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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2017
or

☐ **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 001-36193

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.)
955 Chesterbrook Blvd., Suite 200, Chesterbrook, PA	**19087**
(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**

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

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 ☐ No ☒

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 ☒ No ☐

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 ☒ No ☐

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. ☐

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 ☐	Accelerated filer ☒	Non-accelerated filer ☐ (Do not check if a smaller reporting company)	Smaller reporting company ☐

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

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

The aggregate market value of the voting stock held by non-affiliates of the registrant, as of June 30, 2017, the last business day of the registrant's most recently completed second fiscal quarter, was approximately $94.0 million. Such aggregate market value was computed by reference to the closing price of the Common Stock as reported on the NASDAQ Global Select Market on June 30, 2017. 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, 2017.

The number of shares of the registrant's Common Stock outstanding as of March 2, 2018 was 64,785,659.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2018 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, 2017 are incorporated by reference into Part III of this Form 10-K.

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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;
- our ability to fund future operating expenses and capital expenditures with our current cash resources or to secure additional funding in the future;
- our planned clinical trials and preclinical studies for our product candidates;
- the timing and likelihood of obtaining and maintaining regulatory approvals for our product candidates;
- the extent of clinical trials potentially required by the FDA for our product candidates;
- the clinical utility and potential market acceptance of our product candidates, particularly in light of existing and future competition;
- our sales, marketing and manufacturing capabilities and strategies;
- our intellectual property position; and
- our ability to identify or acquire 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.

PART I

ITEM 1. BUSINESS

Overview

Trevena, Inc. is a biopharmaceutical company developing innovative therapies based on breakthrough science to benefit patients and healthcare providers confronting serious medical conditions. 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 product candidates:

- *OLINVO™ (oliceridine) Injection:* We are developing OLINVO, a G protein biased ligand of the μ opioid receptor, for the management of moderate-to-severe acute pain where intravenous, or IV, administration is preferred. In February 2017, we announced positive top-line results from our Phase 3 APOLLO-1 and APOLLO-2 pivotal efficacy studies of OLINVO in moderate-to-severe acute pain following bunionectomy and abdominoplasty, respectively. In both studies, all dose regimens achieved their primary endpoint of statistically greater analgesic efficacy than placebo, as measured by responder rate. In July 2017, we announced that we had completed enrollment in the Phase 3 open-label ATHENA safety study to support the new drug application, or NDA, for OLINVO. In the study, 768 patients were administered OLINVO to manage pain associated with a wide range of procedures and diagnoses. In January 2018, we announced that the United States Food and Drug Administration, or FDA, had accepted the NDA we submitted for OLINVO. The FDA also indicated that the Prescription Drug User Fee Act, or PDUFA, review date for the OLINVO NDA is November 2, 2018 and that it plans to hold an advisory committee meeting to discuss the NDA. If OLINVO ultimately receives regulatory approval, we plan to commercialize it in the United States, either on our own or with a commercial partner, for use in acute care settings such as hospitals and ambulatory surgery centers; outside the United States, we plan to commercialize OLINVO in certain countries with a commercial partner. We currently hold all worldwide development and commercialization rights to OLINVO.

- *TRV250:* We are developing TRV250, a G protein biased ligand targeting the δ-receptor, as a compound with a potential first-in-class, non-narcotic mechanism for the treatment of migraine. TRV250 also may have utility in a range of other central nervous system, or CNS, indications. Because TRV250 selectively targets the δ-receptor, we believe it will not have the addiction liability of conventional opioids or other μ opioid related adverse effects like those seen with morphine or oxycodone. In the second quarter of 2017, we began a Phase I study of TRV250 in the United Kingdom in healthy volunteers; we expect to complete dosing in this study by the end of the first quarter of 2018.

We have also identified and have completed the initial Phase 1 studies for TRV734, an orally administered new chemical entity expected to be used for first-line treatment of moderate-to-severe acute and chronic pain. We intend to continue to focus our efforts for TRV734 on securing a development and commercialization partner for this asset.

Our Pipeline

OLINVO™ (oliceridine) Injection

OLINVO is a novel μ-receptor G protein Pathway Selective modulator that activates the G protein pathway, which is associated with analgesia and avoids the β-arrestin pathway, which is associated with limiting opioid analgesia and with

promoting opioid-induced adverse events. We are developing OLINVO for the management of moderate-to-severe acute pain where IV administration is preferred.

Disease and treatment options

The typical treatment paradigm in the U.S. for the management of moderate-to-severe acute pain is to initiate injectable or IV pain medication in the preoperative or immediate postoperative period to provide rapid and effective pain relief. Conventional IV opioid analgesics, such as morphine, fentanyl, and hydromorphone, are the mainstays of pain management in the immediate postoperative period and are approximately 50% of the injectable analgesic unit market. The effectiveness of conventional opioid agonists is limited because of severe side effects such as respiratory depression, nausea, vomiting, and constipation. Injectable non-opioid analgesics are often used together with IV opioids for post-surgical pain management; however, these drugs, such as IV non-steroidal anti-inflammatory drugs, or NSAIDs, IV acetaminophen, or local anesthetics such as bupivacaine, have potential cardiovascular, hepatic and gastrointestinal side effects. 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 an effective analgesic agent with an improved safety and tolerability profile.

Clinical development

We are developing OLINVO for the management of moderate-to-severe acute pain where IV administration is preferred. In the future, we also may explore other formulations, such as transmucosal administration for breakthrough pain in additional, separate clinical trials. In the second quarter of 2017, we held a successful Type B meeting with the FDA regarding the Chemistry, Manufacturing and Controls data package of our NDA submission for OLINVO. We also held a successful pre-NDA meeting with the FDA regarding the clinical and non-clinical data package of the NDA in the second quarter of 2017.

Below is a summary of the clinical development work undertaken for OLINVO.

ATHENA Phase 3 Open Label Safety Study

We conducted a Phase 3, open label, multicenter study evaluating the safety and tolerability of OLINVO in patients with moderate-to-severe pain caused by surgery or medical conditions. The trial was designed to model real-world use, including the use of multi-modal analgesia. Patients were treated with OLINVO on an as-needed basis via IV bolus, patient-controlled analgesia, or PCA, or both, as determined by the investigator. The primary objective was to assess the safety and tolerability of OLINVO. Pain intensity was measured as a secondary endpoint.

In the ATHENA study, 768 patients were treated with OLINVO. The most common procedures were orthopedic, gynecologic, colorectal, and general surgeries. Patients at elevated risk of opioid-related adverse events were well represented; more than 30% of patients were 65 years or older, and approximately 50% of patients were obese, with body mass index (BMI) >30 kg/m2. Only 2% of patients discontinued for adverse events, and 4% of patients discontinued for lack of efficacy. The most common adverse events were nausea, constipation, and vomiting, with prevalence lower than in the APOLLO studies. Adverse event rates associated with OLINVO administered by PCA and as-needed bolus dosing were similar, supporting the potential use of OLINVO in both administration paradigms.

APOLLO-1 and APOLLO-2 Phase 3 Studies

We have conducted two pivotal efficacy trials evaluating OLINVO in patients with moderate-to-severe acute pain: the APOLLO-1 study, which evaluated pain for 48 hours following bunionectomy, and the APOLLO-2 study, which evaluated pain for 24 hours following abdominoplasty. In February 2017, we announced positive top-line results from the APOLLO-1 and APOLLO-2 studies. In both studies, all dose regimens achieved the primary endpoint of statistically greater analgesic efficacy than placebo, as measured by responder rate.

The APOLLO-1 and APOLLO-2 studies were both Phase 3, multicenter, randomized, double-blind, placebo- and active-controlled studies of OLINVO. During the study period, a loading dose of placebo, morphine (4 mg), or OLINVO (1.5 mg) was administered first, and then patients used a PCA button to dose themselves as often as every 6 minutes with the same study drug: 1 mg morphine, or 0.1 mg, 0.35 mg, or 0.5 mg OLINVO. If PCA dosing was inadequate to control pain, patients could request supplemental study medication (2 mg morphine or 0.75 mg OLINVO, no more than once an hour). If the study medication regimen did not adequately manage pain, patients could opt for an NSAID rescue analgesic. Placebo loading, demand, and supplemental doses were volume-matched.

All endpoints were the same in both studies, except that dosing and pain assessment were for 48 hours in APOLLO-1 and 24 hours in APOLLO-2. Efficacy was measured by a responder analysis, which defined a responder as a patient who experienced at least a 30% reduction in their sum of pain intensity difference at the end of the treatment period without either early discontinuation (for lack of efficacy or safety/tolerability) or use of rescue medication. Non-inferior efficacy compared to morphine and superior efficacy compared to morphine were key secondary endpoints. Respiratory safety events were defined as clinically relevant worsening of respiratory status, including oxygen saturation, respiratory rate, or sedation. The product of the frequency and conditional duration of these events was reported as respiratory safety burden, a key secondary endpoint. Additional measures of respiratory safety included prevalence of oxygen saturation less than 90% and prevalence of supplemental oxygen use. Measures of gastrointestinal tolerability included use of rescue antiemetics, vomiting, and spontaneously reported nausea.

