part D may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will be developed by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes of Health, and periodic reports on the status of the research and related expenditures will be made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidates. If third-party payors do not consider our product candidates to be cost-effective compared to other available therapies, they may not cover our product candidates, once approved, as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

PPACA became law in March 2010 and substantially changes the way healthcare is financed by both governmental and private insurers. Among other cost containment measures, the PPACA establishes an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents; a new Medicare Part D coverage gap discount program; and a new formula that increases the rebates a manufacturer must pay under the Medicaid Drug Rebate Program. In the future, there may continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit the prices we are able to charge for our product candidates, once approved, or the amounts of reimbursement available for our product candidates once they are approved.

In addition, other legislative changes have been proposed and adopted since PPACA was enacted. In August 2011, the President signed into law the Budget Control Act of 2011, as amended, which, among other things, created the Joint Select Committee on Deficit Reduction to propose spending reductions to Congress. The Joint Select Committee on Deficit Reduction did not achieve its targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, triggering the legislation's automatic reductions to several government programs. These reductions 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 and other healthcare reform initiatives may result in additional reductions in Medicare and other healthcare funding.

Table of Contents

Exclusivity and Approval of Competing Products

Hatch-Waxman Patent Exclusivity

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent with claims that cover the applicant's product or a method of using the product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an abbreviated new drug application, or ANDA, or 505(b)(2) NDA. Generally, an ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths, dosage form and route of administration as the listed drug and has been shown to be bioequivalent through *in vitro* or *in vivo* testing or otherwise to the listed drug. ANDA applicants are not required to conduct or submit results of preclinical or clinical tests to prove the safety or effectiveness of their drug product, other than the requirement for bioequivalence testing. Drugs approved in this way are commonly referred to as "generic equivalents" to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug. 505(b)(2) NDAs generally are submitted for changes to a previously approved drug product, such as a new dosage form or indication.

The ANDA or 505(b)(2) NDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA's Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. Specifically, the applicant must certify with respect to each patent that:

the required patent information has not been filed;

the listed patent has expired;

the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or

the listed patent is invalid, unenforceable or will not be infringed by the new product.

Generally, the ANDA or 505(b)(2) NDA cannot be approved until all listed patents have expired, except when the ANDA or 505(b)(2) NDA applicant challenges a listed drug. A certification that the proposed product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicate that it is not seeking approval of a patented method of use, the ANDA or 505(b)(2) NDA application will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA or 505(b)(2) NDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of notice of the Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) NDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the ANDA applicant.

Hatch-Waxman Non-Patent Exclusivity

Market and data exclusivity provisions under the FDCA also can delay the submission or the approval of certain applications for competing products. The FDCA provides a five-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any

Table of Contents

other new drug containing the same active moiety, which is the molecule or ion responsible for the activity of the drug substance. During the exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA submitted by another company that contains the previously approved active moiety. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or noninfringement.

The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA, or supplement to an existing NDA or 505(b)(2) NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant, are deemed by the FDA to be essential to the approval of the application or supplement. Three-year exclusivity may be awarded for changes to a previously approved drug product, such as new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent exclusivity periods described above. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or Orange Book listed patent protection cover the drug are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve an ANDA or 505(b)(2) application owing to regulatory exclusivity or listed patents. When any of our products is approved, we anticipate seeking pediatric exclusivity when it is appropriate.

Foreign Regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. For example, in the European Union, we must obtain authorization of a clinical trial application, or CTA, in each member state in which we intend to conduct a clinical trial. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Table of Contents

Employees

As of December 31, 2014, we had 42 employees, all of whom are located in the United States. None of our employees is represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

Corporate Information

We were incorporated under the laws of the State of Delaware in November 2007. Our principal executive offices are located at 1018 West 8th Avenue, Suite A, King of Prussia, Pennsylvania 19406. Our telephone number is (610) 354-8840.

Available Information

Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and other filings with the United States Securities and Exchange Commission, or the SEC, and all amendments to these filings, are available, free of charge, on our website at www.trevenainc.com as soon as reasonably practicable following our filing of any of these reports with the SEC. You can also obtain copies free of charge by contacting our Investor Relations department at our office address listed below. The public may read and copy any materials we file with the SEC at the SEC's Public Reference Room at 100 F Street NE, Room 1580, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains an Internet site that contains reports, proxy, and information statements, and other information regarding issuers that file electronically with the SEC at www.sec.gov. The information posted on or accessible through these websites are not incorporated into this filing.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012. We will remain an emerging growth company until the earlier of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of our initial public offering in February 2014, (b) in which we have total annual gross revenue of at least $1.0 billion, or (c) 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 exceeded $700.0 million as of the prior June 30th, and (2) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period. We refer to the Jumpstart Our Business Startups Act of 2012 in this Annual Report on Form 10-K as the "JOBS Act," and references to "emerging growth company" have the meaning associated with it in the JOBS Act.

EXECUTIVE OFFICERS OF THE REGISTRANT

Name	Age	Position
Maxine Gowen, Ph.D.	56	President, Chief Executive Officer and Director
Roberto Cuca	47	Senior Vice President and Chief Financial Officer
Michael W. Lark, Ph.D.	57	Chief Scientific Officer and Senior Vice President, Research
John M. Limongelli, Esq.	45	Senior Vice President, General Counsel and Corporate Secretary
David Soergel, M.D.	47	Senior Vice President, Clinical Development and Chief Medical Officer

Maxine Gowen, Ph.D.

Dr. Gowen has served as our President and Chief Executive Officer and as a member of our board of directors since our founding in November 2007. Prior to joining our company, Dr. Gowen was Senior Vice President for the Center of Excellence for External Drug Discovery at

Table of Contents

GlaxoSmithKline plc, or GSK, where she held a variety of leadership positions during her tenure of 15 years. Before GSK, Dr. Gowen was Senior Lecturer and Head, Bone Cell Biology Group, Department of Bone and Joint Medicine, of the University of Bath, U.K. Dr. Gowen has served as a director of Akebia Therapeutics, Inc. since July 2014. From 2008 until 2012, Dr. Gowen served as a director of Human Genome Sciences, Inc., a public biopharmaceutical company. She received her Ph.D. from the University of Sheffield, U.K., an M.B.A. with academic honors from The Wharton School of the University of Pennsylvania, and a B.Sc. with Honors in Biochemistry from the University of Bristol, U.K. Our board of directors believes that Dr. Gowen's detailed knowledge of our company and her over 20 years in the pharmaceutical industry, including her roles at GSK, provide a critical contribution to our board of directors.

Roberto Cuca

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

Michael W. Lark, Ph.D.

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

John M. Limongelli, Esq.

Mr. Limongelli joined our company as Senior Vice President, General Counsel and Corporate Secretary in May 2014. Prior to that, he was Vice President, Associate Chief Counsel and Corporate Secretary at Cigna Corporation from September 2013 until May 2014. From October 2012 to September 2013, he was a partner at the law firm Royer Cooper Cohen Braunfeld LLC. He served as Senior Vice President, General Counsel and Secretary at Adolor Corporation from September 2008 until Adolor's sale to Cubist Pharmaceuticals, Inc. in December 2011. Prior to Adolor, Mr. Limongelli held roles of increasing responsibility with Cephalon, Inc., most recently serving as Vice President and Associate General Counsel. Mr. Limongelli began his legal career in private practice with Morgan, Lewis & Bockius, LLP, in Philadelphia, Pennsylvania. Prior to his legal career, Mr. Limongelli was a certified public accountant with KPMG LLP. Mr. Limongelli obtained both his J.D. and M.B.A. from Temple University.

Table of Contents

David Soergel, M.D.

Dr. Soergel has served in multiple positions since joining our company in November 2009 and currently serves as our Senior Vice President, Clinical Development and Chief Medical Officer. Prior to joining our company, he served as Senior Director, Clinical Development for Concert Pharmaceuticals, Inc., a biotechnology company, from July 2008 to November 2009. Prior to Concert, Dr. Soergel served as Director, Discovery Medicine, in the Cardiovascular Urogenital Center of Excellence in Drug Discovery at GSK, from 2005 until 2008. Dr. Soergel received an M.D. from Cornell University Medical College and a B.A. from The Johns Hopkins University. Dr. Soergel completed his clinical training in pediatric cardiology at Johns Hopkins Hospital and underwent additional training in heart failure and transplant at the Children's Hospital of Philadelphia.

ITEM 1A. RISK FACTORS

Our business is subject to numerous risks. You should carefully consider the following risks and all other information contained in this Annual Report on Form 10-K, as well as general economic and business risks, together with any other documents we file with the SEC. If any of the following events actually occur or risks actually materialize, it 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.

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 $49.7 million and $23.3 million for the years ended December 31, 2014 and 2013, respectively. As of December 31, 2014, we had an accumulated deficit of $132.0 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

32

Table of Contents

add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts.

To become and remain profitable, we must succeed in developing and eventually commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages 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 our existing cash and cash equivalents as of December 31, 2014 the $16.5 million that we are eligible to draw under our credit facility based on the top-line results of the Phase 2a/b trial of TRV130 announced in November 2014 and the $10.0 million received from Actavis in March 2015, 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

Table of Contents

exercised, potential milestone payments we may receive under our option and license agreements with 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 to enable us to complete Phase 3 development of TRV027 if Actavis chooses not to license the product candidate. 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, 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

Table of Contents

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

Table of Contents

We are very early in our development efforts and have only two product candidates, TRV027 and TRV130, in Phase 2, one, TRV734, in Phase 1, and one, TRV250, in the preclinical stage. 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, one, TRV734, in Phase 1 development, and one TRV250, in preclinical 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.

Table of Contents

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

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

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

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

be delayed in obtaining marketing approval for our product candidates;

Table of Contents

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

Table of Contents

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

Table of Contents

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

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

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

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

Risks Related to the Commercialization of Our Product Candidates

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

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

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

the clinical indications for which the product is approved; and

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

Table of Contents

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

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

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

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- the lack of complementary or other products to be offered by sales personnel, which may put us at a competitive disadvantage from the perspective of sales efficiency relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

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

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

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. In addition to existing therapeutic treatments for the indications we are targeting with our product candidates, which our goal would be to displace if any of our product candidates achieves regulatory approval, we also face potential competition from other drug candidates in development by other companies. With respect to competition for TRV027, we are aware of three product candidates in

Table of Contents

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

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

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

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

Both our and our collaborators' ability to commercialize any of our product candidates successfully will depend, in part, on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government payor programs at the federal and state level authorities, including Medicare and Medicaid, private health insurers, managed care plans and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Coverage and reimbursement may not be available for any drug that we or our collaborators commercialize and, even if these are available, the level of reimbursement may not be satisfactory. Inadequate reimbursement levels may adversely affect the demand for, or the price of, any product candidate for which we or our collaborators obtain marketing approval. Obtaining and

Table of Contents

maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we or our collaborators may not be able to successfully commercialize any product candidates for which marketing approval is obtained.

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

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

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

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

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any products that we may develop. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. If we cannot successfully defend ourselves against claims that our product candidates or

Table of Contents

products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

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

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

Risks Related to Our Dependence on Third Parties

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

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

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

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

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

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

Table of Contents

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 Annual Report also apply to the activities of our therapeutic program collaborators.

If Actavis exercises its option to license TRV027 from us, the license agreement will contain a restriction on our engaging in activities relating to certain product candidates that may compete with TRV027 for a specified period of time. This restriction may have the effect of preventing us from undertaking development and other efforts for TRV027 that we would otherwise prefer to pursue. Additionally, subject to its contractual obligations to us, if Actavis or a future collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our reputation in the business and financial communities could be adversely affected.

For our product candidates other than TRV027, we may in the future determine to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization

Table of Contents

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

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

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

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

The third parties with whom we have contracted to help perform our preclinical studies or clinical trials may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated

Table of Contents

protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

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

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

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

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

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- manufacturing delays if our third-party manufacturers give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreement between us;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

The facilities used by our contract manufacturers to manufacture our product candidates must be approved by the FDA pursuant to inspections that will be conducted after we submit an NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturers for compliance with cGMP regulations for manufacture of our product candidates. Third-party manufacturers may not be able to comply with the cGMP regulations or similar regulatory

Table of Contents

requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products.

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

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

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

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

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

As part of our strategy to mitigate development risk, we seek to develop product candidates with validated mechanisms of action and we utilize biomarkers to assess potential clinical efficacy early in the development process. This strategy necessarily relies upon clinical data and other results obtained by third parties that may ultimately prove to be inaccurate or unreliable. Further, such clinical data and results may be based on products or product candidates that are significantly different from our product candidates. If the third-party data and results we rely upon prove to be inaccurate, unreliable or not applicable to our product candidates, we could make inaccurate assumptions and conclusions about our product candidates and our research and development efforts could be compromised.

Table of Contents

Risks Related to Our Intellectual Property

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

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

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

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

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The United States Patent Office recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

Table of Contents

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

Table of Contents

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.

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

Table of Contents

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.

Table of Contents

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.

Table of Contents

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

Table of Contents

the supply of the compounds used in clinical trials for our product candidates, and, in the future, the 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.

Table of Contents

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 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;
- fines, 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.

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

Table of Contents

patient privacy regulation by U.S. federal and state governments and by governments in foreign 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

Table of Contents

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, 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;

Table of Contents

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

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.

Table of Contents

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 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.

Table of Contents

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 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;

Table of Contents

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

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.

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 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 you may not be able to resell some or all of your shares at a desired price.

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;

Table of Contents

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;

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.

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, the market price of our common stock could decline significantly.

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.

Table of Contents

Additionally, the holders of an aggregate of approximately 15 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. As of December 31, 2014, we had federal net operating loss carryforwards of approximately $22.8 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 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;

Table of Contents

stockholders are not entitled to remove directors other than by a $66^{2}/_{3}\%$ 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.

Our executive officers, directors and current beneficial owners of 5% or more of our common stock and their respective affiliates, in the aggregate, beneficially own approximately 63% of our outstanding common stock. 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.

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 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.

Table of Contents

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.

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

Table of Contents

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.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our principal offices occupy approximately 14,550 square feet of leased office and laboratory space in King of Prussia, Pennsylvania pursuant to a lease agreement that expires in September 2020. In addition, we lease a vivarium space in Exton, Pennsylvania pursuant to a lease agreement that expires in August 2015. We believe that our current facilities are suitable and adequate to meet our current needs, although we have agreed to lease an additional 2,150 square feet of office space later in 2015 to accommodate our expected growth. We intend to add new facilities or expand our existing facilities as we add employees, and we believe that suitable additional or substitute space at our current location will be available as needed to accommodate any such expansion of our operations.

ITEM 3. LEGAL PROCEEDINGS

From time to time, we are subject to litigation and claims arising in the ordinary course of business. We are not currently a party to any material legal proceedings and we are not aware of any pending or threatened legal proceeding against us that we believe could have a material adverse effect on our business, operating results or financial condition.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

Table of Contents

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Market Information and Holders

Our common stock is traded on the NASDAQ Global Select Market under the symbol "TRVN." Prior to January 31, 2014, there was no public market for our common stock. Accordingly, we have only set forth quarterly information with respect to the high and low prices for our common stock for the most recent fiscal year. The following table sets forth, for the periods indicated, the high and low prices for our common stock as reported on the NASDAQ Global Select Market:

	High	Low
2014		
First quarter (from January 31, 2014)	$ 9.95	$ 6.08
Second quarter	$ 7.82	$ 4.07
Third quarter	$ 7.00	$ 5.20
Fourth quarter	$ 6.73	$ 3.80

On February 27, 2015, there were approximately 32 holders of record of our common stock. On February 27, 2015, the closing price of our common stock was $5.39.

Dividends

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.

Securities Authorized for Issuance under Equity Compensation Plans

The following table provides certain information with respect to all of our equity compensation plans in effect as of December 31, 2014:

Plan Category	Number of Securities to be Issued Upon Exercise of Outstanding Options, Warrants and Rights	Weighted-Average Exercise Price of Outstanding Options, Warrants and Rights	Number of Securities Remaining Available for Issuance Under Equity Compensation Plans(1)(2)
Equity compensation plans approved by stockholders	3,574,450	$ 3.75	1,055,170
Equity compensation plans not approved by stockholders			
Total	3,574,450	$ 3.75	1,055,170

(1) Includes 225,806 shares of our common stock issuable under our 2013 Employee Stock Purchase Plan ("ESPP"). The number of shares of our common stock reserved for issuance under our 2013 ESPP will automatically increase on January 1 of each year, beginning on January 1, 2015 and continuing through and including January 1, 2023, by the number of shares equal to the lesser of (1) 225,806, (2) the total number of shares of common stock issued under the 2013 ESPP during the immediately preceding calendar year and (3) such lesser number of shares determined by our board of directors.

68

Table of Contents

(2) Includes 829,364 shares of our common stock issuable under our 2013 Equity Incentive Plan. On January 1, 2015 and annually thereafter through January 1, 2023, the number of authorized shares under our 2013 Equity Incentive Plan will automatically increase by a number of shares equal to the lesser of: 4% of the number of our shares issued and outstanding prior to the preceding December 31; or an amount determined by our Board of Directors.

Recent Sales of Unregistered Securities

In connection with entering into a loan and security agreement with Oxford Finance LLC, or Oxford, and Square 1 Bank, or Square 1, on September 19, 2014 we issued warrants to purchase 4,875, 1,950 and 853 shares of our common stock to Oxford, Square 1 and Three Point Capital, LLC, or Three Point, respectively, which we refer to collectively as the "Warrants". The Warrants issued to Oxford and Square 1 were consideration for Oxford and Square 1 agreeing to provide us with debt financing pursuant to the loan and security agreement, and the Warrants issued to Three Point were consideration to Three Point for its role as placement agent in the transaction. The Warrants issued to Oxford, Square 1 and Three Point were issued in a private transaction made in reliance upon exemptions from registration pursuant to Section 4(a)(2) under the Securities Act of 1933, as amended. The Warrants are exercisable, in whole or in part, immediately, and have a per share exercise price of $5.8610. The Warrants may be exercised on a cashless basis. The Warrants will terminate on the earlier of September 19, 2024 or the closing of a merger or consolidation transaction in which we are not the surviving entity.

Sales of Registered Securities

Our initial public offering of common stock was effected through a Registration Statement on Form S-1 (File No. 333-191643) that was declared effective by the Securities and Exchange Commission on January 30, 2014. On February 5, 2014, we issued and sold 9,250,000 shares of common stock in an initial public offering, or the IPO, at a price of $7.00 per share, for aggregate gross proceeds of $64.8 million. On March 6, 2014, in connection with the partial exercise of the IPO underwriters' over-allotment option, we sold an additional 270,449 shares of common stock at a price of $7.00 per share, for aggregate gross proceeds of approximately $1.9 million. The net offering proceeds to us from both sales were approximately $59.5 million, after deducting underwriting discounts and commissions of approximately $4.7 million and offering costs of approximately $2.5 million. In addition, as part of the IPO, all of our outstanding convertible preferred stock was converted and all but 22,580 of its outstanding warrants were net exercised into an aggregate of 15,728,286 shares of common stock.

In December 2014, we issued and sold 12,848,000 shares of common stock in an offering of shares at a price of $4.00 per share, for aggregate gross proceeds of $51.4 million. The net offering proceeds to us were approximately $47.7 million, after deducting underwriting discounts and commissions of approximately $3.1 million and offering costs of approximately $0.6 million.

Table of Contents

ITEM 6. SELECTED FINANCIAL DATA

(In thousands, except share and per share data)

The following tables set forth our selected financial data for the periods indicated. The following selected financial data for the years ended December 31, 2014 and 2013 and the selected balance sheet data as of December 31, 2014 and 2013 are derived from our audited financial statements appearing elsewhere in this report.

This selected 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 report.

Our historical results are not necessarily indicative of the results that may be expected in the future, and our interim period results are not necessarily indicative of results to be expected for a full year or any other interim period.

	Year Ended December 31,	
	2014	2013
Statement of Operations Data:		
Revenue		
Grant revenue	$	$ 84,980
Collaboration revenue		50,000
Total revenue		134,980
Operating expenses:		
General and administrative	9,403,254	4,718,047
Research and development	40,546,666	18,762,219
Total operating expenses	49,949,920	23,480,266
Loss from operations	(49,949,920)	(23,345,286)
Total other income (expense)	249,045	93,851
Net loss and comprehensive loss	(49,700,875)	(23,251,435)
Accretion of redeemable convertible preferred stock	(28,521)	(333,710)
Net loss attributable to common stockholders	$ (49,729,396)	$ (23,585,145)
Net loss per share basic and diluted	$ (2.02)	$ (29.71)
Weighted average shares of common stock outstanding used in computing net loss per share basic and diluted	24,655,603	793,806

	As of December 31,	
	2014	2013
Balance Sheet Data:		
Cash and cash equivalents	$ 36,205,559	$ 37,965,198
Marketable securities	70,698,640	

Total assets	108,337,459	42,392,926
Total liabilities	9,133,831	3,401,397
Total redeemable convertible preferred stock		120,562,138
Total stockholders' equity (deficit)	99,203,628	(81,570,609)

Table of Contents

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and related notes appearing in this Annual Report. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report, our actual results could differ materially from the results described in or implied by the forward- looking statements contained in the following discussion and analysis.

Overview

Using our proprietary product platform, we have identified and are developing the following three differentiated product candidates:

TRV130: We are developing TRV130 as a first-line treatment for patients experiencing moderate to severe pain where IV administration is preferred. We are currently conducting a second Phase 2 trial of TRV130 with the goal of evaluating analgesic efficacy following soft-tissue surgery and exploring TRV130's safety and tolerability profile benchmarked to morphine. We expect to report top-line data from this trial in mid-2015. In November 2014, we announced top-line data from our Phase 2a/b clinical trial of TRV130 in postoperative pain following bunionectomy surgery. 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. There were no serious adverse events reported in the trial, which we believe suggests that these levels of pain relief can be achieved safely. Based on the data from the recently completed Phase 2a/b study, we plan to move into Phase 3 preparations, which we expect to occur in parallel with the second Phase 2 soft tissue trial for TRV130 that we commenced in December 2014. We also anticipate that we will initiate a Phase 3 clinical trial for TRV130 in the first quarter of 2016. 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 for use in acute care settings such as hospitals and ambulatory surgery centers if it receives regulatory approval.

TRV734: We are developing TRV734 as a first-line, orally administered compound for the treatment of moderate to severe acute and chronic pain. We have completed both a Phase 1 single ascending dose clinical trial and a Phase 1 multiple ascending dose clinical study and reported positive results from these studies in June 2014 and February 2015, respectively. We are commencing a pharmacokinetic study with various formulations of TRV734 to prepare for phase 2 development. We have retained all worldwide development and commercialization rights to TRV734.

TRV027: We are developing TRV027 for the treatment of acute heart failure, or AHF. In early 2014 we initiated a Phase 2b clinical trial of TRV027 (BLAST-AHF) for the treatment of AHF. In January 2015, we conducted a planned interim analysis, evaluating data from approximately 250 patients. Upon reviewing the data, the data safety monitoring board (DSMB) and the BLAST-AHF Steering Committee recommended that future enrollment be weighted to the most promising dose of 5 mg/hr. We announced in March 2015 that remaining enrollment will be weighted 2:1:2:1 for placebo, 1 mg/hr, 5 mg/hr, and 25 mg/hr, respectively, and that we have

Table of Contents

increased target enrollment in the study from 500 patients to 620 patients. In addition, the DSMB and Steering Committee determined that patients with lower baseline systolic blood pressure could safely enroll in the study; inclusion criteria have been modified accordingly. Actavis plc, or Actavis, which holds an exclusive option to license TRV027, has fully funded this expansion of the study via a $10 million payment to us to defray the external and internal costs of increasing the study sample size. As a result of the increased target enrollment, we now expect to release top-line data in the first half of 2016.

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 that would support our submission of an investigational new drug application, or IND, to the U.S. Food and Drug Administration, or FDA.

We were incorporated and commenced operations in the fourth quarter of 2007. Our operations to date have included organizing and staffing our company, business planning, raising capital, developing TRV027, TRV130 and TRV734, and discovering a δ-opioid receptor targeted product candidate, TRV250. We have financed our operations primarily through private placements and public offerings of our equity securities and debt borrowings. As of December 31, 2014, we had an accumulated deficit of $132.0 million. Our net loss was $49.7 million and $23.3 million for the years ended December 31, 2014 and 2013, respectively. Our ability to become and remain profitable depends on our ability to generate revenue. We do not expect to generate significant revenue unless and until we or a collaborator obtain marketing approval for and commercialize TRV027, TRV130, TRV734 or TRV250.

In September 2014, we announced we had entered into a $35.0 million senior secured tranched term loan credit facility with Oxford Finance LLC and Square 1 Bank, of which we have drawn $2.0 million as of December 31, 2014. 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 have met the conditions to draw the $16.5 million second tranche under the credit facility and have until June 30, 2015 to draw the tranche. We may opt to draw the third term loan tranche if we receive positive data from the Phase 2 clinical trial of TRV027.

We expect to incur significant expenses and operating losses for the foreseeable future as we continue the development and clinical trials of, and seek regulatory approval for, our product candidates. If we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses. Furthermore, following our IPO in January 2014, we have incurred and expect to continue to incur additional costs associated with operating as a public company. These costs include significant legal, accounting, investor relations and other expenses that we did not incur as a private company. 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. We will seek to fund our operations through the sale of equity, debt financings or other sources, including potential additional collaborations. However, we may be unable to raise additional funds or enter into such other agreements when needed on favorable terms, or at all. If we fail to raise capital or enter into such other arrangements as, and when, needed, we may have to significantly delay, scale back or discontinue the development and/or commercialization of one or more of our product candidates.

Option and License Agreements with Actavis plc

On May 3, 2013, we entered into an option agreement and a license agreement with Actavis plc (formerly Forest Laboratories Holdings Limited), under which we granted to Actavis an exclusive option to license our product candidate, TRV027. If Actavis exercises this option, the license agreement will become effective and Actavis will have an exclusive worldwide license to develop and

Table of Contents

commercialize TRV027 and specified related compounds. Actavis will be responsible for subsequent development, regulatory approval and commercialization of TRV027 at Actavis' expense. At our request, Actavis will consider in good faith whether to grant us the right to co-promote the licensed products in the United States under terms to be agreed upon by the parties, but Actavis has no obligation to grant us such right.

Under the option agreement, we will conduct, at our expense, a Phase 2b clinical trial of TRV027 in AHF. Actavis may exercise its option at any time during the Phase 2b clinical trial or during a specified time period after we deliver the data from the Phase 2b clinical trial to Actavis. During the option period, we are not permitted to negotiate for or enter into any agreement with a third party for the development and commercialization of TRV027 and its related compounds. Under specified circumstances linked to adverse changes in the market or related to the results from the Phase 2b clinical trial of TRV027, Actavis has the right to renegotiate the terms of the license agreement. If Actavis exercises such right, we will be obligated to negotiate in good faith with Actavis for a period of time the terms of any new arrangement. If we and Actavis are unable to agree on the terms of any new arrangement, then the option agreement will terminate and for a specified period of time thereafter we may not offer a license to any third party on terms better than those last proposed by either us or Actavis during the negotiations. If Actavis does not exercise its option during the specified period, the option will expire and the license agreement will not become effective. In that case, we would be free to enter into a collaboration arrangement with another party for the development and commercialization of TRV027 or to pursue development and commercialization on our own.

We received no consideration upon the grant of the option to Actavis. In March 2015, Actavis and we signed a letter agreement wherein Actavis agreed to pay $10.0 million to fund the expansion of the ongoing Phase 2b trial from 500 patients to 620 patients. The March 2015 letter agreement does not otherwise amend the terms of the May 2013 option agreement. If Actavis exercises the option, we would receive a $65 million option exercise fee and could potentially receive up to $365 million in additional payments depending upon the achievement of future development and commercial milestones. We also could receive tiered royalties between 10% and 20% on net sales of licensed products worldwide, subject to specified deductions and offsets, 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. The term of the royalty on sales of TRV027 for a given country would extend until the latest to occur of (i) ten years from first commercial sale of TRV027 in that country, (ii) the expiration of the last to expire patent claiming TRV027 that is sufficient to block the entrance of a generic version of the product, or (iii) the expiration of any period of exclusivity granted by applicable law or any regulatory authority in such country that confers exclusive marketing rights on the product.

If the license agreement becomes effective, Actavis has the right to grant sublicenses under the license agreement to affiliates and third parties. Any sublicensing does not relieve Actavis of any of its obligations under the license agreement, including Actavis' obligation to make milestone payments to us with respect to TRV027 or pay royalties to us on sales of TRV027 by such sublicensee. Under the license, both we and Actavis have the right to terminate the agreement in the event of an uncured material breach or insolvency of the other party. In addition, Actavis is permitted to terminate the license agreement without cause at any time upon prior written notice or immediately for product safety reasons. Following a termination of the license agreement, all licenses granted to Actavis would terminate, and Actavis would grant to us an exclusive royalty bearing license under specified patents and know-how to develop and commercialize reverted licensed products. If not terminated, the license agreement would remain in effect until the expiration of the last royalty term for the last licensed product.

Table of Contents

Senior Secured Tranched Term Loan Credit Facility

In September 2014, we entered into a loan and security agreement with Oxford Finance LLC and Square 1 Bank, or the lenders, pursuant to which they have agreed to lend us up to $35.0 million in a three-tranche series of term loans. Upon initially entering into the agreement, we borrowed $2.0 million. In addition, we may borrow:

- an additional $16.5 million, at any time on or before June 30, 2015, since we have satisfied specified conditions precedent related to the results of our Phase 2 bunionectomy trial of TRV130; and

- an additional $16.5 million, at any time on or before March 31, 2016, subject to the satisfaction of specified conditions related to the results of our Phase 2b clinical trial of TRV027.

Borrowings accrue interest at a fixed rate of 6.50% per annum. We are required to make payments of interest only on borrowings under this agreement on a monthly basis through and including April 1, 2016, which we refer to as the interest only termination date extended from October 1, 2015, since we have satisfied specified conditions precedent related to the results of our recently concluded Phase 2 bunionectomy study of TRV130 after which payments of principal in equal monthly installments and accrued interest will be due until the loan matures on December 1, 2018. Both the interest only termination date and the maturity date may be further modified as follows if we meet the conditions related to the Phase 2b trial of TRV027 by March 31, 2016:

- the interest only termination date will be extended until October 1, 2016.

- the maturity date will be extended to September 1, 2019 if we have received net cash proceeds of at least $50.0 million from our existing option and license with Actavis or another strategic partnership satisfactory to the lenders.

We paid the lenders a facility fee of $175 thousand in connection with the execution of the agreement. Upon the last payment date of the amounts borrowed under the agreement, we will be required to pay a final payment fee ranging from 6.1% to 7.0% of the aggregate amounts borrowed. In addition, if we repay the borrowings prior to the maturity date, we will be obligated to pay a prepayment fee of 3.0% of the total amount prepaid if the prepayment occurs prior to the first anniversary of the funding of the applicable tranche, 2.0% percent of the total amount prepaid if the prepayment occurs between the first and second anniversary of the funding of the applicable tranche, and 1.0% of the total amount prepaid if the prepayment occurs on or after the second anniversary of the funding of the applicable tranche.

Our obligations are secured by a first priority security interest in substantially all of our assets, other than intellectual property. In addition, we have agreed not to pledge or otherwise encumber our intellectual property, with specified exceptions.

We used a placement agent in connection with the agreement. We paid the agent $65 thousand upon execution of the agreement and will be obligated to pay up to an additional $175 thousand if we draw on the second and third tranches.

In connection with entering into the agreement, we issued to the lenders warrants to purchase an aggregate of 7,678 shares of our common stock. These warrants are exercisable immediately and have an exercise price of $5.8610 per share. The warrants may be exercised on a cashless basis and will terminate on the earlier of September 19, 2024 or the closing of a merger or consolidation transaction in which we are not the surviving entity. If we draw on the second or third tranches, we will issue additional warrants to purchase shares of our common stock, each with an exercise price of $5.8610 per share and on substantially the same terms as those contained in the initial warrants. The number of shares underlying these additional warrants will depend on the amount of additional borrowings we make, but will not exceed 126,685.

Table of Contents

Components of Operating Results

Revenue

To date, we have derived revenue principally from research grants as well as from one research collaboration arrangement. We do not expect further revenue from these sources because we have completed our grant programs and our research collaboration. We have not generated any revenue from commercial product sales. In the future, if any of our product candidates currently under development is approved for commercial sale, we may generate revenue from product sales, or alternatively, we may choose to select a collaborator to commercialize our product candidates in all or selected markets.

General and Administrative Expenses

General and administrative expenses consist principally of salaries and related costs for executive and other personnel, including stock-based compensation and travel expenses. Other general and administrative expenses include facility-related costs; communication expenses; professional fees for legal, patent prosecution and facilities maintenance consulting; and accounting services.

Research and Development Expenses

Our research and development expenses consist primarily of costs incurred for the development of our product candidates, as well as salaries and related costs for executive and other personnel, including stock-based compensation and travel expenses.

Research and development costs are expensed as incurred and are tracked by discovery program and subsequently by product candidate once a product candidate has been selected for development. We record costs for some development activities, such as clinical trials, based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations or information provided to us by our vendors.