APOLLO-1 (bunionectomy)

- All three OLINVO regimens (0.1 mg, 0.35 mg, and 0.5 mg on-demand doses) achieved the primary endpoint with statistically superior responder rates compared to placebo at 48 hours ($p<0.0001$, adjusted for multiplicity).
- The 0.35 mg and 0.5 mg OLINVO dose regimens demonstrated efficacy comparable to morphine at 48 hours based on responder rate (both doses $p<0.005$ for non-inferiority to morphine). Both doses were also comparable to morphine for rates of rescue analgesic use.
- Following the 1.5 mg initial loading dose, all OLINVO regimens demonstrated rapid onset with statistically significant efficacy within 5 minutes ($p<0.05$).
- OLINVO exhibited a dose-related trend of improved respiratory safety burden in all three OLINVO dose regimens ($p<0.05$ for the 0.1 mg regimen vs. morphine). Consistent with this, in all dose regimens OLINVO showed dose-related trends of reduced respiratory safety events ($P<0.05$ for 0.1 mg and 0.35 mg regimens vs. morphine), prevalence of oxygen desaturation ($O2<90\%$) and lower prevalence of supplemental oxygen use ($p<0.05$ for the 0.1 mg regimen vs. morphine for both measures).
- OLINVO exhibited less antiemetic use compared to morphine ($p<0.05$ for all OLINVO regimens vs. morphine). Consistent with this, OLINVO showed dose related trends of lower prevalence of nausea and vomiting in all three OLINVO regimens ($p<0.05$ for the 0.1 mg regimen vs. morphine).

APOLLO-2 (abdominoplasty)

- All three OLINVO dose regimens achieved the primary endpoint with statistically superior responder rates compared to placebo at 24 hours (adjusted $p<0.05$ for the 0.1 mg regimen; adjusted $p<0.001$ for the 0.35 mg and 0.5 mg regimens).
- The 0.35 mg and 0.5 mg OLINVO dose regimens demonstrated efficacy comparable to morphine at 24 hours based on responder rate ($p<0.05$ for non-inferiority of the 0.35 mg regimen vs. morphine). Both doses were also comparable to morphine for rates of rescue analgesic use.
- Following the 1.5 mg initial loading dose, all OLINVO regimens demonstrated rapid onset with statistically significant efficacy within 5 to 15 minutes ($p<0.05$).
- OLINVO showed a dose-related trend of improved respiratory safety burden in all three OLINVO dose regimens ($p<0.05$ for the 0.1 mg regimen vs. morphine). Consistent with this, for all dose regimens OLINVO showed dose-related trends of reduced respiratory safety events, prevalence of oxygen desaturation ($O2<90\%$) and lower prevalence of supplemental oxygen use ($p<0.05$ for the 0.1 mg regimen vs. morphine for all measures).
- OLINVO showed a dose-related trend of less antiemetic use than morphine for all three OLINVO regimens ($p<0.05$ for the 0.1 mg OLINVO regimen vs. morphine). Consistent with this, OLINVO showed dose-related trends of lower prevalence of nausea and vomiting ($p<0.05$ for the 0.1 mg regimen vs. morphine for both nausea and vomiting; $p<0.05$ for the 0.35 mg regimen vs. morphine for vomiting).

In both studies, OLINVO was generally well-tolerated. The most common drug-related adverse events, or AEs, were nausea, vomiting, headache, and dizziness.

Phase 2b trial of OLINVO in acute postoperative pain following abdominoplasty

The aim of our Phase 2b clinical trial was to evaluate the efficacy, safety and tolerability of OLINVO in the management of postoperative pain using morphine as a benchmark, utilizing on-demand dosing to reflect standard clinical practice. This Phase 2b trial was a randomized, double-blind, placebo- and active-controlled trial of OLINVO in which we enrolled 200 patients with moderate-to-severe acute postoperative pain after abdominoplasty surgery. Two regimens of OLINVO were tested: the first consisted of a 1.5 mg intravenous loading dose with 0.1 mg self-administered on-demand doses as often as every six minutes using a PCA device; the second consisted of a 1.5 mg loading dose with 0.35 mg on-demand doses as often as every six minutes using a PCA device. A commonly used morphine PCA regimen also was tested, consisting of a 4 mg loading dose with 1 mg on-demand doses as often as every six minutes. Placebo was administered as a loading dose and on-demand doses were volume-matched to the active regimens. Rescue medication consisting of ibuprofen or oxycodone was used in all groups.

In August 2015, we reported top-line results from this trial. OLINVO demonstrated statistically significant pain reduction compared to placebo and comparable efficacy to morphine. OLINVO provided rapid reduction in average pain scores, consistent with the previous Phase 2 trial where OLINVO showed more rapid onset of meaningful pain relief than morphine. Rescue analgesic use was similar for both OLINVO and morphine, and less than half the rate of rescue analgesic use for placebo. In this study, the OLINVO groups had a significantly lower prevalence (percentage of patients) of hypoventilation events (a measure of respiratory safety), nausea, and vomiting than the morphine group. The most frequently reported AEs, associated with OLINVO were nausea, vomiting, hypoventilation and headache. Opioid-related AEs were generally less frequent in the OLINVO groups compared to morphine. No drug-related serious adverse events were reported in the study.

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

The aim of our Phase 2a/b clinical trial was to evaluate the efficacy and tolerability of OLINVO in the management of postoperative pain using morphine as a benchmark, using fixed dose and dose interval to characterize the performance of OLINVO. 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 OLINVO, 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.

In November 2014, we announced top-line data from this trial. At doses of 2 mg and 3 mg of OLINVO administered every three hours, the trial achieved its primary endpoint of statistically greater pain reduction than placebo for 48 hours, which we believe demonstrated proof of concept for OLINVO. Over the 48-hour trial period, the 3 mg dose of OLINVO 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 3 mg doses of OLINVO demonstrated superior analgesic efficacy in the trial compared to placebo, and the 2 mg, and 3 mg doses of OLINVO demonstrated superior analgesic efficacy compared to the 4 mg dose of morphine.

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

Phase 1 clinical studies of OLINVO

We also have completed a number of Phase 1 clinical studies of OLINVO. These included two single ascending dose studies of OLINVO given as a 60 minute continuous infusion or a 2 minute bolus infusion that 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 OLINVO is metabolized by at least two liver enzymes, CYP2D6 and CYP3A4, we assessed OLINVO pharmacokinetics, pharmacodynamics, safety and tolerability in CYP2D6 “poor metabolizer” healthy volunteers with little to no CYP2D6 activity. This study showed that OLINVO 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 OLINVO 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 OLINVO 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, OLINVO 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, OLINVO was well tolerated in the trial. Subjects receiving OLINVO 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. OLINVO also showed less respiratory depression compared to morphine over 4 hours.

In October 2014 we completed an adaptive, multiple ascending dose study of OLINVO in more than 50 healthy subjects. The safety, tolerability, pharmacokinetic and pharmacodynamics results of this study were consistent with the early Phase 1 studies described above. Recently, we also successfully completed an absorption, distribution, metabolism, and excretion study, with results consistent with the lack of known active OLINVO metabolites. We also completed a QTc interval study, which showed no evidence of concentration-related QTc changes, a renal impairment study which showed no evidence of altered PK/accumulation in patients with renal failure compared to healthy patients, and a human abuse liability study which showed that OLINVO had similar abuse liability as IV morphine when administered at a comparably analgesic dose.

Regulatory

In December 2015, the FDA granted Fast Track designation to OLINVO for the management of moderate-to-severe acute pain. The Fast Track program is designed to facilitate the development and review of drugs intended to treat serious conditions with unmet medical needs by providing sponsors with the opportunity for frequent interactions with the FDA. In February 2016, the FDA granted Breakthrough Therapy designation to OLINVO for the management of moderate-to-severe acute pain. Breakthrough Therapy designation is granted by the FDA to new therapies intended to treat serious conditions and for which preliminary clinical evidence indicates that the drug may demonstrate substantial clinical improvement over available therapies. Breakthrough Therapy designation provides all the benefits of the Fast Track program, as well as more intensive FDA guidance on preparing an efficient drug development program. In January 2018, we announced that the FDA had accepted for review the NDA we submitted for OLINVO. The FDA also indicated that the PDUFA review date for the OLINVO NDA is November 2, 2018 and that it plans to hold an advisory committee meeting to discuss the NDA.

Commercialization

According to 2015 IMS data, approximately 51 million patients in the United States were treated with an IV opioid in the hospital setting. The majority of use is in the inpatient setting where approximately 16 million patients are treated for an average of two days. The World Health Organization estimates that over 230 million major surgical procedures are performed each year worldwide. The Centers for Disease Control and Prevention, or CDC, estimate that 100 million surgical and invasive diagnostic procedures occur annually in the United States. Accordingly, if approved, we believe that there is a large potential commercial opportunity for OLINVO in the management of both surgical and medical acute pain.