Change in Fair Value of Warrant Liability

Prior to our initial public offering, or IPO, we issued warrants for the purchase of our convertible preferred stock that we concluded were financial instruments that might require a transfer of assets because of the redemption features of the underlying preferred stock. Therefore, we classified these warrants as liabilities that we re-measured to fair value at each balance sheet date and we recorded the changes in the fair value of the warrant liability in our statement of operations and comprehensive loss as a change in fair value of warrant liability. At the time of the IPO, certain warrants were net exercised into common stock and the remaining fair value of $145 thousand associated with these warrants was reclassified to additional paid-in capital. Upon the IPO, an outstanding warrant to purchase 125,000 shares of Series B preferred stock was converted into a warrant to purchase up to 20,161 shares of the Company's common stock and remains outstanding with a fair value recorded as a liability of $82,851 at December 31, 2014, as it contains a cash settlement feature upon certain strategic transactions. The fair value of the warrants classified as liabilities on each re-measurement date is estimated using the Black-Scholes option pricing model.

Other Income / Expense

Other income consists principally of interest income earned on cash and cash equivalent balances, marketable securities and miscellaneous income attributable to the sale of research and development tax credits.

Table of Contents

Accretion of Preferred Stock

We accounted for the redemption of issuance costs on our formerly outstanding preferred stock using the effective interest method, accreting such amounts to preferred stock from the date of issuance to the earliest date the holder could demand redemption. Issuance costs were fully accreted through conversion upon IPO.

Critical Accounting Policies and Significant Judgments and Estimates

This discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States of America, or GAAP. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reported period. In accordance with GAAP, we base our estimates on historical experience and on various other assumptions that we believe are reasonable under the circumstances. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are more fully described in Note 2 to our audited financial statements appearing elsewhere in this Annual Report, we believe the following accounting policies are critical to the process of making significant judgments and estimates in the preparation of our financial statements.

Investments

At the time of purchase, we classify investments in marketable securities as either available-for-sale securities, held to maturity securities, or trading securities, based on our intent at that time.

As of December 31, 2014, our investments are classified as available-for-sale pursuant to ASC 320, *Investments Debt and Equity Securities*. We classify investments available to fund current operations as current assets on our balance sheets. We consider all investments that have maturities of three months or less when acquired to be cash equivalents. Investments are classified as long-term assets on the balance sheets if (i) we have the intent and ability to hold the investments for a period of at least one year and (ii) the contractual maturity date of the investments is greater than one year.

Investments are carried at fair value with unrealized gains and losses included as a component of accumulated other comprehensive loss, until such gains and losses are realized. Fair value is determined based on observable market quotes or valuation models using assessments of counterparty credit worthiness, credit default risk of underlying security and overall capital market liquidity. We review unrealized losses associated with available-for-sale securities to determine the classification as "temporary" or "other-than-temporary" impairment. A temporary impairment results in an unrealized loss being recorded in other comprehensive income. If a decline in the fair value is considered other-than-temporary, based on available evidence, the unrealized loss is transferred from other comprehensive loss to the statement of operations. We consider various factors in determining the classification, including the length of time and extent to which the fair value has been less than our cost basis, the financial condition and near-term prospects of the issuer or investee, and our ability to hold the investment for a period of time sufficient to allow for any anticipated recovery in market value. There were no charges taken for other-than-temporary declines in fair value of short-term investments during the year ended December 31, 2014. We recorded unrealized losses of $18,782 during the year ended December 31, 2014. Realized gains and losses are included in interest income in the statement of operations. We did not recorded any realized gains or losses during the year ended December 31, 2014.

Table of Contents

Research and Development

Research and development costs are charged to expense as incurred. These costs include, but are not limited to, employee-related expenses, including salaries, benefits and travel and stock based compensation of our research and development personnel; expenses incurred under agreements with contract research organizations and investigative sites that conduct clinical trials and preclinical studies; the cost of acquiring, developing and manufacturing clinical trial materials; facilities; other supplies; allocated facilities, depreciation and other expenses, which include rent and utilities; insurance; and costs associated with preclinical activities and regulatory operations.

Costs for certain development activities, such as clinical trials, are recognized based on an evaluation of the progress to completion of specific tasks using data such as subject enrollment, clinical site activations or information provided to the Company by its vendors with respect to their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the financial statements as prepaid or accrued research and development expense, as the case may be.

Stock-Based Compensation

We account for all share-based compensation payments issued to employees, directors and non-employees using an option pricing model for estimating fair value. Accordingly, share-based compensation expense is measured based on the estimated fair value of the awards on the date of grant, net of estimated forfeitures. We recognize compensation expense for the portion of the award that is ultimately expected to vest over the period during which the recipient renders the required services to us using the straight-line single option method. In accordance with authoritative accounting guidance, we re-measure the fair value of non-employee share-based awards as the awards vest, and recognize the resulting value, if any, as expense during the period the related services are rendered.

Significant Factors, Assumptions and Methodologies Used in Determining Fair Value

We apply the fair value recognition provisions of Financial Accounting Standards Board Accounting Standards Codification Topic 718, *Compensation Stock Compensation*, or ASC 718. Determining the amount of share-based compensation to be recorded requires us to develop estimates of the fair value of stock options as of their grant date. We recognize share-based compensation expense ratably over the requisite service period, which in most cases is the vesting period of the award. Calculating the fair value of share-based awards requires that we make highly subjective assumptions.

We use the Black-Scholes option pricing model to value our stock option awards. Use of this valuation methodology requires that we make assumptions as to the volatility of our common stock, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield. Until our recently completed IPO, there was no public market for the trading of our common stock. Due to this fact and a lack of company specific historical and implied volatility data, we have based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. We selected companies from the biopharmaceutical industry with similar characteristics to us, including those in the early stage of product development and with a therapeutic focus.

We use the simplified method as prescribed by the Securities and Exchange Commission Staff Accounting Bulletin No. 107, Share-Based Payment, to calculate the expected term of stock option grants to employees as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term of stock options granted to employees. We utilize a dividend yield of zero based on the fact that we have never paid cash dividends and have no current intention to pay cash dividends. The risk-free interest rate used for each grant is based on the U.S. Treasury yield

Table of Contents

curve in effect at the time of grant for instruments with a similar expected life. The weighted-average assumptions used to estimate the fair value of stock options using the Black-Scholes option pricing model were as follows for the years ended December 31, 2014 and 2013:

	Year Ended December 31, 2014	Year Ended December 31, 2013
Risk-free interest rate	1.80%	1.52%
Expected term of options (in years)	5.8	6.1
Expected volatility	75.9%	80.5%
Dividend yield	0.0%	0.0%

We also are required to estimate forfeitures at the time of grant, and revise those estimates in subsequent periods if actual forfeitures differ from our estimates. We use historical data to estimate pre-vesting option forfeitures and record share-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from our estimates, the difference is recorded as a cumulative adjustment in the period the estimates were revised. Through December 31, 2014, actual forfeitures have not been material.

Stock-based compensation expense totaled $2.4 million and $0.93 million for the years ended December 31, 2014 and 2013, respectively. We record stock-based compensation expense as a component of research and development expense or general and administrative expense, depending on the function performed by the optionee. For the year ended December 31, 2014 and 2013, we allocated stock-based compensation as follows:

	Year Ended December 31, 2014	Year Ended December 31, 2013
Research and development	$ 1,129,244	$ 609,483
General and administrative	1,254,155	318,513
Total	$ 2,383,399	$ 927,996

As of December 31, 2014, there was $6.1 million of total unrecognized compensation expense, related to unvested options granted under our 2013 Equity Incentive Plan that will be recognized over the weighted average remaining period of 2.87 years. Our share-based compensation expense is expected to increase as a result of recognizing our existing unrecognized share-based compensation for awards that will vest and as we issue additional share-based awards to attract and retain our employees.

Recent Accounting Pronouncements

In February 2013, FASB issued ASU No. 2013-02, *Comprehensive Income (Topic 220): Reporting of Amounts Reclassified Out of Accumulated Other Comprehensive Income*, or ASU 2013-02. ASU 2013-02 requires companies to present either in a single note or parenthetically on the face of the financial statements, the effect of significant amounts reclassified from each component of accumulated other comprehensive income based on its source and the income statement line items affected by the reclassification. This guidance is effective for annual reporting periods beginning January 1, 2013. The adoption of this standard by the Company for the fiscal year beginning January 1, 2013 did not have a significant impact on our financial position, results of operations or cash flows.

On June 10, 2014, FASB issued ASU No. 2014-10, *Development Stage Entities (Topic 915): Elimination of Certain Financial Reporting Requirements, Including an Amendment to Variable Interest Entities Guidance in Topic 810, Consolidation*, or ASU 2014-10. ASU 2014-10 eliminates the accounting and reporting differences in U.S. GAAP between development stage entities and other operating entities, including the presentation of inception-to-date financial statement information and the development stage entity financial statement label. FASB guidance related to risks and uncertainties

Table of Contents

and FASB guidance utilized to determine if an entity is a variable interest entity now apply to entities that have not commenced planned principal operations. These changes will provide more consistent consolidation analysis and decisions among reporting entities. While these amendments are retrospectively effective for annual reporting periods beginning after December 15, 2014, early adoption is permitted for any annual reporting period or interim period for which the entity's financial statements have not yet been issued. We have elected early adoption in 2014. Our adoption of this standard did not have a significant impact on our financial position, results of operations or cash flows.

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements-Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern*, which defines management's responsibility to assess an entity's ability to continue as a going concern, and to provide related footnote disclosures if there is substantial doubt about its ability to continue as a going concern. The pronouncement is effective for annual reporting periods ending after December 15, 2016 with early adoption permitted. The adoption of this guidance is not expected to have a material impact on our financial statements.

JOBS Act

The JOBS Act contains provisions that, among other things, reduce reporting requirements for an "emerging growth company." As an emerging growth company, we have elected to not take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards and, as a result, will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies.

Results of Operations

Comparison of Years Ended December 31, 2014 and 2013

	Year Ended December 31,		
	2014	**2013**	**Change**
Revenue:			
Grant revenue	$	$ 84,980	$ (84,980)
Collaboration revenue		50,000	(50,000)
Total revenue		134,980	(134,980)
Operating expenses:			
General and administrative	9,403,254	4,718,047	4,685,207
Research and development	40,546,666	18,762,219	21,784,447
Total operating expenses	49,949,920	23,480,266	26,469,654
Loss from operations	(49,949,920)	(23,345,286)	(26,604,634)
Other income (expense):			
Change in fair value of warrant liability	122,412	241,478	(119,066)
Miscellaneous income	184,015	1,245	182,770
Loss on asset disposal	(4,104)		(4,104)
Interest income	17,372	884	16,488
Interest expense	(70,650)	(149,756)	79,106
Total other income	249,045	93,851	155,194
Net loss and comprehensive loss	(49,700,875)	(23,251,435)	(26,449,440)
Accretion of preferred stock	(28,521)	(333,710)	305,189
Net loss attributable to common stockholders	$ (49,729,396)	$ (23,585,145)	$ (26,144,251)

79

Table of Contents

Revenue

We did not record grant revenue in 2014 due to the discontinuation of funding in June 2013 for a research grant from the National Institutes of Health.

General and administrative expense

General and administrative expenses increased by $4.7 million, or 99%, for the year ended December 31, 2014 compared to the same period in 2013, primarily as a result of increased headcount and associated salary costs, increased compensation expense associated with stock options granted and increased insurance, professional fees and other operating costs as a result of becoming a public company.

Research and development expense

Research and development expenses increased by $21.8 million, or 116%, from $18.8 million for the year ended December 31, 2013 to $40.5 million for the year ended December 31, 2014. The increase was primarily driven by an increase of $7.4 million in clinical research expenses associated with our advancement into a Phase 2b clinical trial with TRV027 and an increase of $10.2 million associated with the initiation and completion of a Phase 2a/b clinical trial of TRV130. The remaining increase was primarily driven by other clinical activity for TRV734 and costs associated with increased headcount and associated salary costs, including increased compensation expense associated with stock options granted.

The following table summarizes our research and development expenses for the years ended December 31, 2014 and 2013:

	Year Ended December 31,	
	2014	**2013**
TRV027	$ 11,791,851	$ 4,425,094
TRV130	14,523,136	4,276,973
TRV734	3,408,183	1,987,545
Stock-based compensation	1,129,245	609,485
Other personnel related costs	5,689,895	4,767,603
Other research and development	4,004,356	2,695,519
	$ 40,546,666	$ 18,762,219

Change in fair value of warrant liability

We recognized gains of $122.4 thousand and $241.5 thousand for the years ended December 31, 2014 and 2013, respectively, for the change in fair value on revaluation of our warrant liability associated with the common and preferred stock warrants outstanding. At the time of the IPO, the majority of the preferred stock warrants were net exercised into shares of common stock and are no longer outstanding as of December 31, 2014. The remaining preferred stock warrants were converted into a common stock warrant to purchase 20,161 shares of common stock. This common stock warrant had a fair value recorded as a liability of $82.9 thousand at December 31, 2014 as it contains a cash settlement feature upon certain strategic transactions. We will continue to adjust the liability related to this warrant for changes in fair value until the earlier of the exercise or expiration of the warrant.

Miscellaneous income

We recorded miscellaneous income of $184.0 thousand during 2014 associated with the sale of research and development tax credits awarded by the Commonwealth of Pennsylvania.

Table of Contents

Interest income

We recorded interest income of $17.4 thousand during the year ended December 31, 2014, due to income associated with the investment of funds in marketable securities.

Interest expense

We recorded interest expense of $70.7 thousand during the year ended December 31, 2014, compared to interest expense of $149.8 thousand during the year ended December 31, 2013.

Interest expense consists of interest related to our loans. The decrease in interest expense in the periods presented is due to the repayment of our loan with Comerica Bank in May 2013.

Accretion of Preferred Stock

We recorded $28.5 thousand and $333.7 thousand during the years ended December 31, 2014 and 2013, respectively, related to the accretion of issuance costs associated with our preferred stock, which was fully converted to common stock upon the consummation of our IPO in February 2014.

Liquidity and Capital Resources

We incurred net losses of $49.7 million and $23.3 million for the years ended December 31, 2014 and 2013, respectively. Net cash used in operating activities was $39.8 million and $24.2 million during the years ended December 31, 2014 and 2013, respectively. At December 31, 2014, we had an accumulated deficit of $132.0 million, working capital of $100.6 million, cash and cash equivalents of $36.2 million and marketable securities of $70.7 million. Historically, we have financed our operations principally through private placements of preferred stock. In February 2014, we completed our IPO. In December 2014, we completed a follow-on offering of common stock.

Cash Flows

The following table summarizes our cash flows for the years ended December 31, 2014 and 2013:

	Year Ended December 31,	
	2014	**2013**
Net cash (used in) provided by:		
Operating activities	$ (39,777,930)	$ (24,239,230)
Investing activities	(71,157,803)	(140,036)
Financing activities	109,176,094	55,605,805
Net increase (decrease) in cash and cash equivalents	$ (1,759,639)	$ 31,226,539

Net cash used in operating activities

Net cash used in operating activities was $39.8 million for the year ended December 31, 2014, consisting primarily of a net loss of $49.7 million partially offset by noncash adjustments of $2.5 million and changes in operating assets and liabilities of $7.4 million. The noncash adjustments were primarily attributable to increased expense associated with stock options granted and depreciation and amortization related to leasehold improvements and capital equipment partially offset by a gain recognized on the revaluation of the warrant liability. Changes in operating assets and liabilities were driven by a decrease in prepaid expenses and other assets of $3.2 million and an increase in accounts payable and accrued expenses of $4.2 million. The decrease in prepaid expenses and other assets was primarily due to prepaid IPO costs incurred in 2013 partially offset by prepaid expenses in 2014 related to our Phase 2b clinical trial for TRV027 and our Phase 2a/b clinical trial for TRV130. The increase in

Table of Contents

accounts payable and accrued expenses was primarily due to the timing and volume of our payment of costs related to ongoing development of our product candidates.

Net cash used in operating activities was $24.2 million for the year ended December 31, 2013 and consisted primarily of a net loss of $23.3 million partially offset by noncash increases of $1.5 million and a $2.5 million decrease related to the change in operating assets and liabilities. The noncash increases were primarily attributable to depreciation and amortization related to leasehold improvements and capital equipment, the increase in the fair value of stock options granted and the revaluation of warrant liability. The significant factors that contributed to the change in operating assets and liabilities included an increase in prepaid expenses and other assets of $3.7 million, partially offset by increases in accounts payable and accrued expenses of $1.2 million. The increase in prepaid expenses and other assets was primarily due to expenses incurred in connection with planning for our IPO and costs that were prepaid in association with the initiation of the Phase 2b clinical trial for TRV027. The increase in accounts payable and accrued expenses was primarily due to the timing of our payment of costs related to ongoing development of our product candidates.

Net cash used in investing activities

Net cash used in investing activities for the years ended December 31, 2014 and 2013 was $71.2 million and $140.0 thousand, respectively, and in 2014, consisted primarily of investments in marketable securities. Both periods presented also include expenditures related to leasehold improvements and the purchase of capital equipment.

Net cash provided by financing activities

Net cash provided by financing activities was $109.2 million for the year ended December 31, 2014, which was primarily due to net proceeds from the issuance of common stock in our IPO and our follow-on offering, as well as net proceeds from our initial borrowing under our term loan agreement on September 19, 2014 with Oxford Finance LLC and Square 1 Bank.

Net cash provided by financing activities was $55.6 million for the year ended December 31, 2013, which was primarily due to $59.9 million in net proceeds from the issuance of preferred stock and $550 thousand in proceeds from the exercise of preferred stock warrants partially offset by $4.9 million in repayments of the Comerica Facility.

Operating and Capital Expenditure Requirements

We have not achieved profitability since our inception and we expect to continue to incur net losses for the foreseeable future. We expect our cash expenditures to increase in the near term as we fund our Phase 2 clinical trials of TRV027 and TRV130, any future Phase 3 clinical trials of TRV130, our clinical development of TRV734, and our preclinical development of TRV250. Additionally, if and when we believe a regulatory approval of a product candidate appears likely, we anticipate that our payroll and other general and administrative expenses will increase as we prepare for commercial operations, particularly with respect to expenses associated with the sales and marketing of any future products. As a result of our 2014 IPO, we are a publicly traded company and incur significant legal, accounting and other expenses that we were not required to incur as a private company. In addition, the Sarbanes-Oxley Act, as well as rules adopted by the SEC and the NASDAQ Stock Market, require public companies to implement specified corporate governance practices that were inapplicable to us as a private company. These rules and regulations have increased our legal and financial compliance costs and make some activities more time-consuming and costly.

We believe that our existing cash and cash equivalents, marketable securities, the $16.5 million that we are currently eligible to draw under the second tranche of our credit facility, together with interest thereon, and the $10.0 million received from Actavis in March 2015 will be sufficient to fund our

Table of Contents

operating expenses and capital expenditure requirements through the fourth quarter of 2016. However, we anticipate that we will need to raise substantial additional financing in the future to fund our operations. To meet these additional cash requirements, we may seek to sell additional equity or convertible securities that may result in dilution to our stockholders. If we raise additional funds through the issuance of convertible securities, these securities could have rights senior to those of our common stock and could contain covenants that restrict our operations. There can be no assurance that we will be able to obtain additional equity or debt financing on terms acceptable to us, if at all. Our future capital requirements will depend on many factors, including:

- the progress, timing and results of the Phase 2 clinical programs for TRV130 and TRV027;
- whether Actavis exercises its option to license TRV027;
- our ability to enter into collaborative agreements for the development and commercialization of our product candidates, for example TRV734;
- the number and development requirements of any other product candidates that we pursue;
- the scope, progress, results and costs of researching and developing our product candidates or any future product candidates, both in the United States and in territories outside the United States;
- 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 our intellectual property-related claims, both in the United States and in territories outside the United States.

Please see "Risk Factors" for additional risks associated with our substantial capital requirements.

Contractual Obligations and Commitments

The following is a summary of our long-term contractual cash obligations as of December 31, 2014:

	Payments Due By Period			
Total	**Less than 1 year**	**1 - 3 years**	**3 - 5 years**	**More than 5 years**

	(in thousands)				
Operating lease obligations(1)	$ 1,607,771	$ 262,352	$ 830,728	$ 514,691	$
Long term debt	2,346,667	130,000	1,463,788	752,879	
Total	$ 3,954,438	$ 392,352	$ 2,294,516	$ 1,267,570	$

(1) Operating lease obligations reflect our obligation to make payments in connection with the lease for our office space.

Table of Contents

Purchase Commitments

We have no material non-cancelable purchase commitments with contract manufacturers or service providers as we have generally contracted on a cancelable basis.

Option and License Agreements and Other Commitments

For a description of our agreement with Actavis, see " Option and License Agreement with Actavis plc" above.

In addition, in the course of normal business operations, we have agreements with contract service providers to assist in the performance of our research and development and manufacturing activities. We can elect to discontinue the work under these agreements at any time. We could also enter into additional collaborative research, contract research, manufacturing and supplier agreements in the future, which may require upfront payments and even long-term commitments of cash.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements, as defined by applicable SEC regulations.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Not applicable to smaller reporting companies.

Table of Contents

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

REPORT OF MANAGEMENT

Management's Report on Financial Statements

Our management is responsible for the preparation, integrity and fair presentation of information in our financial statements, including estimates and judgments. The financial statements presented in this Annual Report on Form 10-K have been prepared in accordance with accounting principles generally accepted in the United States of America. Our management believes the financial statements and other financial information included in this Annual Report on Form 10-K fairly present, in all material respects, our financial condition, results of operations and cash flows as of and for the periods presented in this Annual Report on Form 10-K. The financial statements have been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report, which is included herein.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Our internal control system was designed to provide reasonable assurance to our management and board of directors regarding the preparation and fair presentation of published consolidated financial statements. Internal control over financial reporting is defined in Rule 13a-15(f) or 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect our transactions and dispositions of our assets;

- provide reasonable assurance that our transactions are recorded as necessary to permit preparation of our financial statements in accordance with accounting principles generally accepted in the United States of America, and that our receipts and expenditures are being made only in accordance with authorization of our management and our directors; and

- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of our assets that could have a material effect on our financial statements.

Our management, including our Chief Executive Officer and Chief Financial Officer, do not expect that our internal control over financial reporting will prevent all error and all fraud. A control system, no matter how well designed and implemented, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Further, the design of a control system must reflect the fact that there are resource constraints, and the benefits of controls must be considered relative to their costs. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues within a company are detected. The inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple errors or mistakes. Controls can also be circumvented by the individual acts of some persons, by collusion of two or more people or by management override of the controls. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and may not be detected.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2014. In making this assessment, our management used the criteria based on the framework set forth by the Committee of Sponsoring Organizations of the Treadway Commission in "Internal Control Integrated Framework" (COSO). Based on our assessments we believe that, as of December 31, 2014, our internal control over financial reporting is effective based on those criteria.

Table of Contents

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of Trevena, Inc.

We have audited the accompanying balance sheets of Trevena, Inc. (the Company) as of December 31, 2014 and 2013, and the related statements of operations and comprehensive loss, redeemable convertible preferred stock and stockholders' equity (deficit), and cash flows for the years then ended. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audit included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Trevena, Inc. at December 31, 2014 and 2013, and the results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

/s/ ERNST & YOUNG LLP

Philadelphia, PA
March 18, 2015

Table of Contents

TREVENA, INC.

Balance Sheets

	December 31,	
	2014	**2013**
Assets		
Current assets:		
Cash and cash equivalents	$ 36,205,559	$ 37,965,198
Marketable securities	70,698,640	
Prepaid expenses and other current assets	669,155	1,957,765
Offering costs		1,999,279
Total current assets	107,573,354	41,922,242
Property and equipment, net	553,294	343,059
Restricted cash	112,410	112,000
Other assets	98,401	15,625
Total assets	$ 108,337,459	$ 42,392,926
Liabilities, redeemable convertible preferred stock and stockholders' equity (deficit)		
Current liabilities:		
Accounts payable	$ 4,342,480	$ 545,053
Accrued expenses and other current liabilities	2,578,269	2,158,792
Deferred rent	38,359	33,114
Total current liabilities	6,959,108	2,736,959
Loans payable, net of current portion	1,791,285	
Capital lease, net of current portion	10,677	
Deferred rent, net of current portion	281,885	313,919
Warrant liability	82,851	350,519
Other long term liabilities	8,025	
Total liabilities	9,133,831	3,401,397
Commitments and contingencies (Note 10)		
Redeemable convertible preferred stock:		
Series A $0.001 par value; 0 and 25,074,999 shares authorized, issued and outstanding at December 31, 2014 and 2013 (liquidation preference of $25,074,999 at December 31, 2013)		25,024,373
Series B $0.001 par value; 0 and 35,500,000 shares authorized, 0 and 30,800,000 shares issued and outstanding at December 31, 2014 and 2013 (liquidation preference of $30,800,000 at December 31, 2013)		30,778,700
Series B-1 $0.001 par value; 0 and 6,000,000 shares authorized, 0 and 4,750,000 shares issued and outstanding at December 31, 2014 and 2013, respectively (liquidation preference of $4,200,000 at December 31, 2013)		4,823,079
Series C $0.001 par value; 0 and 37,000,000 shares authorized, 0 and 36,764,704 shares issued and outstanding at December 31, 2014 and 2013, respectively (liquidation preference of $59,999,997 at December 31, 2013)		59,935,986
Total redeemable convertible preferred stock		120,562,138
Stockholders' equity (deficit):		
Common stock $0.001 par value; 100,000,000 and 132,000,000 shares authorized, 39,241,173 and 957,756 shares issued and outstanding at December 31, 2014 and 2013, respectively	39,241	958
Additional paid-in capital	231,152,894	697,283
Accumulated deficit	(131,969,725)	(82,268,850)

Accumulated other comprehensive loss	(18,782)	
Total stockholders' equity (deficit)	99,203,628	(81,570,609)
Total liabilities, redeemable convertible preferred stock and stockholders' equity (deficit)	$ 108,337,459	$ 42,392,926

See accompanying notes to financial statements.

Table of Contents

TREVENA, INC.

Statements of Operations and Comprehensive Loss

	Year Ended December 31,	
	2014	**2013**
Revenue:		
Grant revenue	$	$ 84,980
Collaboration revenue		50,000
Total revenue		134,980
Operating expenses:		
General and administrative	9,403,254	4,718,047
Research and development	40,546,666	18,762,219
Total operating expenses	49,949,920	23,480,266
Loss from operations	(49,949,920)	(23,345,286)
Other income (expense):		
Change in fair value of warrant liability	122,412	241,478
Miscellaneous income	184,015	1,245
Loss on asset disposal	(4,104)	
Interest income	17,372	884
Interest expense	(70,650)	(149,756)
Total other income	249,045	93,851
Net loss	(49,700,875)	(23,251,435)
Accretion of redeemable convertible preferred stock	(28,521)	(333,710)
Net loss attributable to common stockholders	$ (49,729,396)	$ (23,585,145)
Other comprehensive income, net:		
Change in unrealized loss	(18,782)	
Other comprehensive loss	(18,782)	
Comprehensive loss	$ (49,748,178)	$ (23,585,145)
Per share information:		
Net loss per share of common stock, basic and diluted	$ (2.02)	$ (29.71)
Weighted average shares outstanding, basic and diluted	24,655,603	793,806

See accompanying notes to financial statements.

Table of Contents

TREVENA, INC.
Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)
For the Period From January 1, 2013 to December 31, 2014

	Redeemable Convertible Preferred Stock								Stockholders' Equity (Deficit)				
	Series A		Series B		Series B-1		Series C			Common Stock			Acc
	r of es	Amount	Number of Shares	Amount	Number of Shares	Amount	Number of Shares	Amount	Total	Number of Shares	$0.001 Par Value	Additional Paid-in Capital	Accumulated Deficit	Com
	4,999	$ 25,004,123	30,800,000	$ 30,770,194	4,200,000	$ 3,183,517		$	$ 58,957,834	682,494	$ 682	$ 19,718	$ (59,017,415)	$
Issuance of Series C convertible preferred stock, net of issuance costs of $1,081,083							36,764,704	59,918,917	59,918,917					
Stock-based compensation												927,996		
Exercise of stock options										275,262	276	83,279		
Issuance of Series B-1 convertible preferred stock, net of issuance costs of $148,323					550,000	1,351,677			1,351,677					
Accretion of redeemable convertible preferred stock to redemption value		20,250		8,506		287,885		17,069	333,710			(333,710)		
Net loss													(23,251,435)	
	4,999	25,024,373	30,800,000	30,778,700	4,750,000	4,823,079	36,764,704	59,935,986	120,562,138	957,756	958	697,283	(82,268,850)	
Stock-based compensation												2,383,399		
Exercise of stock options										186,682	186	111,592		
Accretion of redeemable convertible preferred stock to redemption value		1,688		709		23,990		2,134	28,521			(28,521)		
	4,999)	(25,026,061)							(25,026,061)	4,044,354	4,044	25,022,017		

(30,800,000)	(30,779,409)			(30,779,409)	4,967,741	4,968	30,774,441	
	(4,750,000)	(4,847,069)		(4,847,069)	766,129	766	4,846,303	
			(36,764,704)	(59,938,120)	(59,938,120)	5,929,789	5,930	59,932,190
					20,273	20	(20)	
							145,256	
							1,000	
					22,368,449	22,369	107,267,954	
								(49,700,875)
$	$	$	$	$	39,241,173	$ 39,241	$ 231,152,894	$ (131,969,725)

See accompanying notes to financial statements.

Table of Contents

TREVENA, INC.

Statements of Cash Flows

	Year Ended December 31,	
	2014	**2013**
Operating activities:		
Net loss	$ (49,700,875)	$ (23,251,435)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	239,390	706,779
Stock-based compensation	2,383,399	927,996
Noncash interest expense on loans	33,442	121,160
Loss on disposal of assets	5,015	
Revaluation of warrant liability	(122,412)	(241,478)
Changes in operating assets and liabilities:		
Prepaid expenses, offering costs and other assets	3,196,559	(3,667,605)
Accounts payable and accrued expenses	4,187,552	1,165,353
Net cash used in operating activities	(39,777,930)	(24,239,230)
Investing activities:		
Purchase of property and equipment	(440,381)	(140,036)
Purchase of marketable securities	(70,717,422)	
Net cash used in investing activities	(71,157,803)	(140,036)
Financing activities:		
Proceeds from issuance of redeemable convertible preferred stock and warrants, net		59,918,917
Proceeds from exercise of common stock options	111,778	83,555
Proceeds from exercise of preferred stock warrants		550,000
Proceeds from loans payable	1,775,012	
Proceeds from issuance of common stock, net	107,290,323	
Repayment of loans payable		(4,946,667)
Capital lease payments	(1,019)	
Net cash provided by financing activities	109,176,094	55,605,805
Net increase (decrease) in cash and cash equivalents	(1,759,639)	31,226,539
Cash and cash equivalents beginning of period	37,965,198	6,738,659
Cash and cash equivalents end of period	$ 36,205,559	$ 37,965,198
Supplemental disclosure of cash flow information:		
Cash paid for interest	$ 37,209	$ 85,422
Capital lease additions	$ 14,259	$
Fair value of common stock warrants issued	$ 1,000	$

See accompanying notes to financial statements.

Table of Contents

TREVENA, INC.

Notes to Financial Statements

December 31, 2014

1. Organization and Description of the Business

Trevena, Inc. (the "Company") was incorporated in Delaware as Parallax Therapeutics, Inc. on November 9, 2007. The Company began operations in December 2007, and its name was changed to Trevena, Inc. on January 3, 2008. The Company is a clinical stage biopharmaceutical company that discovers, develops and intends to commercialize therapeutics that use a novel approach to target G protein coupled receptors. The Company operates in one segment and has its principal office in King of Prussia, Pennsylvania. The Company's revenue has been derived from research grants and a research collaboration with a pharmaceutical company.

Reverse Stock Split

During 2013, the Company's Board of Directors and stockholders approved a one-for-6.2 reverse stock split of the company's common stock that became effective on October 30, 2013. All share and per share amounts in the financial statements and notes thereto have been retroactively adjusted for all periods presented to give effect to this reverse stock split.

Public Offerings

On February 5, 2014, the Company issued and sold 9,250,000 shares of common stock in an initial public offering (the "IPO") at a price of $7.00 per share, for aggregate gross proceeds of $64.8 million. On March 6, 2014, in connection with the partial exercise of the IPO underwriters' over-allotment option, the Company sold an additional 270,449 shares of common stock at a price of $7.00 per share, for aggregate gross proceeds of approximately $1.9 million. The net offering proceeds to the Company from both sales were approximately $59.5 million, after deducting underwriting discounts and commissions of approximately $4.7 million and offering costs of approximately $2.5 million. In addition, as part of the IPO, all of the Company's outstanding convertible preferred stock was converted and all but 22,580 of its outstanding warrants were net exercised into an aggregate of 15,728,286 shares of common stock.

On December 10, 2014, the Company issued and sold 11,250,000 shares of common stock in a public offering as well as 1,598,000 shares of common stock pursuant to the partial exercise of the underwriters' over-allotment option for a total of 12,848,000 shares at a price of $4.00 per share, for aggregate gross proceeds of approximately $51.4 million. The net offering proceeds to the Company from the combined sales were approximately $47.7 million, after deducting underwriting discounts and commissions of approximately $3.1 million and offering costs of approximately $0.6 million.

Liquidity

At December 31, 2014, the Company had an accumulated deficit of $132.0 million and its net loss was $49.7 million and $23.3 million for the year ended December 31, 2014 and 2013, respectively. The Company expects its cash and cash equivalents of $36.2 million and marketable securities of $70.7 million as of December 31, 2014 and the $16.5 million that the Company currently can draw under the second tranche of our credit facility, together with interest thereon, to be sufficient to fund its operating expenses and capital expenditure requirements through the end of 2016.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Update ("ASU") of the Financial Accounting Standards Board ("FASB"). The Company considers the U.S. dollar to be its functional currency.