If OLINVO ultimately receives regulatory approval, we plan to commercialize it in the United States, either on our own or with a commercial partner. Assuming approval on the November 2, 2018 PDUFA review date and allowing for DEA scheduling of OLINVO within 90 days of FDA approval (as mandated by the Improving Regulatory Transparency for New Medicinal Therapies Act), we anticipate launching OLINVO in the first quarter of 2019. Outside the United States, we expect to seek collaborators to commercialize OLINVO to offset risk and preserve capital.

To commercialize OLINVO in the United States, we intend to utilize a hospital-focused specialty sales force targeting surgeons, anesthesiologists, hospitalists, and other healthcare providers with acute post-surgical or medical pain management responsibility. We believe the greatest opportunity for OLINVO will be in the hospital inpatient setting where we estimate that approximately 50% of the 16 million patients may be at higher risk of opioid-related adverse events such as respiratory depression or post-operative nausea and vomiting. These events are common and result in a significant cost burden to the hospital system. We believe that many of these patients are complex, and have comorbid conditions. Population and hospital trend data indicates that these patient groups will continue to grow and be an area of focus for inpatient care. We expect that the aging population will also continue to drive surgical volumes and hospital length of stay will increase. Elderly patients are also twice at risk of experiencing an opioid-related adverse event.

Approximately 1,200 US hospitals are responsible for 70% of the annual volume of conventional IV opioid drugs prescribed. We have selected a subset of these hospitals that have rapidly adopted new branded agents in the past as the initial

account targets for OLINVO at launch. We will work to secure Pharmacy and Therapeutics Committee approval and subsequent utilization of OLINVO at these hospitals. Because many of our priority customers also provide care in other hospital settings, we anticipate that we will target a select number of hospital outpatient departments and ambulatory surgery centers. Given the changing dynamics in the hospital marketplace and the increased emphasis on clinical and economic outcomes, we expect our commercialization plans to include health economic information designed to demonstrate the value of OLINVO through a potential reduction in adverse events related to the use of conventional IV opioids.

Manufacturing

We have completed process development of the active pharmaceutical ingredient, or API, and have manufactured multiple commercial scale batches using our proposed commercial process under current good manufacturing practices, or cGMP, conditions. We also have completed drug product process development and have manufactured multiple batches of drug product using the proposed commercial process under cGMP conditions.

For OLINVO, we have established commercial supply agreements for the manufacture of the API and finished (compounded, filled and packaged) drug product. Alcami Corporation, or Alcami, is contracted to supply 100% of our commercial API from its Germantown, WI manufacturing facility. We have existing commercial supply agreements with two separate companies for the supply of drug product. Alcami is contracted to supply commercial drug product from its facilities in Charleston, SC and Wilmington, NC. Pfizer CentreOne (formerly Hospira) is also contracted to supply commercial drug product from its facility in McPherson, KS. We anticipate that OLINVO will be classified as a Schedule II controlled substance. All third-party facilities throughout the supply chain have the appropriate DEA licenses for handling Schedule II controlled substances according to each of their respective contractual roles (manufacturing, testing, distribution, etc.).

Competition

If OLINVO is approved for IV management of moderate-to-severe acute pain, it will compete with generic IV 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, vomiting, constipation, and post-operative ileus. OLINVO also may compete against, or be used in combination with, OFIRMEV® (IV acetaminophen), marketed by Mallinckrodt plc, EXPAREL® (liposomal bupivacaine), marketed by Pacira Pharmaceuticals, Inc., CALDOLOR® (IV ibuprofen), marketed by Cumberland Pharmaceuticals, and DYLOJECT™ (IV diclofenac) marketed by Hospira. Together with generic versions of IV NSAIDs such as ketorolac, 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 also are aware of a number of products in mid- and late-stage clinical development that are aimed at improving the treatment of moderate-to-severe acute pain and may compete with OLINVO. AcelRx Pharmaceuticals, Inc. is developing a range of acute pain products involving sufentanil oral nanotabs in hand-held dispensers including DSUVIA™ and ZALVISO™. Innocoll Holdings plc. and Heron Therapeutics Inc. have proprietary long-acting reformulations of bupivacaine in development. Recro Pharma, Inc. is developing an IV version of the NSAID meloxicam. Cara Therapeutics Inc. is developing IV and oral dose forms of a peripherally restricted K-opioid receptor agonist, which has been administered in combination with μ-opioids in clinical trials. Avenue Therapeutics, Inc. is developing an IV version of generic opioid tramadol for moderate-to-severe acute pain.

Intellectual property

Our OLINVO patent portfolio is wholly owned by us. The portfolio includes three issued U.S. patents (U.S. Patent Nos. 8,835,488, 9,309,234, and 9,642,842), which claim, among other things, OLINVO, compositions comprising OLINVO, and methods of using OLINVO. The issued patents are expected to expire no earlier than 2032, subject to any disclaimers or extensions, and any U.S. patent to issue in the future is also expected to expire no earlier than 2032, subject to any disclaimers or extensions. We also have issued patents in Australia, China, Europe, Hong Kong, Eurasia, Japan, and New Zealand, which claim among other things, OLINVO, compositions comprising OLINVO and methods of making or using OLINVO. The foreign portfolio also includes an application that has been allowed by the European Patent Office, which claim among other things, OLINVO, compositions comprising OLINVO and methods of using OLINVO. We have patent applications pending in the United States, South Korea, Brazil, Canada, Israel, India, and Hong Kong. The issued patents and patents that could issue in the future from these allowed or pending applications outside the United States are expected to expire no earlier than 2032, subject to any disclaimers or extensions.

TRV250

TRV250 is under investigation as a potential new mechanism of action for the treatment of acute migraine. The first-time-in-human Phase 1 trial was a single ascending dose study of safety, tolerability, and pharmacokinetics of subcutaneous TRV250 in healthy volunteers, and included a separate cohort who received a single oral dose of TRV250. In November, the Company announced positive interim results for the initially planned doses, which demonstrated dose-proportional exposure after subcutaneous administration and adequate oral bioavailability to support further clinical development. Following this interim readout, the Company extended the trial to study additional subcutaneous doses. Dosing is now complete, having reached a top subcutaneous dose of 30 mg. The Company expects to release data in the coming months.

Based on the profile of TRV250, we believe it has the potential to be a first-in-class treatment for migraine. 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.

Triptans, a generic family of 5HT1B agonists, are the current standard treatment for acute treatment of migraine, and account for 80% of migraine therapies prescribed during physician office visits. Other less commonly prescribed acute treatments include ergot alkaloids, and analgesics such as opioids and NSAIDs. Various branded reformulations of triptan molecules have been launched, and we are aware of others in development. In May 2016, Avanir Pharmaceuticals, Inc. launched a dry powder nasal delivery formulation of sumatriptan, called ONZETRA™ Xsail™. RedHill Biopharma, Ltd. and IntelGenx Corp. resubmitted the 505(b)(2) NDA for RIZAPORT®, an oral thin film rizatriptan formulation, to the FDA in November 2017. In addition, Allergan is developing an orally inhaled formulation of dihydroergotamine, called Semprana™. Lasmiditan, a selective 5HT1F agonist, is in late stage development by Colucid Pharmaceuticals, Inc., recently acquired by Eli Lilly and Company. Allergan (ubrogepant) and Biohaven (rimegepant) both have an oral anti-calcitonin gene-related peptide, or CGRP, antagonist in Phase 3 testing for the acute treatment of migraine.

Patients suffering from frequent or chronic migraine headaches may also use preventative agents to decrease the frequency and severity of migraines. Botox® is currently the most widely prescribed migraine prophylactic, but certain anticonvulsants, such as topiramate, and beta-blockers, such as propranolol, are also used. We are aware of four companies with anti-CGRP antibody products in late stage development for preventative treatment of migraine: Amgen, Inc. has submitted a biologics license application, or BLA, to the FDA for Aimovig (erenumab), which will be co-commercialized with Novartis; Eli Lilly and Company has submitted a BLA for galcanezumab; Teva Pharmaceutical Industries Limited has submitted a BLA for fremanezumab; and Alder BioPharmaceuticals Inc. is completing Phase 3 trials with eptinezumab. Allergan also has an oral CGRP antagonist molecule, atogepant, in Phase 2 trials for migraine prevention.

We believe our preclinical data support targeting the δ-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-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. In the future, we may decide to seek a collaborator for TRV250 with CNS development and commercialization expertise outside the United States.

We have one non-provisional patent application in the United States directed to compounds that modulate the δ-receptor. This application is solely owned by us. We have also filed, or are in the process of filing, foreign national phase applications in Australia, Brazil, Canada, China, Europe, Israel, India, Japan, South Korea, and New Zealand. Any patents that may issue from these applications are expected to expire no earlier than 2036, subject to any disclaimers or extensions.

TRV734

TRV734 is a small molecule G protein biased ligand of the μ opioid receptor that we discovered and have developed through Phase 1 as a first-line, orally administered compound for the treatment of moderate-to-severe acute and chronic pain. Like OLINVO, 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 intend to continue to focus our efforts for TRV734 on securing a worldwide development and commercialization partner for this asset.