Use of Estimates

Management considers many factors in selecting appropriate financial accounting policies and controls, and in developing the estimates and assumptions that are used in the preparation of these financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of reasonable estimates. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made. In preparing these financial statements, management used significant estimates in the following areas, among others: stock-based compensation expense, the determination of the fair value of stock-based awards, the fair value of liability-classified preferred and common stock warrants, and the accounting for research and development costs, accrued expenses and the recoverability of the Company's net deferred tax assets and related valuation allowance.

Cash and Cash Equivalents

The Company considers all highly liquid investments that have maturities of three months or less when acquired to be cash equivalents. Cash and cash equivalents subject the Company to concentrations of credit risk. However, the Company has invested in U.S. Treasury Bonds and money market mutual funds that invest substantially all of their assets in U.S. government securities. Cash equivalents are valued at cost, which approximates their fair market value.

Restricted Cash

At December 31, 2014 and 2013, the Company maintained letters of credit totaling $112,000, as collateral for the Company's facility and laboratory equipment lease obligations in Pennsylvania. In 2014, the Company earned interest of $410 related to these funds.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

2. Summary of Significant Accounting Policies (Continued)

Investments

At the time of purchase, the Company classifies investments in marketable securities as either available-for-sale securities, held to maturity securities, or trading securities, based on the Company's intent at that time.

As of December 31, 2014, the Company's investments are classified as available-for-sale pursuant to ASC Topic 320, *Investments Debt and Equity Securities ("ASC 320")*. The Company classifies investments available to fund current operations as current assets on its balance sheets. The Company considers all investments that have maturities of three months or less when acquired to be cash equivalents. Investments are classified as long-term assets on the balance sheets if (i) the Company has the intent and ability to hold the investments for a period of at least one year and (ii) the contractual maturity date of the investments is greater than one year. As of December 31, 2014, the Company had $70.7 million in available-for-sale investments, all classified as current assets.

Investments are carried at fair value with unrealized gains and losses included as a component of accumulated other comprehensive loss, until such gains and losses are realized. Fair value is determined based on observable market quotes or valuation models using assessments of counterparty credit worthiness, credit default risk of underlying security and overall capital market liquidity. The company reviews unrealized losses associated with available-for-sale securities to determine the classification as "temporary" or "other-than-temporary" impairment. A temporary impairment results in an unrealized loss being recorded in other comprehensive income. If a decline in the fair value is considered other-than-temporary, based on available evidence, the unrealized loss is transferred from other comprehensive loss to the statement of operations. The Company considers various factors in determining the classification, including the length of time and extent to which the fair value has been less than the Company's cost basis, the financial condition and near-term prospects of the issuer or investee, and the Company's ability to hold the investment for a period of time sufficient to allow for any anticipated recovery in market value. There were no charges taken for other-than-temporary declines in fair value of short-term or long-term investments during the year ended December 31, 2014. The Company recorded unrealized (gains)/ losses of $18,782 during the year ended December 31, 2014. Realized gains and losses are included in interest income in the statement of operations and comprehensive loss. The Company did not record any realized gains or losses during the year ended December 31, 2014.

Property and Equipment

Property and equipment consists of computer and laboratory equipment, software, office equipment, furniture and leasehold improvements and is recorded at cost. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred. Upon disposal, retirement or sale the related cost and accumulated depreciation is removed from the accounts and any resulting gain or loss is included in the results of operations. Property and equipment are depreciated on a straight-line basis over their estimated useful lives. The Company uses a life of three years for computer equipment, and five years for laboratory equipment, office equipment, furniture and software. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the asset.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

2. Summary of Significant Accounting Policies (Continued)

The Company reviews long-lived assets when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparison of the book values of the assets to future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book value of the assets exceed their fair value, which is measured based on the projected discounted future net cash flows arising from the assets. No impairment losses have been recorded since inception.

Preferred Stock and Common Stock Warrants

Freestanding warrants that are related to the purchase of preferred and common stock are classified as liabilities and recorded at fair value regardless of the timing of the redemption feature or the redemption price or the likelihood of redemption. The warrants are subject to re-measurement at each balance sheet date and any change in fair value is recognized as a component of change in fair value of warrant liability in the statements of operations and comprehensive loss. Pursuant to the terms of the preferred warrants, upon the conversion to common stock of the series of preferred stock underlying the warrant, the warrants automatically became exercisable for shares of common stock based upon the conversion ratio of the underlying preferred stock. The Company will continue to adjust the liability for changes in fair value until the earlier of the exercise or expiration of the warrants. The preferred (at December 31, 2013) and common stock (at December 31, 2014) warrants are classified as Level 3 liabilities (see Fair Value of Financial Instruments).

Fair Value of Financial Instruments

The carrying amount of the Company's financial instruments, which include cash and cash equivalents, marketable securities, grants receivable, restricted cash, accounts payable and accrued expenses approximate their fair values, given their short-term nature. The carrying amount of the Company's loans payable at December 31, 2014 approximates fair value because the interest rate is reflective of the rate the Company could obtain on debt with similar terms and conditions. The preferred stock warrants are carried at fair value as disclosed above. The Company has evaluated the estimated fair value of financial instruments using available market information and management's estimates. The use of different market assumptions and/or estimation methodologies could have a significant effect on the estimated fair value amounts.

ASC Topic 820, *Fair Value Measurement* ("ASC 820"), establishes a fair value hierarchy for instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and the Company's own assumptions (unobservable inputs). Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the asset or liability, and are developed based on the best information available in the circumstances.

ASC 820 identifies fair value as the exchange price, or exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As a basis for considering market participant assumptions in fair value

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

2. Summary of Significant Accounting Policies (Continued)

measurements, ASC Topic 820 establishes a three-tier fair value hierarchy that distinguishes among the following:

Level 1 Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities that the Company has the ability to access.

Level 2 Valuations based on quoted prices for similar assets or liabilities in active markets, quoted prices for identical or similar assets or liabilities in markets that are not active and models for which all significant inputs are observable, either directly or indirectly.

Level 3 Valuations based on inputs that are unobservable and significant to the overall fair value measurement.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Items measured at fair value on a recurring basis include money market mutual funds, restricted cash and warrants to purchase redeemable convertible preferred stock. During the periods presented, the Company has not changed the manner in which it values assets and liabilities that are measured at fair value using Level 3 inputs. The following fair value hierarchy table presents information about each

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

2. Summary of Significant Accounting Policies (Continued)

major category of the Company's financial assets and liabilities measured at fair value on a recurring basis:

	Quoted Prices in Active Markets for Identical Items (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)	Total
December 31, 2014				
Assets				
Money market mutual funds	$ 29,064,011	$	$	$ 29,064,011
U.S. Treasury Bonds	70,698,640			70,698,640
Restricted cash	112,410			112,410
Total assets	$ 99,875,061	$	$	$ 99,875,061
Liabilities				
Warrants to purchase common stock	$	$	$ 82,851	$ 82,851
Total liabilities	$	$	$ 82,851	$ 82,851
December 31, 2013				
Assets				
U.S. Treasury Bills	$ 35,551,000			$ 35,551,000
Restricted cash	112,000			112,000
Total assets	$ 35,663,000	$	$	$ 35,663,000
Liabilities				
Warrants to purchase redeemable preferred stock	$	$	$ 350,519	$ 350,519
Total liabilities	$	$	$ 350,519	$ 350,519

The following table sets forth a summary of changes in the fair value of the Company's warrant liability, which represents a recurring measurement that is classified within Level 3 of the fair value hierarchy, wherein fair value is estimated using significant unobservable inputs:

	Warrant Liability
Balance as of December 31, 2012	$ 1,393,674

Amounts acquired or issued		(801,677)
Changes in estimated fair value		(241,478)
Balance as of December 31, 2013		350,519
Amounts acquired or issued		
Changes in estimated fair value		(122,412)
Amounts reclassified to additional paid-in capital		(145,256)
Balance as of December 31, 2014	$	82,851

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

2. Summary of Significant Accounting Policies (Continued)

The money market mutual funds and U.S. Treasury Bills noted above are included in cash and cash equivalents in the accompanying balance sheets. The U.S. Treasury Bonds are included in marketable securities in the accompanying balance sheets. The Company recognizes transfers between levels of the fair value hierarchy as of the end of the reporting period. There were no transfers within the hierarchy during the years ended December 31, 2014 or 2013.

In connection with the issuance of debt, on September 19, 2014, the Company issued to the lenders and the placement agent in the transaction warrants to purchase an aggregate of 7,678 shares of the Company's common stock. These detachable warrant instruments have qualified for equity classification and have been allocated upon the relative fair value of the base instrument and the warrants, according to the guidance of ASC 470-20-25-2. See Note 7 for additional information.

In connection with the issuance and sale of the Company's Series B-1 preferred shares in 2011, the Company issued a warrant to purchase 125,000 shares of Series B preferred stock. Upon the IPO, the warrant to purchase 125,000 shares of Series B preferred stock was converted into a warrant to purchase up to 20,161 shares of the Company's common stock and remains outstanding with a fair value recorded as a liability of $82,851 at December 31, 2014 as it contains a cash settlement feature upon certain strategic transactions. See Note 8 for additional information.

The fair value of the warrants classified as liabilities on each re-measurement date is estimated using the Black-Scholes option pricing model. For this liability, the Company develops its own assumptions that do not have observable inputs or available market data to support the fair value. This method of valuation involves using inputs such as the fair value of the Company's common stock and various classes of preferred stock, stock price volatility, the contractual term of the warrants, risk-free interest rates and dividend yields. Due to the nature of these inputs, the valuation of the warrants is considered a Level 3 measurement. The following assumptions were used at December 31, 2014 and December 31, 2013:

	December 31, 2014	December 31, 2013	
	Common stock warrant liability	Series B-1 preferred stock warrant liability	Series B preferred stock warrant liability
Estimated remaining term	7.34 years	0.25 years	8.4 years
Dividend yield	0.00%	0.00%	0.00%
Risk-free interest rate	1.99%	0.38%	2.75%
Fair value of underlying instrument	$ 5.98	$ 7.00	$ 7.00
Volatility	72%	71%	70%

The warrant liability is recorded on its own line item on the Company's Balance Sheet and is marked-to-market at each reporting period with the change in fair value recorded on its own line in the Statement of Operations and Comprehensive Loss.

Concentration of Credit Risk and Off-Balance Sheet Risk

Financial instruments that potentially subject the Company to concentrations of credit risk are primarily cash, cash equivalents, marketable securities and restricted cash. The Company maintains its cash, and cash equivalent balances in the form of money market mutual funds that invest substantially

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

2. Summary of Significant Accounting Policies (Continued)

all of their assets in U.S. government securities with financial institutions that management believes are creditworthy. The Company maintains its marketable securities balances in the form of U.S. Treasury Bonds. The Company's investment policy includes guidelines on the quality of the institutions and financial instruments and defines allowable investments that the Company believes minimizes the exposure to concentration of credit risk.

The Company routinely assesses the creditworthiness of its collaborators. The Company has not experienced any material losses related to receivables from collaborators. The Company does not require collateral from its collaborators.

The Company has not recognized any losses from credit risks on such accounts since inception. The Company believes it is not exposed to significant credit risk on cash.

Segment Information

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision maker, or decision-making group, in making decisions on how to allocate resources and assess performance. The Company's chief operating decision maker is the chief executive officer. The Company and the chief executive officer view the Company's operations and manage its business as one operating segment. All long-lived assets of the Company reside in the United States.

Revenue

The Company recognizes grant revenue when persuasive evidence of an arrangement exists, delivery has occurred or services have been rendered, the price is fixed and determinable, and collectibility is reasonably assured. The Company recognizes revenue under grants in earnings in the period in which the related expenditures are incurred. The Company recognizes collaboration revenue when persuasive evidence of an arrangement exists, delivery has occurred or services have been rendered, the price is fixed and determinable, and collectibility is reasonably assured.

Research and Development

Research and development costs are charged to expense as incurred. These costs include, but are not limited to, employee-related expenses, including salaries, benefits and travel and stock based compensation of our research and development personnel; expenses incurred under agreements with contract research organizations and investigative sites that conduct clinical trials and preclinical studies; the cost of acquiring, developing and manufacturing clinical trial materials; facilities; other supplies; allocated facilities, depreciation and other expenses, which include rent and utilities; insurance; and costs associated with preclinical activities and regulatory operations.

Costs for certain development activities, such as clinical trials, are recognized based on an evaluation of the progress to completion of specific tasks using data such as subject enrollment, clinical site activations or information provided to the Company by its vendors with respect to their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the financial statements as prepaid or accrued research and development expense, as the case may be.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

2. Summary of Significant Accounting Policies (Continued)

As part of the process of preparing its financial statements, the Company is required to estimate its expenses resulting from its obligations under contracts with vendors, clinical research organizations and consultants and under clinical site agreements in connection with conducting clinical trials. The financial terms of these contracts are subject to negotiations, which vary from contract to contract and may result in payment flows that do not match the periods over which materials or services are provided under such contracts. The Company's objective is to reflect the appropriate trial expenses in its financial statements by matching those expenses with the period in which services are performed and efforts are expended. The Company accounts for these expenses according to the progress of the trial as measured by subject progression and the timing of various aspects of the trial. The Company determines accrual estimates through financial models taking into account discussion with applicable personnel and outside service providers as to the progress or state of consummation of trials, or the services completed. During the course of a clinical trial, the Company adjusts its clinical expense recognition if actual results differ from its estimates. The Company makes estimates of its accrued expenses as of each balance sheet date based on the facts and circumstances known to it at that time. The Company's clinical trial accruals are dependent upon the timely and accurate reporting of contract research organizations and other third-party vendors. Although the Company does not expect its estimates to be materially different from amounts actually incurred, its understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in it reporting amounts that are too high or too low for any particular period. For the years ended December 31, 2014 and 2013, there were no material adjustments to the Company's prior period estimates of accrued expenses for clinical trials.

Stock-Based Compensation

At December 31, 2014, the Company had one stock-based compensation plan, which is more fully described in Note 9. The Company accounts for stock-based compensation in accordance with the provisions of ASC Topic 718, *Compensation Stock Compensation* ("ASC 718"), which requires the recognition of expense related to the fair value of stock-based compensation awards in the Statements of Operations and Comprehensive Loss.

For stock options issued to employees and members of the Board for their services on the Board, the Company estimates the grant date fair value of each option using the Black-Scholes option-pricing model. The use of the Black-Scholes option pricing model requires management to make assumptions with respect to the expected term of the option, the expected volatility of the common stock consistent with the expected life of the option, risk-free interest rates, the value of the common stock and expected dividend yields of the common stock. For awards subject to service-based vesting conditions, the Company recognizes stock-based compensation expense, net of estimated forfeitures, equal to the grant date fair value of stock options on a straight-line basis over the requisite service period, which is generally the vesting term. For awards subject to both performance and service-based vesting conditions, the Company recognizes stock-based compensation expense using the accelerated attribution method when it is probable that the performance condition will be achieved. Forfeitures are required to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

2. Summary of Significant Accounting Policies (Continued)

Share-based payments issued to non-employees are recorded at their fair values, and are periodically revalued as the equity instruments vest and are recognized as expense over the related service period in accordance with the provisions of ASC 718 and ASC Topic 505, *Equity*. See Note 9 for a discussion of the assumptions used by the Company in determining the grant date fair value of options granted under the Black-Scholes option pricing model, as well as a summary of the stock option activity under the Company's stock-based compensation plan for the years ended December 31, 2014 and 2013.

Income Taxes

Income taxes are recorded in accordance with ASC Topic 740, *Income Taxes* ("ASC 740"), which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. Deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Valuation allowances are provided, if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2014 and 2013, the Company does not have any significant uncertain tax positions.

Comprehensive Loss

Comprehensive loss is defined as the change in equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. Comprehensive loss relates to unrealized investment losses on the Company's marketable securities for the year ended December 31, 2014. Comprehensive loss was equal to net loss for the year ended December 31, 2013.

Basic and Diluted Net Loss Per Share of Common Stock

Basic net loss per share of common stock is computed by dividing net loss attributable to common stockholders by the weighted-average number of shares of common stock outstanding during the period, excluding the dilutive effects of preferred stock, warrants to purchase preferred stock and stock options. Diluted net loss per share of common stock is computed by dividing the net loss attributable to common stockholders by the sum of the weighted-average number of shares of common stock outstanding during the period plus the potential dilutive effects of preferred stock and warrants to purchase preferred stock, and stock options outstanding during the period calculated in accordance with the treasury stock method, although these shares, options and warrants are excluded if their effect is anti-dilutive. Because the impact of these items is anti-dilutive during periods of net loss, there was no difference between basic and diluted net loss per share of common stock for the years ended December 31, 2014 and 2013.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

2. Summary of Significant Accounting Policies (Continued)

Recent Accounting Pronouncements

In February 2013, FASB issued ASU No. 2013-02, *Comprehensive Income (Topic 220): Reporting of Amounts Reclassified Out of Accumulated Other Comprehensive Income* ("*ASU 2013-02*"). ASU 2013-02 requires companies to present either in a single note or parenthetically on the face of the financial statements, the effect of significant amounts reclassified from each component of accumulated other comprehensive income based on its source and the income statement line items affected by the reclassification. This guidance is effective for annual reporting periods beginning January 1, 2013. The adoption of this standard by the Company for the fiscal year beginning January 1, 2013 did not have a significant impact on our financial position, results of operations or cash flows.

On June 10, 2014, FASB issued ASU No. 2014-10, *Development Stage Entities (Topic 915): Elimination of Certain Financial Reporting Requirements, Including an Amendment to Variable Interest Entities Guidance in Topic 810, Consolidation* ("*ASU 2014-10*"). ASU 2014-10 eliminates the accounting and reporting differences in U.S. GAAP between development stage entities and other operating entities, including the presentation of inception-to-date financial statement information and the development stage entity financial statement label. FASB guidance related to Risks and Uncertainties and FASB guidance utilized to determine if an entity is a variable interest entity now applies to entities that have not commenced planned principal operations. These changes will provide more consistent consolidation analysis and decisions among reporting entities. While these amendments are retrospectively effective for annual reporting periods beginning after December 15, 2014, early adoption is permitted for any annual reporting period or interim period for which the entity's financial statements have not yet been issued. The Company has elected early adoption in the current period. The Company's adoption of this standard did not have a significant impact on its financial position, results of operations or cash flows.

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements-Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern,* which defines management's responsibility to assess an entity's ability to continue as a going concern, and to provide related footnote disclosures if there is substantial doubt about its ability to continue as a going concern. The pronouncement is effective for annual reporting periods ending after December 15, 2016 with early adoption permitted. The adoption of this guidance is not expected to have a material impact on the Company's financial statements.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

3. Net Loss Per Common Share

The following table sets forth the computation of basic and diluted net loss per share for the periods indicated:

	Year Ended December 31,	
	2014	**2013**
Basic and diluted net loss per common share calculation:		
Net loss	$ (49,700,875)	(23,251,435)
Accretion of redeemable convertible preferred stock	(28,521)	(333,710)
Net loss attributable to common stockholders	$ (49,729,396)	$ (23,585,145)
Weighted average common shares outstanding	24,655,603	793,806
Net loss per share of common stock basic and diluted	$ (2.02)	$ (29.71)

The following outstanding securities at December, 31, 2014 and 2013 have been excluded from the computation of diluted weighted shares outstanding, as they would have been anti-dilutive:

	December 31,	
	2014	**2013**
Redeemable convertible preferred stock		15,707,986
Options outstanding	3,574,450	2,795,746
Warrants	30,258	199,996
Total	3,604,708	18,703,728

4. Comprehensive Loss

The following table presents changes in the components of accumulated other comprehensive income or loss, net of tax:

Balance, January 1, 2014	$
Net unrealized loss arising during the period	18,782
Balance, December 31, 2014	$ 18,782

There were no reclassifications out of accumulated other comprehensive income or loss during the year ended December 31, 2014. There was no tax effect during the year ended December 31, 2014.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

5. Property and Equipment

Property and equipment consisted of the following:

	December 31,	
	2014	**2013**
Laboratory equipment	$ 1,616,420	1,853,685
Computers and software	554,658	509,109
Office equipment and furniture	270,845	193,781
Leasehold improvements	1,986,156	1,718,922
Leased assets	14,259	
Total property and equipment	4,442,338	4,275,497
Less accumulated depreciation and amortization	(3,889,044)	(3,932,438)
Property and equipment, net	$ 553,294	$ 343,059

Depreciation and amortization expense was $239,390 and $706,779 for the years ended December 31, 2014 and 2013, respectively.

6. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following:

	December 31,	
	2014	**2013**
Compensation and benefits	$ 1,628,102	$ 859,444
Clinical trial fees	846,199	762,687
Other research and development expenses	96,088	507,845
Professional services		24,005
Other accrued expenses and other current liabilities	7,880	4,811
Total accrued expenses and other current liabilities	$ 2,578,269	$ 2,158,792

7. Long Term Debt

Debt Outstanding at December 31, 2014

On September 19, 2014, the Company entered into a loan and security agreement with Oxford Finance LLC, as collateral agent and lender and Square 1 Bank, as lender pursuant to which the lenders have agreed to lend the Company up to $35.0 million in a series of term loans. Upon entering into the agreement, the Company borrowed $2.0 million from the lenders ("Term Loan A"). The Company may, at its sole discretion, borrow from the lenders:

an additional $16.5 million, at any time on or before June 30, 2015 ("Term Loan B") since the Company has satisfied specified conditions precedent related to the results of the Company's ongoing Phase 2 studies of TRV130; and

an additional $16.5 million, at any time on or before March 31, 2016 ("Term Loan C" and together with Term Loan A and Term Loan B, the "Term Loans"), subject to the Company's

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

7. Long Term Debt (Continued)

satisfaction of specified conditions precedent related to the results of the Company's ongoing Phase 2 studies of TRV027.

The proceeds from Term Loan A and future proceeds, if any, from Term Loan B and/or Term Loan C may be used to satisfy the Company's future working capital needs, potentially including the development of its clinical and preclinical product candidates.

The Company's obligations under the loan and security agreement are secured by a first priority security interest in substantially all of the assets of the Company, other than intellectual property. The Company has agreed not to pledge or otherwise encumber its intellectual property, other than through grants of certain permitted non-exclusive or exclusive licenses or other conveyances of its intellectual property.

The term loans will accrue interest at a fixed rate of 6.50% per annum. The Company is required to make payments of interest only on Term Loan A on a monthly basis through and including April 1, 2016 extended from October 1, 2015, since the Company has satisfied specified conditions precedent related to the results of the Company's recently concluded Phase 2 bunionectomy study of TRV130 after which consecutive equal monthly payments of principal, plus accrued interest, will be due until December 1, 2018. Both of these dates may be modified further with respect to the term loans, as applicable, as follows:

If the Company meets the conditions to draw Term Loan C on or before March 31, 2016, then the date until which the Company is required to make payments of interest only will be extended from April 1, 2016 to October 1, 2016.

If the Company meets the condition to draw Term Loan C on or before March 31, 2016, and the Company has received net cash proceeds of at least $50,000,000 from its existing strategic partnership and collaborative license option agreement with Actavis or another strategic partnership in form and substance satisfactory to the lenders, then the date until which consecutive equal monthly payments of principal, plus accrued interest, will be due will be extended from December 1, 2018 to September 1, 2019.

The Company has paid the lenders a facility fee of $175,000 in connection with the execution of the loan and security agreement. Upon the last payment date of the amounts borrowed under the agreement, the Company will be required to pay the lenders a final payment fee equal to 6.1% of the term loans borrowed increased from 5.25% since the Company has satisfied specified conditions precedent related to the results of the Company's recently concluded Phase 2 bunionectomy study of TRV130 and subject to further adjustment as follows:

If the Company further meets the condition to draw Term Loan C on or before March 31, 2016, then the Company will be required to pay the lenders a final payment fee equal to 6.6% of the term loans borrowed; and

If the Company further meets the condition to draw Term Loan C on or before March 31, 2016, and the Company has received net cash proceeds of at least $50,000,000 from its existing strategic partnership and collaborative license option agreement with Actavis or another strategic partnership in form and substance satisfactory to the lenders, then the Company will be required to pay the lenders a final payment fee equal to 7.0%.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

7. Long Term Debt (Continued)

In addition, if the Company repays the term loans before the applicable maturity date, it will pay the lenders a prepayment fee of 3.00% of the total amount prepaid if the prepayment occurs prior to the first anniversary of the funding of the applicable term loan, 2.00% percent of the total amount prepaid if the prepayment occurs between the first and second anniversary of the funding of the applicable term loan, and 1.00% percent of the total amount prepaid if the prepayment occurs on or after the second anniversary of the funding of the applicable term loan.

The loan and security agreement includes affirmative and restrictive covenants, including: (a) financial reporting requirements; (b) limitations on the incurrence of indebtedness; (c) limitations on liens; (d) limitations on certain merger and acquisition transactions; (e) limitations on dispositions of certain assets; (f) limitations on fundamental corporate changes (including changes in control); (g) limitations on investments; (h) limitations on payments and distributions and (i) other covenants. The agreement also contains certain events of default, including for payment defaults, breaches of covenants, a material adverse change in the collateral, the Company's business, operations or condition (financial or otherwise), certain levies, attachments and other restraints on the Company's business, insolvency, defaults under other agreements and misrepresentations.

Three Point Capital, LLC served as a placement agent in connection with the term loans. The Company paid Three Point $65,000 upon execution of the loan and security agreement and will be obligated to pay up to an additional $175,000 if the Company draws on Term Loan B and Term Loan C.

In connection with entering into the loan and security agreement, the Company issued to each of Oxford, Square 1 and Three Point warrants to purchase shares of the Company's common stock. The warrants are exercisable, in whole or in part, immediately, and have a per share exercise price of $5.8610, which is the average closing price of the Company's common stock on the NASDAQ Global Market for the ten trading days prior to the effective date of the agreement. The warrants may be exercised on a cashless basis. The warrants will terminate on the earlier of September 19, 2024 or the closing of a merger or consolidation transaction in which the Company is not the surviving entity. If the Company borrows Term Loan B and/or Term Loan C, upon the funding of such Term Loan, the Company will issue additional warrants to purchase shares of the Company's common stock, each with a per share exercise price of $5.8610 and on substantially the same terms as those contained in the warrants. The number of warrants issued or issuable by the Company is as follows:

Entity	Shares Underlying Warrants Issued on the Effective Date	Maximum Number of Shares Underlying Warrants Issuable Assuming Full Draw of Term Loan B	Maximum Number of Shares Underlying Warrants Issuable Assuming Full Draw of Term Loan C
Oxford	4,875	40,217	40,217
Square 1	1,950	16,087	16,087
Three Point	853	7,038	7,038

In connection with the issuance of debt, on September 19, 2014, the Company issued to the lenders and the placement agent in the transaction warrants to purchase an aggregate of 7,678 shares of the Company's common stock. These detachable warrant instruments have qualified for equity classification and have been allocated upon the relative fair value of the base instrument and the warrants, according to the guidance of ASC 470-20-25-2. The maximum aggregate number of shares

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

7. Long Term Debt (Continued)

underlying additional warrants that can be issued by the Company to the lenders under the loan and security agreement and to Three Point under the placement agent arrangement is 126,685.

As of December 31, 2014, only Term Loan A has been issued, all of which remains outstanding as of such date. The initial maturity date is December 1, 2018 and the loan bears interest at an annual rate of 6.5%. The loan is not convertible and is secured by substantially all of the Company's assets. Interest expense of $36,833 was recorded since inception in September 2014, excluding the amortization of debt discount.

The Company incurred lender and third party costs of $0.2 million and $0.1 million, respectively, related to the issuance of Term Loan A. The lender costs are classified as a debt discount, a contra-liability on our balance sheet. The third party costs are classified as deferred financing fees, an asset on our balance sheet. Both the debt discount and deferred financing fees will be amortized over the life of the Term Loan using the effective interest method.

The following table summarizes how the issuance of Term Loan A is reflected on the balance sheet at December 31, 2014:

	December 31, 2014
Gross proceeds	$ 2,000,000
Debt discount	(208,715)
Carrying value	$ 1,791,285

Debt Outstanding at December 31, 2013

In December 2011, the Company entered into a loan facility with Comerica Bank (the "Comerica Facility"). Interest expense related to the Comerica Facility was $64,292 for the year ended December 31, 2013. Amortization expense of deferred financing costs was $42,047 for the year ended December 31, 2013. On May 3, 2013, the Company used a portion of the proceeds from the Series C Preferred Stock (Note 8) to repay the remaining Comerica Facility outstanding balance of $4,073,485, including unpaid interest and fees.

In connection with the borrowings under the Comerica Facility, the Company issued a ten-year warrant to purchase 125,000 shares of Series B preferred stock at $1.00 per share, exercisable through December 2021. The Company recorded a total of $101,707 as debt discount related to the estimated fair value of the preferred stock warrants issued, with a corresponding credit to the warrant liability. The debt discount was being amortized to interest expense over the term of the Comerica Facility. Interest expense related to the amortization of the debt discount was $78,460 for the year ended December 31, 2013.

8. Stockholders' Equity (Deficit)

Common Stock

On December 10, 2014, the Company issued and sold 11,250,000 shares of common stock in a public offering of shares as well as 1,598,000 shares of common stock pursuant to the partial exercise of

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

8. Stockholders' Equity (Deficit) (Continued)

the underwriters' over-allotment option for a total of 12,848,000 shares at a price of $4.00 per share, for aggregate gross proceeds of approximately $51.4 million.

On February 5, 2014, the Company issued and sold 9,250,000 shares of common stock in an IPO at a price of $7.00 per share, for aggregate gross proceeds of approximately $64.8 million. On March 6, 2014, in connection with the partial exercise of the IPO underwriters' over-allotment option, the Company sold an additional 270,449 shares of common stock at a price of $7.00 per share, for aggregate gross proceeds of approximately $1.9 million.

As of December 31, 2013, the Company had outstanding the following redeemable convertible preferred stock that converted into common shares on a one-for-6.2 basis upon consummation of the Company's IPO:

	Preferred Shares Outstanding	Conversion into Common Shares upon IPO
Series A	25,074,999	4,044,354
Series B	30,800,000	4,967,741
Series B-1	4,750,000	766,129
Series C	36,764,704	5,929,789
Total	97,389,703	15,708,013

In connection with the issuance of the Company's Series B-1 preferred shares in 2011, the Company issued warrants to purchase 1,650,000 shares of the Company's Series B-1 Preferred Stock. Additionally, in connection with a banking facility entered into in 2011, the Company issued a warrant to purchase 125,000 shares of Series B preferred stock. As of December 31, 2013, the fair value of the warrants outstanding of $350,519 was recognized as a liability in the Company's balance sheet. Upon the Company's IPO, 1,100,000 of the outstanding Series B-1 warrants were net exercised into 20,273 shares of common stock and the remaining fair value of $145,256 associated with these particular warrants was reclassified to additional paid-in capital. The warrant to purchase 125,000 shares of Series B preferred stock was converted into a warrant to purchase up to 20,161 shares of the Company's common stock and remains outstanding with a fair value recorded as a liability of $82,851 at December 31, 2014 as it contains a cash settlement feature upon certain strategic transactions.

Under its certificate of incorporation, the Company was authorized to issue up to 100,000,000 and 132,000,000 shares of common stock as of December 31, 2014 and December 31, 2013, respectively. The Company also was authorized to issue up to 5,000,000 shares of preferred stock as of December 31, 2014. The Company is required, at all times, to reserve and keep available out of its authorized but unissued shares of common stock sufficient shares to effect the conversion of the shares of the preferred stock and all outstanding stock options and warrants.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

8. Stockholders' Equity (Deficit) (Continued)

Preferred Stock

As part of the IPO, on February 5, 2014, all of the Company's outstanding convertible preferred stock was converted and all but 22,580 of its outstanding warrants were net exercised into an aggregate of 15,728,286 shares of common stock.

On January 4, 2008, the Company authorized the sale and issuance of up to 25,000,000 shares of Series A Convertible Preferred Stock (the Series A). On January 7, 2008, the Company completed the first closing of its sale of the Series A and issued 501,562 shares at $1.00 per share generating gross proceeds of $501,562. On January 31, 2008, the Company completed a second closing of its sale of the Series A and issued an additional 4,514,062 shares at $1.00 per share generating gross proceeds of $4,514,062. Costs associated with these offerings were $200,137. In September 2008, the Company completed a third closing of its sale of the Series A and issued an additional 8,025,000 shares at $1.00 per share generating gross proceeds of $8,025,000. Costs associated with this offering were $2,154. On June 30, 2009, the Company completed a fourth closing of its sale of the Series A and issued 11,034,375 shares at $1.00 per share generating gross proceeds of $11,034,375. Costs associated with this offering were $561. On November 16, 2009, the Company amended the stock purchase agreement associated with the Series A financing and issued an additional 1,000,000 shares at $1.00 per share generating gross proceeds of $1,000,000. Costs associated with this offering were $3,398. All offering costs associated with the Series A were being accreted into the carrying value of the Series A until its conversion upon IPO.