TRV734 has shown a similar profile to OLINVO 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. We have completed three Phase 1 trials of TRV734 in healthy volunteers, including a single ascending dose study, a multiple ascending dose study, and a pharmacokinetic study. In these studies, a total of 127 healthy volunteers were exposed to TRV734 at doses between 2 mg and 250 mg. We incorporated measures to assess the potential for analgesic efficacy and tolerability advantages in these studies. Based on these data and data for OLINVO, we believe that TRV734 may offer an improved efficacy profile as compared to current opioid therapies or equivalent efficacy with an improved gastrointestinal tolerability and respiratory safety profile.

Our TRV734 patent portfolio is wholly owned by us and includes one issued U.S. patent (U.S. Patent No, 9,044,469) claiming TRV734, other compounds and/or methods of making or using the same. This patent is expected to expire no earlier than 2032, subject to any disclaimers or extensions. We also have issued patents in Australia, China, Europe, Eurasia, Hong Kong, Israel, Japan, and New Zealand claiming TRV734, other compounds and/or methods of making or using the same. We also have patent applications pending in South Korea, Brazil, Canada, Israel, India, and Hong Kong. The issued patents and patents that could issue in the future from these allowed or pending applications outside the United States are expected to expire no earlier than 2032, subject to any disclaimers or extensions.

TRV027

TRV027 is a peptide β-arrestin biased ligand that targets the angiotensin II type 1 receptor (AT1R), inhibiting angiotensin II-mediated G protein signaling and activating β-arrestin signaling. On May 3, 2013, we entered into an option agreement and a license agreement with Allergan plc (formerly Actavis plc and Forest Laboratories Holdings Limited), under which we granted to Allergan an exclusive option to license TRV027. In March 2015, we signed a letter agreement with Allergan pursuant to which Allergan paid us $10.0 million to fund the expansion of the Phase 2b (BLAST-AHF) trial of TRV027 in AHF from 500 patients to 620 patients. In May 2016, we announced that TRV027 did not meet either the primary or secondary endpoints of this Phase 2b (BLAST-AHF) trial. In August 2016, Allergan notified us of its decision to not exercise its exclusive option. As such, we have retained all rights to TRV027. At this time, we have no plans for further clinical development of TRV027.

Our TRV027 patent portfolio is wholly owned by us. The portfolio includes four issued U.S. patents (U.S. Patent Nos. 8,486,885; 8,796,204; 8,809,260; and 8,993,511) that claim, among other things, TRV027, compositions comprising TRV027, and methods of using TRV027. We also have issued patents in Europe, Australia, Japan, New Zealand, China, and Hong Kong. The issued U.S. patents covering the composition of matter and methods of using TRV027 are expected to expire no earlier than 2031 (U.S. Patent No. 8,486,885) and 2029 (U.S. Patent Nos. 8,796,204; 8,809,260; and 8,993,511), subject to any disclaimers or extensions. The issued European Patent is expected to provide coverage for TRV027 throughout most of European Union until at least 2029, subject to any disclaimers or extensions.

S1P Modulators

In July 2017, we disclosed a new preclinical lead optimization program targeting S1P receptors. Our compounds are all new chemical entities are, expected to be non-addictive, and use a new mechanism of action that in preclinical models avoids the immune suppression associated with approved and investigational S1P receptor targeted drugs. These molecules have demonstrated activity in preclinical models of chemotherapy-induced peripheral neuropathy, neuropathic pain, and inflammatory pain. We expect to complete characterization of the lead compounds in 2018 to determine if any merit IND-enabling studies to support Phase 1 clinical trials.

We are aware of a certain U.S. patent owned by a third party with claims that are broadly directed to a method of treating chemotherapy induced neuropathic pain with an S1P receptor agonist or an S1P receptor antagonist. Although we do not believe that this is a valid patent, this patent could be construed to cover our S1P compounds.

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 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 GCPRs 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 for our product candidates. 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 also may 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 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 own or operate 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.

Commercialization

We have not yet fully established sales, marketing or product distribution infrastructure. Subject to successfully completing product development and receiving marketing approvals, we expect to commence commercialization activities for our wholly owned products by insourcing or outsourcing a sales organization, initially in the hospital market, or by seeking a commercial partner in the United States. If we choose to insource or outsource a sales organization, we believe that it 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. Outside the United States, we expect to enter into distribution and other commercial 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. In parallel with building our commercial 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 also may 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 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 implementing 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, covering 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 of an NDA to the FDA;
- 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 an NDA; and
- in certain cases, 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 the

data submitted in the IND or the proposed clinical trials and 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 covering 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 a marketing application.

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 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 GCPs.

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 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.

Expedited Review and Approval

The FDA has various programs, including Fast Track, Breakthrough Therapy designation, priority review, and accelerated approval, that are intended to expedite or simplify the process for reviewing drugs, and/or provide for the approval of a drug on the basis of a surrogate endpoint. Even if a drug qualifies for one or more of these programs, the FDA may later decide that the drug no longer meets the conditions for qualification or that the time period for FDA review or approval will be shortened. Generally, drugs that are eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs and those that offer meaningful benefits over existing treatments. For example, Fast Track is a process designed to facilitate the development and expedite the review of drugs to treat serious or life-threatening diseases or conditions and fill unmet medical needs. In December 2015, FDA granted Fast Track designation to OLINVO for the management of moderate-to-severe acute pain. Priority review is designed to give drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists an initial review within six months as compared to a standard review time of ten months.

Although Fast Track and priority review do not affect the standards for approval, the FDA will attempt to facilitate early and frequent meetings with a sponsor of a Fast Track designated drug and expedite review of the application for a drug designated for priority review. Accelerated approval, which is described in Subpart H of 21 Code of Federal Regulations, or 21 CFR Part 314, provides for an earlier approval for a new drug that is intended to treat a serious or life-threatening disease or condition and that fills an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a clinical measurement or other biomarker used as an indirect or substitute measurement to predict a clinically meaningful outcome. As a condition of

approval, the FDA may require that a sponsor of a product candidate receiving accelerated approval perform post-marketing clinical trials.

A Breakthrough Therapy designation is intended to expedite the development and FDA review of drugs for serious or life-threatening conditions or where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies. A request for Breakthrough Therapy designation should be submitted concurrently with, or as an amendment to an IND. In February 2016, OLINVO received a Breakthrough Therapy designation from the FDA for the management of moderate-to-severe acute pain in patients 18 years of age or older for whom a parenteral opioid is warranted.

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 program user fee requirements, 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;
- 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 OLINVO and TRV734, if approved, 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. OLINVO 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, exports, or conducts research with 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.

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 federal 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 exceptions and regulatory safe harbors protecting

some common activities from prosecution, the exceptions 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 exception 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 federal 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 federal 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 criminal and civil false claims laws, including the federal False Claims Act, prohibit 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 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 additional 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 for Economic 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 on "covered entities," including certain healthcare providers, health plans, and healthcare clearinghouses. 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 exceptions and regulatory safe harbors, 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, integrity oversight and reporting obligations to resolve allegations of non-compliance with these laws, 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 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, in the United States, 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. In addition, for hospital products, a private health insurer or Medicare will typically reimburse a fixed fee for certain procedures, including in-patient surgeries. Pharmaceutical products such as OLINVO, if approved, that may be used in connection with the surgery generally will not be separately reimbursed and, therefore, a hospital would have to assess the cost of OLINVO, if approved, relative to its benefits. Current or future efforts to limit the level of reimbursement for in-patient hospital procedures could cause a hospital to decide not to use OLINVO, if approved by the FDA. 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 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 years since its enactment, there have been, and continue to be, significant developments in, and continued legislative activity around, attempts to repeal or repeal and replace the PPACA. Due to these efforts, there is significant uncertainty regarding the future of the PPACA, and its impact on the healthcare system. 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 Budget Control Act of 2011, as amended, was signed into law. Among other things, this law 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, due to subsequent legislative amendments, will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012 became law, 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.

Further, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. These and other healthcare reform initiatives may result in additional reductions in Medicare and other healthcare funding. We cannot anticipate what impact these or other future healthcare reform initiatives will have on coverage and reimbursement of our products or our business more generally.

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* and/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, 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 patent of 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 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

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.

Employees

As of December 31, 2017, we had 51 employees, all of whom are located in the United States. None of our employees are 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 955 Chesterbrook Boulevard, Suite 200, Chesterbrook, PA 19087. 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.	59	President, Chief Executive Officer and Director
Carrie L. Bourdow	55	Executive Vice President and Chief Operating Officer
Roberto Cuca	50	Senior Vice President and Chief Financial Officer
David P. Geoghegan	52	Senior Vice President, Operations
Yacoub Habib, Ph.D.	50	Senior Vice President, Business Development and Corporate Planning
John M. Limongelli, Esq.	48	Senior Vice President, General Counsel and Chief Administrative Officer
Jonathan Violin, Ph.D.	42	Senior Vice President, Scientific Affairs and Investor Relations 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 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 and Idera Pharmaceuticals, Inc. since January 2016. From 2008 until 2012, Dr. Gowen served as a director of Human Genome Sciences, Inc., a public biopharmaceutical company. Dr. Gowen also serves on the boards of BIO, the biotechnology industry association, and its affiliate, Life Sciences PA. 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.