On July 8, 2010, the Company authorized the sale and issuance of up to 35,000,000 shares of Series B Preferred Stock (the Series B) and up to 4,300,000 of Series B-1 Preferred Stock (the Series B-1). In connection with the authorization of the Series B and the Series B-1, the Company also authorized the sale and issuance of warrants to purchase up to 1,700,000 shares of the Series B-1 (the Series B-1 Warrants). On July 8, 2010, the Company completed the first closing of its sale of the Series B and issued 17,500,000 shares at $1.00 per share generating gross proceeds of $17,500,000. Costs associated with this offering were $38,568. On July 8, 2011, the Company completed its second closing, issuing 5,700,000 shares of its Series B at $1.00 per share and 1,800,000 shares of its Series B-1 at $1.00 per share. Costs associated with this offering were $8,229. On December 15, 2011, the Company completed its third closing issuing 7,600,000 shares of its Series B at $1.00 per share and 2,400,000 shares of its Series B-1 at $1.00 per share. Costs associated with this offering were $4,989. All offering costs associated with the Series B and Series B-1 were being accreted into the carrying value of the preferred stock until its conversion upon IPO.

In connection with the issuance of the Series B-1 shares in the second and third closings, the Series B-1 shareholders received ten-year warrants to purchase a total of 1,650,000 shares of the Company's Series B-1 Preferred Stock at an exercise price of $1.00 per share. The estimated fair value of the preferred stock warrants on the dates of issuance of $1,347,428 was recorded as a reduction to the carrying value of the Series B-1 Preferred stock and was being accreted into the carrying value of the Series B-1 until its conversion upon IPO. The preferred stock warrants were recorded as a liability pursuant to the guidance for accounting for certain financial instruments with characteristics of both liabilities and equity and are revalued at each reporting period to reflect any changes in fair value. In November 2013, one of the Company's warrant holders exercised its warrants to purchase 550,000 shares of the Company's Series B preferred stock. Of the remaining 1,225,000 outstanding warrants to

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

8. Stockholders' Equity (Deficit) (Continued)

purchase preferred stock at December 31, 2013, 1,100,000 were net exercised immediately prior to the consummation of the Company's initial public offering in February 2014. Upon consummation of the Company's initial public offering, the remaining warrant to purchase up to 125,000 shares of the Company's Series B preferred stock was converted into a warrant to purchase up to 20,161 shares the Company's common stock, and the fair value of the warrant liability at that time was reclassified to additional paid-in capital.

In May, 2013, the Company authorized the sale and issuance of up to 37,000,000 shares of Series C Preferred Stock (the Series C). On May 3, 2013, the Company completed the closing of its sale of the Series C and issued 36,764,704 shares at $1.632 per share generating gross proceeds of $59,999,997. Costs associated with this offering were $81,080. All offering costs associated with the Series C were recorded as a discount and were being accreted into the carrying value of the Series C until its conversion upon IPO.

Each share of the Series A, the Series B, the Series B-1 and the Series C preferred stock was convertible into approximately 0.1613 shares of common stock at any time at the option of the holder. The preferred stock was automatically convertible in the event of (i) an initial public offering at a price of at least $4.00 per share of common stock (subject to adjustment to reflect stock splits, stock dividends, stock combinations, recapitalizations and like occurrences) and net proceeds to the Company of at least $40 million; or (ii) the affirmative vote or written consent of the holders of at least 60% of shares of the preferred stock then outstanding. Each share of Series A, B or B-1 preferred stock was also subject to a special mandatory conversion feature. In the event that any holder of shares of Series A, B or B-1 preferred stock did not participate in a Qualified Financing (as defined in the Company's Certificate of Incorporation) by purchasing, in the aggregate, in such Qualified Financing and within the time period specified by the Company, such holder's pro rata amount, then such holder's shares of preferred stock would automatically convert into common stock at the respective Conversion Price (as defined). The Company evaluated each series of its Preferred Stock and determined that each individual series was considered an equity host under ASC 815. As a result of the Company's conclusion that the Preferred Stock represented an equity host, the conversion feature of all series of Preferred Stock was considered to be clearly and closely related to the associated Preferred Stock host instrument. Accordingly, the conversion feature of all series of Preferred Stock was not considered an embedded derivative that required bifurcation. The Company accounted for potential beneficial conversion features under FASB ASC Topic 470-20, *Debt with Conversion and Other Options*. At the time of each of the issuances of Preferred Stock, the Company's common stock into which each series of the Company's Preferred Stock is convertible had an estimated fair value less than the effective conversion prices of the Preferred Stock. Therefore, there was no intrinsic value on the respective commitment dates.

Holders of the preferred stock were entitled to receive non-cumulative dividends at the rate of 8% of the applicable purchase price per share per annum if and when declared by the board of directors. No dividends were declared through conversion upon IPO.

Holders of the preferred stock, voting as a class, were entitled to elect five members of the board of directors.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

8. Stockholders' Equity (Deficit) (Continued)

Holders of the Series A, the Series B, and the Series B-1 were entitled to a liquidation preference in an amount equal to $1.00 per share plus all declared and unpaid dividends in the event of a liquidation, dissolution, or winding-up of the Company, or in the event the Company merged with or was acquired by another entity. Holders of the Series C were entitled to a liquidation preference in an amount equal to $1.632 per share plus all declared and unpaid dividends in the event of a liquidation, dissolution, or winding-up of the Company, or in the event the Company merged with or ws acquired by another entity.

At any time on or after July 8, 2016, the holders of at least 60% of the outstanding shares of the preferred stock may have required the Company to redeem, in three annual installments beginning on the date of the initial redemption, all of the outstanding shares of the preferred stock for an amount equal to the original issue price per share plus any declared and unpaid dividends.

9. 2008 and 2013 Equity Incentive Plans

In January 2008, the Company adopted the 2008 Equity Incentive Plan, as amended on February 29, 2008, January 7, 2010, July 8, 2010, December 10, 2010, June 23, 2011 and June 17, 2013 (collectively, the "2008 Plan") that authorized the Company to grant up to 3,310,990 shares of common stock to eligible employees, directors and consultants to the Company, in the form of restricted stock and stock options.

In 2013, the Company adopted the 2013 Equity Incentive Plan, as amended on May 14, 2014 (collectively, the "2013 Plan"), that reserves for issuance under the plan up to 1,711,290 shares of common stock. The 2013 Plan contains an "evergreen" provision, pursuant to which the number of shares of common stock available for issuance under the plan will automatically increase on January 1 of each year beginning in 2015. The 2013 plan became effective upon the January 2014 IPO and, as of such date, the Company may not make further grants under the 2008 plan. The 2013 plan provides for the grant of incentive stock options, or ISOs, nonstatutory stock options, or NSOs, stock appreciation rights, restricted stock awards, restricted stock unit awards, performance-based stock awards and other forms of equity compensation (collectively, stock awards), all of which may be granted to employees, including officers, non- employee directors and consultants of the Company. Additionally, the 2013 plan provides for the grant of cash and stock based performance awards.

Under both the 2008 and 2013 Plans, the amount, terms of grants and exercisability provisions are determined by the board of directors or its designee. The term of the options may be up to 10 years, and options are exercisable in cash or as otherwise determined by the board of directors. Vesting generally occurs over a period of not greater than four years.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

9. 2008 and 2013 Equity Incentive Plans (Continued)

The estimated grant-date fair value of the Company's share-based awards is amortized ratably over the awards' service periods. Share-based compensation expense recognized was as follows:

	Year Ended December 31,	
	2014	2013
Research and development	$ 1,129,244	$ 609,483
General and administrative	1,254,155	318,513
Total stock-based compensation	$ 2,383,399	$ 927,996

		Options Outstanding		
	Shares Available for Grant	Number of Shares	Weighted-Average Exercise Price	Weighted Average Remaining Contractual Term (in years)
Balance, December 31, 2012	171,803	1,523,156	$ 0.56	7.89
Authorized	1,459,514			
Granted	(1,730,156)	1,730,156	3.73	
Exercised		(275,262)	0.30	
Forfeitures	182,304	(182,304)	0.95	
Balance, December 31, 2013	83,465	2,795,746	$ 2.52	8.45
Authorized	1,711,290			
Granted	(1,095,042)	1,095,042	6.75	
Exercised		(186,687)	0.60	
Forfeitures	129,651	(129,651)	7.20	
Balance, December 31, 2014	829,364	3,574,450	$ 3.75	8.06
Vested or expected to vest at December 31, 2014		3,528,809	$ 3.71	8.05
Exercisable at December 31, 2014		1,602,623	$ 2.26	7.10

The intrinsic value of the options exercisable as of December 31, 2014 was $6.4 million, based on the Company's closing stock price of $5.98 per share and a weighted average exercise price of $2.26 per share.

The Company uses the Black-Scholes option-pricing model to estimate the fair value of stock options at the grant date. The Black-Scholes model requires the Company to make certain estimates and assumptions, including estimating the fair value of the Company's common stock, assumptions related to the expected price volatility of the Company's stock, the period during which the options will be outstanding, the rate of return on risk-free investments and the expected dividend yield for the Company's stock.

The per-share weighted-average grant date fair value of the options granted to employees and directors during the year ended December 31, 2014 and 2013 was estimated at $4.43 and $2.52 per

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

9. 2008 and 2013 Equity Incentive Plans (Continued)

share, respectively, on the date of grant using the Black-Scholes option-pricing model with the following weighted-average assumptions:

	Year Ended December 31, 2014	Year Ended December 31, 2013
Risk-free interest rate	1.80%	1.52%
Expected term of options (in years)	5.8	6.1
Expected volatility	75.9%	80.5%
Dividend yield	0%	0%

The weighted-average valuation assumptions were determined as follows:

Risk-free interest rate: The Company based the risk-free interest rate on the interest rate payable on U.S. Treasury securities in effect at the time of grant for a period that is commensurate with the assumed expected option term.

Expected term of options: Due to its lack of sufficient historical data, the Company estimates the expected life of its employee stock options using the "simplified" method, as prescribed in Staff Accounting Bulletin (SAB) No. 107, whereby the expected life equals the arithmetic average of the vesting term and the original contractual term of the option.

Expected stock price volatility: The Company estimated the expected volatility based on actual historical volatility of the stock price of similar companies with publicly-traded equity securities. The Company calculated the historical volatility of the selected companies by using daily closing prices over a period of the expected term of the associated award. The companies were selected based on their enterprise value, risk profiles, position within the industry and with historical share price information sufficient to meet the expected term of the associated award. A decrease in the selected volatility would have decreased the fair value of the underlying instrument.

Expected annual dividend yield: The Company estimated the expected dividend yield based on consideration of its historical dividend experience and future dividend expectations. The Company has not historically declared or paid dividends to stockholders. Moreover, it does not intend to pay dividends in the future, but instead expects to retain any earnings to invest in the continued growth of the business. Accordingly, the Company assumed an expected dividend yield of 0.0%.

Estimated forfeiture rate: The Company's estimated annual forfeiture rate on 2014 and 2013 stock option grants was 7% and 5%, respectively, based on the historical forfeiture experience.

The fair value of the Company's common stock, prior to the Company's initial public offering, was determined by its board of directors with assistance from its management. The board of directors and management considered numerous objective and subjective factors in the assessment of fair value, including the price for the Company's preferred stock that was sold to investors and the rights, preferences and privileges of the preferred stock and common stock, the Company's financial condition and results of operations during the relevant periods and the status of strategic initiatives. These estimates involved a significant level of judgment.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

9. 2008 and 2013 Equity Incentive Plans (Continued)

As of December 31, 2014, there was $6.1 million of total unrecognized compensation expense related to unvested options that will be recognized over the weighted average remaining period of 2.87 years.

Shares Reserved for Future Issuance

At December 31, 2014, the Company has reserved the following shares of common stock for issuance:

Common stock options outstanding	3,574,450
Common stock options and restricted stock available for future grant (2013 Plan)	829,364
Common stock warrants outstanding	30,258
	4,434,072

10. Commitments and Contingencies

Licenses

On May 3, 2013, the Company entered into an option agreement and a license agreement with Actavis plc (formerly Forest Laboratories Holdings Limited), under which the Company granted to Actavis an exclusive option to license its product candidate, TRV027. If Actavis exercises this option, the license agreement between the Company and Actavis will become effective and Actavis will have an exclusive worldwide license to develop and commercialize TRV027 and specified related compounds. At the Company's request, Actavis will consider in good faith whether to grant the Company the right to co-promote the licensed products in the United States under the terms ot be agreed upon by the parties. Actavis will be responsible for subsequent development, regulatory approval and commercialization of TRV027 at Actavis' sole cost and expense.

Under the option agreement, the Company is conducting, at its expense, a Phase 2b trial of TRV027 in acute heart failure, or AHF. Actavis may exercise its option during the pendency of the Phase 2b clinical trial or during a specified time period after the Company delivers the data from the Phase 2b clinical trial to Actavis. During the option period, the Company is not permitted to negotiate for or enter into any agreement with a third party for the development and commercialization of TRV027 and its related compounds. Under specified circumstances linked to adverse changes in the market or related to the results from the Phase 2b trial of TRV027, Actavis has the right to renegotiate the terms of the license agreement. If Actavis exercises such right, the Company will be obligated to negotiate in good faith with Actavis for a period of time the terms of any new arrangement. If the Company and Actavis are unable to agree on the terms of any new arrangement, then the option agreement will terminate and for a specified period of time thereafter the Company may not offer a license to any third party on terms better than those last proposed by either the Company or Actavis during the negotiations.

If Actavis does not exercise its option during the specified period, the option will expire and the license agreement will not become effective. In that case, the Company would be free to enter into a

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

10. Commitments and Contingencies (Continued)

collaboration arrangement with another party for the development and commercialization of TRV027 or to pursue development and commercialization on its own. The Company received no consideration upon the grant of the option to Actavis. If Actavis exercises the option, the Company would receive a $65 million option exercise fee and could potentiall receive up to $365 million depending upon the achievement of future development and commercial milestones. The Company also could 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. The term of the royalty on sales of TRV027 for a given country would extend until the latest to occur of (i) 10 years from first commercial sale of TRV027 in that country, (ii) the expiration of the last to expire patent claiming TRV027 that is sufficient to block the entrance of a generic version of the product, or (iii) the expiration of any period of exclusivity granted by applicable law or any regulatory authority in such country that confers exclusive marketing rights on the product.

If the license agreement becomes effective, Actavis has the right to grant sublicenses under the license agreement to affiliates and third parties. Any sublicensing does not act to relieve Actavis of any of its obligations under the license agreement, including Actavis' obligation to make milestone payments to the Company with respect to TRV027 or pay royalties to the Company on sales of TRV027 by such sublicensee. Under the license, both Actavis and the Company have the right to terminate the agreement in the event of an uncured material breach or insolvency of the other party. In addition, Actavis is permitted to terminate the license agreement without cause at any time upon prior written notice or immediately for product safety reasons. Following a termination of the license agreement, all licenses granted to Actavis would terminate, and Actavis would grant the Company an exclusive royalty bearing license under specified patents and know-how to develop and commercialize reverted licensed products. If not terminated, the license agreement would remain in effect until the expiration of the last royalty term for the last licensed product.

Actavis participated in the Series C Preferred Stock financing and purchased $30 million of Series C Preferred Stock. Because the Series C Preferred Stock was acquired at the same time as the option agreement, management considered whether the Preferred Stock was issued at fair value and if not, whether the consideration received for the Preferred Stock should be allocated in the financial statements in a manner differently than the price stated in the agreement. The Series C Preferred Stock acquired by Actavis was acquired at the same time and at the same price per share as all of the other investors in the Series C Preferred Stock financing and therefore the preferred stock sold to Actavis was deemed to be issued at fair value and no value was allocated to the option agreement. The Series C Preferred Stock held by Actavis was converted into common shares on a one-for-6.2 basis upon consummation of the Company's IPO.

Operating Leases

The Company leases office and laboratory space in Pennsylvania. The Company's leases contain escalating rent clauses, which require higher rent payments in future years. The Company expenses rent on a straight-line basis over the term of the lease, including any rent-free periods. In July 2013, the Company extended the lease for the Company's office and laboratory lease in Pennsylvania until September 2020. In March 2014, the Company extended the square footage of the lease. The Company

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

10. Commitments and Contingencies (Continued)

has the option to terminate the lease after May 31, 2018 with a required termination payment of $150,000. In addition, the Company leases vivarium space in Pennsylvania. The vivarium lease can be terminated at any time upon 90 days' written notice by the Company.

Rent expense under operating leases was $489,810 and $459,288 in 2014 and 2013, respectively.

Future minimum lease payments, including termination fees, under noncancelable lease agreements as of December 31, 2014, are as follows:

	Operating Lease
2015	$ 262,352
2016	269,631
2017	276,909
2018	284,188
2019 and beyond	514,691
Total minimum lease payments	$ 1,607,771

The Company had deferred rent of $320,244 and $347,033 at December 31, 2014 and 2013, respectively. This balance related entirely to the Pennsylvania office and laboratory lease.

Legal Proceedings

The Company is not involved in any legal proceeding that it expects to have a material effect on its business, financial condition, results of operations and cash flows.

11. Income Taxes

The Company provides for income taxes under ASC 740. Under ASC 740, the liability method is used in accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on differences between financial reporting and tax bases of assets and liabilities, and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse.

The Company did not record a current or deferred income tax expense or benefit since its inception.

The Company's loss before income taxes was $49.7 million and $23.3 million for the years ended December 31, 2014 and 2013, respectively, and was generated entirely in the United States.

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

11. Income Taxes (Continued)

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets are the following:

	December 31,	
	2014	2013
Deferred tax assets:		
Net operating losse carryforwards	$ 9,245,934	$ 5,159,176
Research and development credits	5,101,755	2,801,924
Research and development expenses capitalized for tax purposes	43,038,057	26,936,217
Deferred rent	129,998	140,873
Depreciation	476,799	652,104
Other temporary differences	458,413	628,296
Total deferred tax assets	58,450,956	36,318,590
Deferred tax liabilities:		
Prepaid expenses	(90,385)	(80,311)
Total deferred tax liabilities	(90,385)	(80,311)
Net deferred tax assets	58,360,571	36,238,279
Less valuation allowance	(58,360,571)	(36,238,279)
Net deferred tax asset	$	$

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Based on the Company's history of operating losses since inception, the Company has concluded that it is more likely than not that the benefit of its deferred tax assets will not be realized. Accordingly, the Company has provided a full valuation allowance for deferred tax assets as of December 31, 2014 and 2013. The valuation allowance increased by $22.1 million and $10.4 million during the years ended December 31, 2014 and 2013, respectively, due primarily to the generation of net operating losses during the periods.

A reconciliation of income tax expense computed at the statutory federal income tax rate to income taxes as reflected in the financial statements is as follows:

	December 31,	
	2014	2013
Percent of pre-tax income:		
U.S. federal statutory income tax rate	34.0%	34.0%
Permanent Differences	(0.6)%	(0.5)%
State taxes, net of federal benefit	6.5%	6.5%
Research and development credit	3.9%	1.9%
Change in valuation allowance	(43.8)%	(41.9)%
Effective income tax rate	0.0%	0.0%

116

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

11. Income Taxes (Continued)

As of December 31, 2014 and 2013, the Company had U.S. federal net operating loss carryforwards of $22.8 million and $12.7 million, respectively, which may be available to offset future income tax liabilities and will begin to expire at various dates starting in 2027. As of December 31, 2014 and 2013, the Company also had U.S. state net operating loss carryforwards of $22.8 million and $12.7 million, respectively, which may be available to offset future income tax liabilities and will begin to expire at various dates starting in 2027.

As of December 31, 2014 and 2013, the Company had federal research and development tax credit carryforwards of $4.7 million and $2.5 million, respectively, available to reduce future tax liabilities which will begin to expire at various dates starting in 2027. As of December 31, 2014 and 2013, the Company had state research and development tax credit carryforwards of approximately $0.7 million and $0.4 million, respectively, available to reduce future tax liabilities which will begin to expire at various dates starting in 2022.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50 percent, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed several financings since its inception which may have resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code, or could result in a change in control in the future.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2014 and 2013, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's statements of operations and comprehensive loss.

For all years through December 31, 2014, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position for these years. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

The Tax Increase Prevention Act of 2014, enacted December 19, 2014, reinstated the research and development credit through December 31, 2014, and the Company recorded a credit of $1.8 million for 2014. In 2013 the Company recorded credits of approximately $1.0 million related to 2012 and 2013 as a result of a previous retroactive reinstatement under the American Tax Relief Act of 2012.

The Company files income tax returns in the United States, and various state jurisdictions. The federal and state income tax returns are generally subject to tax examinations for the tax years ended

Table of Contents

TREVENA, INC.

Notes to Financial Statements (Continued)

December 31, 2014

11. Income Taxes (Continued)

December 31, 2010 through December 31, 2013. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service or state tax authorities to the extent utilized in a future period.

12. Employee Benefit Plan

The Company sponsors a 401(k) defined contribution plan for its employees. Employee contributions are voluntary. The Company matches employee contributions in an amount equal to 100% of the first 3% of eligible compensation and 50% of the next 2% of eligible compensation, and such employer contributions are immediately vested. During 2014 and 2013, the Company provided matching contributions of $204,537 and $175,943, respectively.

13. Subsequent Events

In March 2015, Actavis and the Company signed a letter agreement wherein Actavis agreed to pay the Company $10.0 million to fund the expansion of the Company's ongoing Phase 2b trial of TRV027 from 500 patients to 620 patients. The March 2015 letter agreement does not otherwise amend the terms of the May 2013 option agreement described in Note 10 above.

Table of Contents

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

An evaluation was performed under the supervision and with the participation of our management, including our Chief Executive Officer, or CEO, and our Chief Financial Officer, or CFO, of the effectiveness of our disclosure controls and procedures, as such term is defined under Rule 13a-15(e) promulgated under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), as of December 31, 2014.

Based on that evaluation, our management, including our CEO and CFO, concluded that as of December 31, 2014 our disclosure controls and procedures were effective to ensure that information required to be disclosed by us in reports that we file or submit under the Exchange Act, is recorded, processed, summarized and reported within the time periods specified in the rules and forms of the Securities and Exchange Commission and that such information is accumulated and communicated to the Company's management, including our CEO and CFO, as appropriate to allow timely decisions regarding required disclosure.

Changes in Internal Control over Financial Reporting

There have been no changes in our internal control over financial reporting during our most recent fiscal quarter that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Management's Report on Internal Control Over Financial Reporting and Attestation Report of the Registered Public Accounting Firm

Management's Report on Internal Control Over Financial Reporting is included in Part II, Item 8 of this Annual Report on Form 10-K and incorporated in this Item 9A by reference.

Attestation Report of the Registered Public Accounting Firm

This Annual Report on Form 10-K does not include an attestation report of our registered public accounting firm regarding internal control over financial reporting as required by Section 404(c) of the Sarbanes Oxley Act of 2002. Because the Company qualifies as an emerging growth company under the JOBS Act, management's report was not subject to attestation by our registered public accounting firm.

ITEM 9B. OTHER INFORMATION

None.

Table of Contents

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

Directors

The information required by this Item 10 with respect to our Directors is incorporated herein by reference to the information contained under the caption "Item 1. Election of Directors" in our definitive proxy statement related to the 2015 annual meeting of stockholders, to be filed within 120 days after the end of the year covered by this Annual Report on Form 10-K.

Executive Officers

The information concerning our executive offers required by this Item 10 is provided under the caption "Executive Officers" in Part I, Item 1 of this Annual Report on Form 10-K.

Section 16(a) Beneficial Ownership Reporting Compliance

The information concerning Section 16(a) Beneficial Ownership Reporting Compliance by our directors and executive officers is incorporated by reference to the information contained under the caption "Section 16(a) Beneficial Ownership Reporting Compliance" in our definitive proxy statement related to the 2015 annual meeting of stockholders, to be filed within 120 days after the end of the year covered by this Annual Report on Form 10-K.

Code of Ethics

The information concerning our Code of Business Conduct and Ethics is incorporated by reference to the information contained under the caption "Code of Ethics" in our definitive proxy statement related to the 2015 annual meeting of stockholders, to be filed within 120 days after the end of the year covered by this Annual Report on Form 10-K.

Audit Committee

The information required by this Item 10 with respect to our Audit Committee is incorporated herein by reference to the information contained under the caption "Corporate Governance" in our definitive proxy statement related to the 2015 annual meeting of stockholders, to be filed within 120 days after the end of the year covered by this Annual Report on Form 10-K.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item 11 is incorporated by reference to the information contained in our definitive proxy statement related to the 2015 annual meeting of stockholders, to be filed within 120 days after the end of the year covered by this Annual Report on Form 10-K.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by Item 12 is incorporated by reference to the information contained in our definitive proxy statement related to the 2015 annual meeting of stockholders, to be filed within 120 days after the end of the year covered by this Annual Report on Form 10-K.

Table of Contents

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by Item 13 is incorporated by reference to the information contained in our definitive proxy statement related to the 2015 annual meeting of stockholders, to be filed within 120 days after the end of the year covered by this Annual Report on Form 10-K.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by Item 14 is incorporated by reference to the information contained in our definitive proxy statement related to the 2015 annual meeting of stockholders, to be filed within 120 days after the end of the year covered by this Annual Report on Form 10-K.

Table of Contents

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) DOCUMENTS FILED AS PART OF THIS REPORT

The following is a list of our consolidated financial statements and our subsidiaries and supplementary data included in this Annual Report on Form 10-K under Item 8 of Part II hereof:

1. FINANCIAL STATEMENTS AND SUPPLEMENTAL DATA

Report of Independent Registered Public Accounting Firm.

Balance Sheets as of December 31, 2014 and 2013.

Statements of Operations and Comprehensive Loss for the years ended December 31, 2014 and 2013.

Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit) for the years ended December 31, 2013 and 2014.

Consolidated Statements of Cash Flows for the years ended December 31, 2014 and 2013.

Notes to Financial Statements for the years ended December 31, 2014 and 2013.

(b) EXHIBITS

The following is a list of exhibits filed as part of this Annual Report on Form 10-K. Where so indicated by footnote, exhibits that were previously filed are incorporated by reference. For exhibits incorporated by reference, the location of the exhibit in the previous filing is indicated.

Exhibit Number	Description
3.1	Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K, filed with the SEC on February 5, 2014).
3.2	Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K, filed with the SEC on February 5, 2014).
4.1	Reference is made to Exhibits 3.1 and 3.2.
4.2	Specimen stock certificate evidencing shares of Common Stock of the Registrant (incorporated by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).
4.3	Form of Warrant dated September 19, 2014 issued by Trevena, Inc. to Oxford Finance LLC, Square 1 Bank and Three Point Capital, LLC (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K, filed with the SEC on September 22, 2014).
10.1*	License Agreement, dated as of May 3, 2013, by and between the Registrant and Forest Laboratories Holdings Limited (now Actavis plc) (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-191643), originally filed with the SEC on October 9, 2013).

Table of Contents

Exhibit Number	Description
10.2*	Option Agreement, dated as of May 3, 2013, by and between the Registrant and Forest Laboratories Holdings Limited (now Actavis plc) (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-191643), originally filed with the SEC on October 9, 2013).
10.3	Warrant to purchase shares of Series B preferred stock issued to Comerica Bank, dated December 9, 2011 (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).
10.4	Warrant to purchase shares of Common Stock issued to Silicon Valley Bank, dated June 24, 2008 (incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).
10.5	Amended and Restated Investor Rights Agreement, dated as of May 3, 2013, by and among the Registrant and certain of its stockholders (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-191643), originally filed with the SEC on October 9, 2013).
10.6	Commercial Lease Agreement, dated as of August 4, 2008, by and between the Registrant and Pios Grande KOP Business Center, L.P. (successor- in-interest to KOPBC, Inc.) (incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).
10.7	Amendment No. 1 to Commercial Lease Agreement, dated as of December 8, 2008, by and between the Registrant and Pios Grande KOP Business Center, L.P. (successor-in-interest to KOPBC, Inc.) (incorporated by reference to Exhibit 10.7 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).
10.8	Amendment No. 2 to Commercial Lease Agreement, dated as of July 3, 2013, by and between the Registrant and Pios Grande KOP Business Center, L.P. (successor-in-interest to KOPBC, Inc.) (incorporated by reference to Exhibit 10.8 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).
10.9	Third Amendment to Commercial Lease Agreement, dated as of February 21, 2014, by and between the Registrant and Pios Grande KOP Business Center, L.P. (successor-in-interest to KOPBC, Inc.) (incorporated by reference to Exhibit 10.9 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-200386), originally filed with the SEC on November 20, 2014).
10.10+	2008 Equity Incentive Plan, as amended to date (incorporated by reference to Exhibit 10.9 to the Registrant's Registration Statement on Form S- 1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).
10.11+	Form of Stock Option Agreement under 2008 Equity Incentive Plan (incorporated by reference to Exhibit 10.10 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).

Table of Contents

Exhibit Number	Description
10.12+	2013 Equity Incentive Plan (incorporated by reference to Exhibit 10.11 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).
10.13+	Form of Stock Option Grant Notice and Stock Option Agreement under 2013 Equity Incentive Plan (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).
10.14+	Form of Restricted Stock Grant Notice and Restricted Stock Unit Award Agreement under 2013 Equity Incentive Plan (incorporated by reference to Exhibit 10.13 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-191643), originally filed with the SEC on October 9, 2013).
10.15+	Non-Employee Director Compensation Plan (incorporated by reference to Exhibit 10.14 to the Registrant's Current Report on Form 8-K filed with the SEC on July 1, 2014).
10.16+	2013 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.15 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).
10.17+	Form of Indemnity Agreement with executives and directors (incorporated by reference to Exhibit 10.16 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333- 191643), originally filed with the SEC on October 9, 2013).
10.18+	Employment Agreement, dated as of January 31, 2014, by and between the Registrant and Maxine Gowen (incorporated by reference to Exhibit 10.17 to the Registrant's Form 10-K filed with the SEC on March 20, 2014).
10.19+	Employment Agreement, dated as of January 31, 2014, by and between the Registrant and Michael Lark (incorporated by reference to Exhibit 10.18 to the Registrant's Form 10-K filed with the SEC on March 20, 2014).
10.20+	Employment Agreement, dated as of January 31, 2014, by and between the Registrant and Roberto Cuca (incorporated by reference to Exhibit 10.19 to the Registrant's Form 10-K filed with the SEC on March 20, 2014).
10.21+	Employment Agreement, dated as of January 31, 2014, by and between the Registrant and David Soergel (incorporated by reference to Exhibit 10.20 to the Registrant's Form 10-K filed with the SEC on March 20, 2014).
10.22+	Employment Agreement, dated as of January 31, 2014, by and between the Registrant and Rosamond Deegan (incorporated by reference to Exhibit 10.21 to the Registrant's Form 10-K filed with the SEC on March 20, 2014).
10.23+	Employment Agreement dated as of May 12, 2014, by and between the Registrant and John M. Limongelli (incorporated by reference to Exhibit 10.1 to the Registrant's Form 8-K filed with the SEC on May 15, 2014).
10.24	Loan and Security Agreement, dated September 19, 2014, by and among Trevena, Inc., as borrower, Oxford Finance LLC, as collateral agent and lender, and Square 1 Bank, as lender (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, filed with the SEC on September 22, 2014).
23.1#	Consent of Independent Registered Public Accounting Firm.

Table of Contents

Exhibit Number	Description
24.1#	Power of Attorney. Reference is made to the signature page hereto.
31.1#	Certification of the Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.
31.2#	Certification of the Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.
32.1#	Certification of the Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2#	Certification of the Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101#	The following financial information from this Annual Report on Form 10-K for the periods ended December 31, 2014 and 2013, formatted in XBRL (eXtensible Business Reporting Language): (i) Balance Sheets as of December 31, 2014 and 2013, (ii) Statements of Operations and Comprehensive Loss for the years ended December 31, 2014 and 2013, (iii) Statement of Redeemable Convertible Preferred Stock and Stockholders' (Deficit) Equity as of December 31, 2014, (iv) Statements of Cash Flows for the years ended December 31, 2014 and 2013 and (v) Notes to Financial Statements, tagged as blocks of text.

#
Filed herewith.

##
Previously filed.

+
Indicates management contract or compensatory plan.

*
Portions of this exhibit, indicated by asterisks, have been omitted pursuant to a request for confidential treatment and have been separately filed with the Securities and Exchange Commission.

Table of Contents

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: March 18, 2015

TREVENA, INC.

By: /s/ MAXINE GOWEN

Maxine Gowen
President and Chief Executive Officer

Pursuant to the requirements of the Securities Act, this registration statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ MAXINE GOWEN Maxine Gowen	President and Chief Executive Officer (Principal Executive Officer) and Director	March 18, 2015
/s/ ROBERTO CUCA Roberto Cuca	Senior Vice President and Chief Financial Officer (Principal Financial and Accounting Officer)	March 18, 2015
/s/ LEON O. MOULDER, JR. Leon O. Moulder, Jr.	Chairman, Board of Directors	March 18, 2015
/s/ MICHAEL R. DOUGHERTY Michael R. Dougherty	Director	March 18, 2015
/s/ ADAM M. KOPPEL Adam M. Koppel, M.D., Ph.D.	Director	March 18, 2015
/s/ JULIE H. MCHUGH Julie H. McHugh	Director	March 18, 2015
/s/ FRANCOIS NADER Francois Nader, M.D.	Director	March 18, 2015

Table of Contents

Signature	Title	Date
/s/ JAKE R. NUNN Jake R. Nunn	Director	March 18, 2015
/s/ ANNE M. PHILLIPS Anne M. Phillips, M.D.	Director	March 18, 2015
/s/ BARBARA YANNI Barbara Yanni	Director	March 18, 2015

Table of Contents

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