Carrie L. Bourdow

Ms. Bourdow served as our Senior Vice President and Chief Commercial Officer from May 2015 until January 2018, and, since then, as our Executive Vice President and Chief Operating Officer. From May 2013 to May 2015, she was Vice President of Marketing at Cubist Pharmaceuticals, Inc. Prior to joining Cubist in 2013, Ms. Bourdow served for more than 20 years at Merck & Co., Inc., where she held positions of increasing responsibility across several therapeutic areas including anti-infectives, acute heart failure, and pain. Ms. Bourdow has served as a director of Nabriva Therapeutics PLC since June 2017. Ms. Bourdow earned her B.A. from Hendrix College and her M.B.A. from Southern Illinois University.

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, an A.B. from Princeton University, and he is a CFA charterholder.

David P. Geoghegan

Mr. Geoghegan joined our company in 2015 as Vice President of Manufacturing and Pharmaceutical Technology, and became Senior Vice President, Operations, in January 2018. Mr. Geoghegan established and manages our third-party supply chain for clinical and commercial supply, and is responsible for pharmaceutical process development. Prior to joining us, Mr. Geoghegan served as the Executive Director, Manufacturing Quality Site Head at Endo Pharmaceuticals Inc. (formerly Auxilium Pharmaceuticals, Inc.) from 2014 to 2015. From 2012 to 2014, he was Vice President of Quality for Savient Pharmaceuticals, Inc. Before that, he served in roles of increasing responsibility for several other large and small biopharmaceutical companies, including Adolor Corporation, Aviron, MedImmune, LLC, and Wyeth. Mr. Geoghegan holds a degree in Mechanical Engineering from Villanova University and an M.B.A. from Northeastern University.

Yacoub Habib, Ph.D.

Dr. Habib has served as our Senior Vice President, Business Development and Corporate Planning since July 2015. Previously, from 2009 to June 2015, he served as Vice President of Business Development at Ikaria, Inc. and led the business development strategy for the company until its acquisition. From 2007 to 2009, he served as Executive Director of New Business Development for Pfizer Inc. Before joining Pfizer, Dr. Habib was Executive Director of Global Business Development for Organon Pharmaceuticals, a division of Akzo Nobel, where he was responsible for the identification, evaluation, and negotiation of in-licensing, out-licensing and divestiture opportunities in neuroscience, fertility, and women health. He started his career at Bristol-Myers Squibb where he spent nine years in various research, corporate, and business development roles including as Director of Corporate and Business Development. Dr. Habib holds a Ph.D. in pharmaceutical sciences from the University of Maryland and an M.B.A. with a major in finance and marketing from New York University Stern School of Business.

John M. Limongelli, Esq.

Mr. Limongelli joined our company as Senior Vice President, General Counsel and Corporate Secretary in May 2014 and was appointed Chief Administrative Officer in March 2016. Prior to this, 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 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. 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.

Jonathan Violin, Ph.D.

Dr. Violin is one of our scientific founders, and joined us at our inception in 2008. He became Senior Vice President of Scientific Affairs and Investor Relations Officer in January of 2018. He has held a variety of leadership roles at our company, including corporate strategy, investor relations, and discovery biology. He co-led the discovery of OLINVO, and contributed to the identification and advancement of three other novel molecules to clinical development. Prior to joining our company, Dr. Violin was a post-doctoral fellow in the laboratory of Dr. Robert Lefkowitz at Duke University Medical Center, where he studied novel mechanisms of G protein-coupled receptor pharmacology. Dr. Violin holds a Ph.D. from the Department of Pharmacology at the University of California, San Diego, an M.B.A. from the Fuqua School of Business at Duke University, and a B.S. in Chemical Pharmacology from Duke University

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$71.9 million, $103.0 million, and $50.5 million for the years ended December 31, 2017, 2016, and 2015, respectively. As of December 31, 2017, we had an accumulated deficit of$357.5 million. To date, we have financed our operations primarily through private placements and public offerings of our equity securities and debt borrowings. We have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and clinical trials. We still have not completed development of any of our product candidates. 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 as we:

- establish sales, marketing and distribution capabilities and scale up external manufacturing capabilities to commercialize OLINVO, if approved, and any other products that we choose not to license to a third party and for which we may obtain regulatory approval;
- conduct clinical trials for TRV250, our δ-receptor product candidate, as well as any additional clinical trials of OLINVO that may be required by FDA;
- seek to identify and discover additional product candidates;
- conduct clinical trials and seek regulatory approvals for any product candidates that successfully complete clinical trials;
- maintain, expand, and protect our intellectual property portfolio;

- hire additional sales, marketing, medical, clinical and scientific personnel; and

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

To become and remain profitable, we must succeed in developing and eventually commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages 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 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, making necessary regulatory filings, 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, continue our development efforts, diversify our product offerings, or even continue our operations. A decline in the value of our company also could 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.

Over the next several years, we expect to incur significant expenses in connection with our current operations and the servicing and repayment of our outstanding debt obligations. In preparation for the potential regulatory approval of OLINVO, we expect to incur significant expenses related to our product manufacturing, marketing, sales, and distribution efforts. Accordingly, we will need to obtain substantial additional funding for these efforts and for the repayment, beginning in January 2018, of our outstanding term loans; we would seek to obtain this funding through the sale of equity, debt financings, and/or other sources, including potential collaborations. Ultimately, we may be unable to raise additional funds or enter into such other arrangements when needed, on favorable terms, or at all. If we fail to raise additional capital or enter into such arrangements as, and when, needed, we could be forced to:

- significantly delay, scale back, or discontinue our operations, development programs, and/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 and marketable securities as of December 31, 2017, together with interest thereon, will enable us to fund our operating expenses and capital expenditure requirements for at least twelve months from the filing date of this Form 10-K. If we are unable to raise additional funds prior to this date, or we do not take steps to reduce our expenses, our lenders may conclude that there has been a material adverse change in the Company's financial condition, or a material impairment in the value of the loan collateral or in the prospect of repayment of our obligations to the lenders. In this case, the lenders have the right to foreclose on the available collateral, including our cash and cash equivalents and marketable securities.

The extent of our future capital requirements will depend on many factors, including:

- the costs, timing, and outcome of regulatory review of the OLINVO NDA or any future product candidates, both in the United States and in territories outside the United States;
- our ability to enter into collaborative agreements for the development and commercialization of our product candidates, including OLINVO;
- 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 scope, progress, results and costs of preclinical development, laboratory testing, and clinical trials for our other product candidates, including TRV250;
- the expenses needed to attract and retain skilled personnel;
- the number and development requirements of other product candidates that we pursue;
- 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. Despite these efforts, 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 or meet our expectations. Our commercial revenue, if any, will be derived from sales of products that we do not expect to be commercially available until, at the earliest, the first quarter of 2019, 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 and positive cash flows from operations, we expect to finance our cash needs through a combination of equity offerings, debt financings, and license and development agreements in connection with any collaborations. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, either at the time of such capital raise or thereafter, 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 activities to date have been limited to, among other things, organizing and staffing our company, business planning, raising capital, developing our product platform, identifying potential product candidates, undertaking preclinical studies, and conducting clinical trials. With the exception of OLINVO, our product

candidates are early in development. We have not yet demonstrated our ability to obtain regulatory approvals, manufacture a product at commercial scale or arrange for a third party to do so on our behalf, or conduct sales, marketing, and distribution activities necessary for successful product commercialization. Consequently, any predictions you make about our future success or viability may not be as reliable 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 significantly expand our capabilities to support future activities related to the approval, manufacture, and commercialization of our product candidates. We may be unsuccessful 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 Regulatory Approval of Our Product Candidates

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 we have relied and expect to continue to rely on third parties 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. For OLINVO, we have submitted an NDA to the FDA. The FDA has indicated to us that the Prescription Drug User Fee Act review date for the NDA is November 2, 2018. It is possible that FDA may not meet this target date for any number of reasons, including if it considers the submission of additional information or data during the review process to constitute a major amendment to the NDA. Ultimately, the OLINVO NDA may not be approved by or on the November 2, 2018 target date, if at all.

The FDA also has indicated to us that it expects to convene an Advisory Committee as part of the review process. The Advisory Committee will discuss and advise FDA on the risk-benefit profile of OLINVO. In advance of this Advisory Committee meeting, we and the FDA will submit briefing documents for the committee's review, and these briefing documents will be made available to the public and may include information from the OLINVO development program that have not previously been disclosed. Historically, for some companies, disclosure of information in this manner has led to increased volatility in their stock price. The Advisory Committee and FDA may interpret nonclinical and clinical data differently than we and our experts have. Press coverage and public scrutiny of the materials that will be discussed at the Advisory Committee meeting may negatively affect the potential for our NDA to receive approval. Even if we ultimately obtain approval of the NDA, the matters discussed at the Advisory Committee meeting could limit our ability to successfully commercialize OLINVO.

The feedback received from an Advisory Committee can have a substantial impact on the FDA's decision to approve or reject a product candidate. 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, among other things. 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.

The FDA has not yet provided feedback on our proposed proprietary name of OLINVO, and will only approve a tradename, if at all, when approving the NDA. Any goodwill or market recognition that we may have built up for this proposed tradename would be lost if we are forced to propose different tradenames to ensure lack of confusion in the marketplace and safe use of oliceridine.

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, dosages, or presentations 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 or that includes language, such as a black box warning, that may impair our ability to successfully commercial that product candidate. Any of these scenarios could compromise the commercial prospects for our product candidates.

Our μ opioid receptor targeted product candidates, including OLINVO, may 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.

Risk Evaluation and Mitigation Strategy, or REMS, are imposed by FDA to assure safe use of the product candidates, either as a condition of product candidate approval or on the basis of new safety information. Our μ opioid receptor product candidates, including OLINVO, if approved, may 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 may 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 OLINVO, are expected to 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 OLINVO, are likely to 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 OLINVO to be regulated by the DEA as a Schedule II controlled substance.

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

For any of our product candidates classified as controlled substances, we and our suppliers, manufacturers, contractors, customers and distributors are required to obtain and maintain applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation, exportation and distribution of controlled substances. There is a risk that DEA regulations may limit the supply of the compounds used in clinical trials for our product candidates, and, in the future, the 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, Asia, and many other jurisdictions, we or any future third party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or our collaborators may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, the failure to obtain approval in one jurisdiction may compromise our ability to obtain approval elsewhere. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

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

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

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

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, both on their own and together with other medications.

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

We currently have limited resources focused on the manufacturing, marketing, sales, and distribution of pharmaceutical products and have limited experience and capabilities in this area. To commercialize any product candidates that receive marketing approval, we would need to build manufacturing, 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 or outsource a targeted specialist sales force to market or co-promote the product in the United States; we currently do not expect to build sales, manufacturing and distribution capabilities outside of the United States, although this expectation could change in the future. There are substantial risks involved with establishing 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 is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred certain 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 or to outsource these tasks to a third party;

- the inability of sales personnel to obtain access to physicians or educate adequate numbers of physicians on the benefit of our 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 a 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, particularly in markets outside of the United States. 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 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.

For OLINVO, we will need to partner with one or more third parties to sell, market and distribute this product, if approved, outside the United States. We may be unsuccessful in our efforts to secure such partnerships.

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, if any of our product candidates achieves regulatory approval, we also face potential competition from other drug candidates in development by other companies. OLINVO also may compete against, or be used in combination with, OFIRMEV® (IV acetaminophen), marketed by Mallinckrodt plc, with EXPAREL® (liposomal bupivacaine), marketed by Pacira Pharmaceuticals, Inc., CALDOLOR® (IV ibuprofen), marketed by Cumberland Pharmaceuticals, DYLOJECT™ (IV diclofenac), and marketed by Hospira. In addition to currently marketed IV analgesics, we are aware of a number of products in development that are aimed at improving the treatment of moderate-to-severe acute pain. AcelRx Pharmaceuticals, Inc. is developing a range of acute pain products involving sufentanil oral nanotabs in hand-held dispensers including DSUVIA™ and ZALVISO™. Innocoll Holdings plc, and Heron Therapeutics Inc. have proprietary long-acting reformulations of bupivacaine

in development. Recro Pharma, Inc. is developing an IV version of the NSAID meloxicam. Cara Therapeutics Inc. is developing IV and oral dose forms of a peripherally restricted ê-opioid receptor agonist, which has been administered in combination with µ-opioids in clinical trials. Avenue Therapeutics, Inc. is developing an IV version of generic opioid tramadol for moderate-to-severe acute pain. 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.

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 than we do in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and selling and marketing approved products. 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 also may 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 any future 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, healthcare reform initiatives, or regulatory or political concerns.

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, 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. In addition, for hospital products, a private health insurer or Medicare will typically reimburse a fixed fee for certain procedures, including in-patient surgeries. Pharmaceutical products such as OLINVO, if approved, that may be used in connection with the surgery generally will not be separately reimbursed and, therefore, a hospital would have to assess the cost of OLINVO, if approved, relative to its benefits. Current or future efforts to limit the level of reimbursement for in-patient hospital procedures could cause a hospital to decide not to use OLINVO, if approved by the FDA. 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 or procedures. 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 for a product or procedure may not be satisfactory. Inadequate reimbursement levels may adversely affect the demand for, or the price of, any product candidate for which we or our collaborators obtain marketing approval. Obtaining and maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to seek 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 analogous 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.

In addition to the above factors, the approval and commercialization of OLINVO may be negatively impacted by changing perceptions in the United States and elsewhere among regulators, legislators, and the general public concerning the approval, use, and abuse of prescription opioid products. In the future, the FDA and other regulatory and legislative bodies may enact regulations that seek to limit opioid prescribing and use. In response to these efforts and changing perceptions, physicians may determine to reduce the volume of opioid prescriptions they prescribe to patients. Any of these changes could negatively impact both the timing and likelihood of FDA approval of OLINVO, as well as the commercial opportunity, if approved.

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

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

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

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

- the inability to commercialize any products that we may develop.

We currently maintain $15 million in product liability insurance coverage, which may be inadequate 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 the Discovery and Development of Our Product Candidates

Our research and development efforts have been 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 development of drugs based on biased ligands is an emerging field, and the scientific discoveries that form the basis for our historical 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 or will ultimately lead to the approval of any current or future product candidate.

We are early in our development efforts and have only one product candidate, OLINVO, for which we have submitted an NDA to the FDA. If we are unable to successfully complete development and commercialization of our product candidates, either on our own or with a partner, or experience significant delays in doing so, our business will be materially harmed.

We are early in our development efforts and have only one product candidate, OLINVO, for which we have completed Phase 3 development and submitted an NDA to the FDA. To this point, 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 until, at the earliest, the first quarter of 2019, 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 has been 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. Until recently, we maintained an active discovery research effort. In October 2017, we made the decision to halt our early stage research, although we continue to assess the future development of a series of novel S1P modulators. Without internal discovery research capabilities, we will

need to expand our pipeline through other means, including, for example, by in-licensing product candidates for further development. We may not be able to identify, acquire, and 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 or in-license 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, we will not be able to obtain product revenue in future periods, which would make it unlikely that we would ever achieve profitability.

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, can take many years to complete, and has a high risk of failure. 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 often are 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, which 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 prospective trial sites;
- 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;
- 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 and/or reporting 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, thereby harming 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. 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 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 or significantly limited its commercial opportunity. 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 require additional warnings on the label or even withdraw approvals of such product;
- 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 in connection with regulatory 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.

OLINVO 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 may need to conduct additional drug interaction studies and OLINVO may be limited in its co-administration with other drugs using these pathways as their safety and effectiveness, as well as OLINVO'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 continue to discuss this question with the FDA 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 OLINVO.

OLINVO 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 OLINVO and TRV734 also modulate the μ-opioid receptor, these adverse reactions and risks likely will apply to the use of OLINVO and TRV734. One healthy subject in the 0.25 mg dosing cohort of our Phase 1 clinical trial of OLINVO experienced a severe episode of vasovagal syncope during which he fainted and his pulse stopped. These were considered severe adverse events. It is possible that serious adverse vasovagal events could occur in other patients dosed with OLINVO. 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. In such case, we likely would discontinue further development of TRV250 for the treatment of migraines.

We may expend our limited resources to pursue a particular product candidate or indication and thereby fail to capitalize on other 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 fewer clinical or regulatory risks and/or greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. 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 Our Dependence on Third Parties

Any future relationships or collaborations we may enter into may be important to us. If we are unable to maintain our relationship with any of these collaborations, or if our relationship with these collaborators is not successful, our business could be adversely affected.

We have limited capabilities for product development, sales, marketing, and distribution. For our product candidates, we may in the future determine to collaborate with pharmaceutical and biotechnology companies for the development and

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

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 development or commercialization programs or may not pursue commercialization of any product candidates that achieve regulatory approval based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing;
- collaborators could fail to make timely regulatory submissions for a product candidate;
- collaborators may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to limit or eliminate efforts and 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 any 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. 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 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.

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 parties, such as contract research organizations, clinical research organizations, clinical data management organizations, medical institutions, and clinical investigators to conduct our preclinical studies and clinical trials for our product candidates. 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 also may have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines, or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

If any of our relationships with these third party contract research organizations or clinical research organizations terminate, we may not be able to enter into arrangements with alternative contract research organizations or clinical research organizations or to do so on commercially reasonable terms. Switching or adding additional contract research organizations or clinical research organizations involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new contract research organization or clinical research organization commences work. As a result, delays could occur that could compromise our ability to meet our desired development timelines. Although we seek to carefully

manage our relationships with our contract research organizations and 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 have limited internal manufacturing capabilities and do not have any manufacturing facilities. In addition, our product candidates have never been manufactured at commercial scale. 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.

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 and, potentially in the future, our products 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 current cGMP regulations for manufacture of our product candidates. Third party manufacturers may not be able to comply with the cGMP regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products.

Our product candidates and any products that we may commercialize likely will 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 OLINVO. 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 OLINVO. 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 OLINVO is approved for sale in the United States.

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

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

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

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

Risks Related to Our Intellectual Property

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

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

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Should we enter into collaborations with third parties, 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.

The Leahy-Smith America Invents Act, or the Leahy-Smith Act, 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 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 and Trademark Office continues to develop and implement new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

Moreover, we may be subject to a third party preissuance submission of prior art to the United States 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.

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 United States 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 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 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.

Risks Related to Legal Compliance Matters

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 current and future arrangements with healthcare providers, 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 conduct research, sell, market, and distribute any drugs for which we obtain marketing approval. In addition, we may be subject to transparency laws and patient privacy regulation by U.S. federal and state governments and by governments in foreign 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, among other things, 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, among other things, 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, among other things, 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 physicians and their immediate family members, requirements for manufacturers to submit reports to CMS by the 90th day of each calendar year, and subsequent disclosure of such information by CMS on a publicly available website; and

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

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations may involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, including, without limitation, damages, fines, imprisonment, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, integrity oversight and reporting obligations to resolve allegations of non-compliance with these laws, 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 also could 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 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% (and 70% commencing January 1, 2019) 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, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- 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.

Some of the provisions of the PPACA have yet to be implemented, and there have been judicial and Congressional challenges to certain aspects of the PPACA, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the PPACA. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the PPACA or otherwise circumvent some of the requirements for health insurance mandated by the PPACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the PPACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the PPACA have been signed into law. The Tax Cuts and Jobs Act of 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain PPACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amends the PPACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole".

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, due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2027 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012, 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.

Further, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. While any proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

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

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

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

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

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

We are subject to numerous environmental, health, and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and 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 development, clinical, business development, legal, financial, and commercial 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, clinical, manufacturing, sales and marketing, and other personnel also will be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our 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 development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

We expect to expand our development, regulatory, manufacturing, 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 continue to experience growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs, manufacturing, 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 also could 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 seek to market our product candidates abroad through third party collaborators. 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 seek 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, in lieu of our own sales force and distribution systems, which would indirectly expose us to these risks. Our business and financial results in the future could be adversely affected due to a variety of factors associated with conducting development and marketing of our product candidates, if approved, outside of the United States, including:

- efforts to develop an international sales, marketing and distribution organization may increase our expenses, divert our management's attention from the development of product candidates or cause us to forgo profitable licensing opportunities in these geographies;
- changes in a specific country's or region's political and cultural climate or economic condition;
- unexpected changes in foreign laws and regulatory requirements;
- difficulty of effective enforcement of contractual provisions in local jurisdictions;
- inadequate intellectual property protection in foreign countries;

- differing payor reimbursement regimes, governmental payors or patient self-pay systems and price controls;
- 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.

We utilize information technology systems and networks to process, transmit and store electronic information in connection with our business activities. As use of digital technologies has increased, cyber incidents, including deliberate attacks and attempts to gain unauthorized access to computer systems and networks, have increased in frequency and sophistication. These threats pose a risk to the security of our systems and networks and the confidentiality, availability and integrity of our data. There can be no assurance that we will be successful in preventing cyber-attacks or successfully mitigating their effects.

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 highly volatile, with closing stock prices ranging from a high of $13.30 per share to a low of $1.34 per share. The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors in our stock may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including:

- actual or anticipated variations in our operating results;
- changes in financial estimates by us or by any securities analysts who might cover our stock;
- the timing and results of our clinical trials for any of our product candidates;
- failure or discontinuation of any of our development programs;

- conditions or trends in our industry;
- stock market price and volume fluctuations of comparable companies and, in particular, those that operate in the biopharmaceutical industry;
- announcements by us or our competitors of significant acquisitions, strategic partnerships or divestitures;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- capital commitments;
- investors' general perception of our company and our business;
- recruitment or departure of key personnel;
- 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 the operation of 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 industry, 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 relatively new 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.

Sales of a substantial number of shares of our common stock 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 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, and the restrictions of Rule 144 in the case of our affiliates.

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, 2017, we had federal net operating loss carryforwards of approximately$55.7 million that could be limited if we have experienced, or if in the future we experience, an ownership change.

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

There are provisions in our amended and restated certificate of incorporation and amended and restated bylaws that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change in control was considered favorable by you and other stockholders. For example, our board of directors has the authority to issue up to 5,000,000 shares of preferred stock. The board of directors can fix the price, rights, preferences, privileges, and restrictions of the preferred stock without any further vote or action by our stockholders. The issuance of shares of preferred stock may delay or prevent a change in control transaction. As a result, the market price of our common stock and the voting and other rights of our stockholders may be adversely affected. An issuance of shares of preferred stock may result in the loss of voting control to other stockholders.

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

- only one of our three classes of directors will be elected each year;
- stockholders are not entitled to remove directors other than by a 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 a majority 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.

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. Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. For our fiscal year ended December 31, 2017, 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(a) 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. 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(a) of the Sarbanes-Oxley Act in a timely manner, or if we are unable to implement or 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. In addition, any testing by us conducted in connection with Section 404(a) of the Sarbanes-Oxley Act, or the subsequent testing by our independent registered public accounting firm conducted in connection with Section 404(b) of the Sarbanes-Oxley Act once we no longer qualify as an "emerging growth company," may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses; or may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement.

We are required to disclose changes made in our internal control procedures on a quarterly basis and our management is required to assess the effectiveness of these controls annually. However, for as long as we are an "emerging growth company" under the JOBS Act, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal control over financial reporting pursuant to Section 404(b). We will cease to be an "emerging growth company" in 2018 if any of the following occur on or before December 31, 2018: (1) we generate $1.0 billion of annual revenue at an earlier date, (2) we issue more than $1.0 billion in non-convertible debt, or (3) we qualify as a large accelerated

filer under SEC rules. If and when we cease to be an "emerging growth company," an assessment of the effectiveness of our internal controls by our independent registered public accounting firm will be very expensive and could detect problems that our management's assessment might not.

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

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

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our principal offices are located in Chesterbrook, Pennsylvania, where we currently lease approximately 40,565 square feet of developed office space on the second floor and an additional 8,231 square feet of unimproved office space on the first floor. The lease term for these spaces extends through May 2028.

In October 2017, in connection with our restructuring and reduction in force, we terminated our lease related to vivarium space in Exton, Pennsylvania, under an agreement expiring on December 31, 2018. We incurred termination fees equivalent to three months rent, totaling less than $0.1 million, in relation to the early termination of this agreement. Additionally, in November 2017, we provided notice of our intent to terminate our facility lease of approximately 16,714 square feet of office and laboratory space in King of Prussia, Pennsylvania, under an agreement that expires in September 2020. We paid the landlord a $0.15 million termination fee on the date we exercised the termination option. As a result, this lease will be deemed terminated on August 15, 2018.

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.

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." The following table sets forth, for the periods indicated, the high and low prices per share for our common stock as reported on the NASDAQ Global Select Market:

	High	Low
2017		
First quarter	$ 8.00	$ 3.26
Second quarter	$ 3.80	$ 2.16
Third quarter	$ 3.10	$ 2.15
Fourth quarter	$ 2.64	$ 1.35
2016		
First quarter	$ 10.51	$ 6.55
Second quarter	$ 9.49	$ 5.58
Third quarter	$ 7.63	$ 6.13
Fourth quarter	$ 6.90	$ 3.76

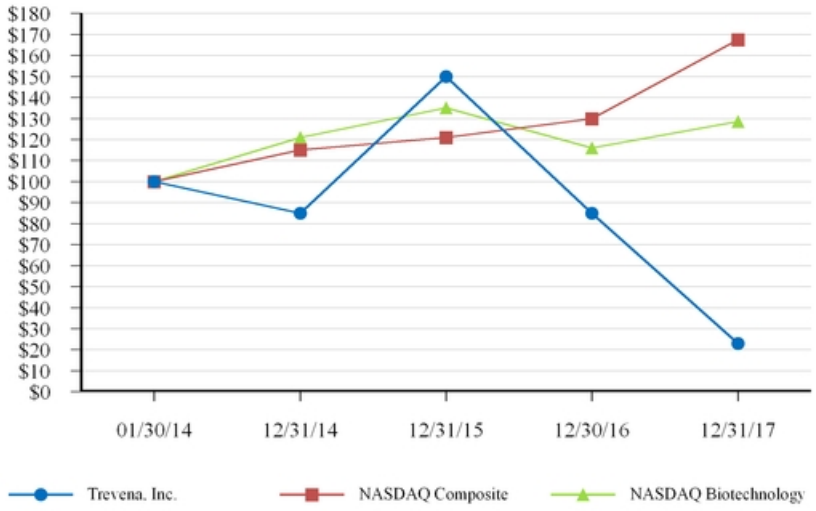
On March 2, 2018, there were 6 holders of record of our common stock and the closing price of our common stock was $1.85 per share.

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 Pacific Western Bank.

Performance Graph

The following graph compares the performance of our common stock since January 30, 2014, the date preceding our initial public offering, or IPO, with the performance of the NASDAQ Composite and NASDAQ Biotechnology indexes. The comparison assumes a $100 investment on January 30, 2014 in our common stock at our IPO price, the stocks comprising the NASDAQ Composite index, and the stocks comprising the NASDAQ Biotechnology index, and assumes reinvestment of the full amount of all dividends, if any. Historical stockholder return is not necessarily indicative of the performance to be expected for any future periods.



The performance graph shall not be deemed to be incorporated by reference by means of any general statement incorporating by reference this Form 10-K into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent that we specifically incorporate such information by reference, and shall not otherwise be deemed filed under such acts.

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, 2017:

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)(3)
Equity compensation plans approved by stockholders	8,417,223	$ 5.28	991,613
Equity compensation plans not approved by stockholders	207,000	2.62	293,000
Total	8,624,223	$ 5.22	1,284,613

(1) Includes 225,806 shares of our common stock issuable under our 2013 Employee Stock Purchase Plan, or the 2013 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 least of (i) 225,806, (ii) the total number of shares of common stock issued under the 2013 ESPP during the immediately preceding calendar year, and (iii) such lower number of shares determined by our Board of Directors.

(2) Includes 991,613 shares of our common stock available for issuance 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: (i) 4% of the number of our shares issued and outstanding prior to the preceding December 31; or (ii) an amount determined by our Board of Directors.

(3) On December 15, 2016, our Board of Directors adopted the Trevena, Inc. Inducement Plan, or the Inducement Plan, which became effective on January 1, 2017, pursuant to which we reserved 500,000 shares of our common stock for issuance under the Inducement Plan. As of December 31, 2017, 293,000 shares remain eligible for issuance under the Inducement Plan.

ITEM 6. SELECTED FINANCIAL DATA

The following tables set forth our selected financial data for the periods indicated. The following statement of operations data for the years ended December 31, 2017, 2016 and 2015 and the selected balance sheet data as of December 31, 2017 and 2016 are derived from our audited financial statements appearing elsewhere in this report. The statement of operations data for the years ended December 31, 2014 and 2013, and the balance sheet data as of December 31, 2015, 2014, and 2013, have been derived from our audited financial statements that are not included herein.

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,				
	2017	2016	2015	2014	2013
Statement of Operations Data:	(in thousands, except share and per share data)				
Revenue					
Total revenue	$ —	$ 3,750	$ 6,250	$ —	$ 135
Operating expenses:					
General and administrative	19,639	16,077	12,797	9,403	4,718
Research and development	48,974	89,956	44,074	40,547	18,762
Restructuring charges	1,774	—	—	—	—
Total operating expenses	70,387	106,033	56,871	49,950	23,480
Loss from operations	(70,387)	(102,283)	(50,621)	(49,950)	(23,345)
Total other income	(1,478)	(711)	93	249	94
Net loss	(71,865)	(102,994)	(50,528)	(49,701)	(23,251)
Accretion of redeemable convertible preferred stock	—	—	—	(29)	(334)
Net loss attributable to common stockholders	$ (71,865)	$ (102,994)	$ (50,528)	$ (49,730)	$ (23,585)
Net loss per share—basic and diluted	$ (1.21)	$ (1.97)	$ (1.15)	$ (2.02)	$ (29.71)
Weighted average shares of common stock outstanding used in computing net loss per share—basic and diluted	59,436,649	52,398,521	43,794,276	24,655,603	793,806

	As of December 31,				
	2017	2016	2015	2014	2013
	(in thousands)				
Balance Sheet Data:					
Cash and cash equivalents	$ 16,557	$ 24,266	$ 46,774	$ 36,206	$ 37,965
Marketable securities	49,543	86,335	125,864	70,699	—
Total assets	72,722	114,654	175,354	108,337	42,393
Total liabilities	38,089	36,073	32,223	9,134	3,401
Total redeemable convertible preferred stock	—	—	—	—	120,562
Total stockholders' equity (deficit)	34,633	78,581	143,131	99,204	(81,571)

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 product candidates:

- *OLINVO™ (oliceridine) Injection:* We are developing OLINVO, a G protein biased ligand of the μ opioid receptor, for the management of moderate-to-severe acute pain where intravenous, or IV, administration is preferred. In February 2017, we announced positive top-line results from our Phase 3 APOLLO-1 and APOLLO-2 pivotal efficacy studies of OLINVO in moderate-to-severe acute pain following bunionectomy and abdominoplasty, respectively. In both studies, all dose regimens achieved their primary endpoint of statistically greater analgesic efficacy than placebo, as measured by responder rate. In July 2017, we announced that we had completed enrollment in the Phase 3 open-label ATHENA safety study to support the new drug application, or NDA, for OLINVO. In the study, 768 patients were administered OLINVO to manage pain associated with a wide range of procedures and diagnoses. In January 2018, we announced that the United States Food and Drug Administration, or FDA, had accepted the NDA we submitted for OLINVO. The FDA also indicated that the Prescription Drug User Fee Act, or PDUFA, review date for the OLINVO NDA is November 2, 2018 and that it plans to hold an advisory committee meeting to discuss the NDA. If OLINVO ultimately receives regulatory approval, we plan to commercialize it in the United States, either on our own or with a commercial partner, for use in acute care settings such as hospitals and ambulatory surgery centers; outside the United States, we plan to commercialize OLINVO in certain countries with a commercial partner. We currently hold all worldwide development and commercialization rights to OLINVO.

- *TRV250:* We are developing TRV250, a G protein biased ligand targeting the δ-receptor, as a compound with a potential first-in-class, non-narcotic mechanism for the treatment of migraine. TRV250 also may have utility in a range of other central nervous system, or CNS, indications. Because TRV250 selectively targets the δ-receptor, we believe it will not have the addiction liability of conventional opioids or other μ opioid related adverse effects like those seen with morphine or oxycodone. In the second quarter of 2017, we began a Phase I study of TRV250 in the United Kingdom in healthy volunteers; we expect to complete dosing in this study by the end of the first quarter of 2018.

We have also identified and have completed the initial Phase 1 studies for TRV734, an orally administered new chemical entity expected to be used for first-line treatment of moderate-to-severe acute and chronic pain. We intend to continue to focus our efforts for TRV734 on securing a development and commercialization partner for this asset.

Since our incorporation in late 2007, our operations have included organizing and staffing our company, business planning, raising capital, and discovering and developing our product candidates. We have financed our operations primarily through private placements and public offerings of our equity securities and debt borrowings. As of December 31, 2017, we had an accumulated deficit of $357.5 million. Our net loss was $71.9 million, $103.0 million and $50.5 million for the years ended December 31, 2017, 2016 and 2015, respectively. Our ability to become and remain profitable depends on our ability to generate revenue or sales. We do not expect to generate significant revenue or sales unless and until we or a collaborator obtain marketing approval for and commercialize OLINVO, TRV250 or TRV734.

In September 2014, we announced we had entered into a $35 million senior secured tranched term loan credit facility with Oxford Finance LLC and Pacific Western Bank (formerly Square 1 Bank), of which we have drawn $28.5 million as of December 31, 2017. As of January 1, 2018, we began making monthly payments of both principal and interest, which will be required until the loan maturity of March 1, 2020.

On October 11, 2017, upon the approval of our board of directors, we announced a restructuring and reduction in force of approximately 30% of our workforce, or 21 employees, as well as other cost saving initiatives. The restructuring was completed as of October 13, 2017. In connection with the restructuring, we announced an updated strategy to focus our resources on the potential approval and commercialization of OLINVO in the United States. With this strategic repositioning,

we halted our investment in early stage research. We intend to complete the ongoing Phase 1 trial of TRV250 for acute migraine, after which we will assess options for further development of this asset, as well as for our series of novel S1P modulators for neuropathic pain.

We expect to incur significant expenses and operating losses for the foreseeable future as we continue the development and clinical trials of, seek regulatory approval for, and prepare for commercialization of our product candidates and repay our outstanding loan obligations. If we obtain regulatory approval for OLINVO, we expect to incur significant expenses associated with the launch of this product. We will need to obtain substantial additional funding in connection with our continuing operations. We will seek to fund our operations through the sale of equity, debt financings or other sources, including potential 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 our operations, development programs, and/or any future commercialization efforts.

Senior Secured Tranched Term Loan Credit Facility

In September 2014, we entered into a loan and security agreement with Oxford Finance LLC and Pacific Western Bank, or the lenders, pursuant to which they agreed to lend us up to $35 million in a three-tranche series of term loans (Term Loans A, B, and C). Upon initially entering into the agreement, we borrowed $2 million under Term Loan A. On April 13, 2015, we amended the agreement with the lenders to change the draw period for Term Loan B. On December 23, 2015, we further amended the agreement with the lenders to, among other things, change the draw period for Term Loan C, modify the interest only period, and modify the maturity date of the loan. In December 2015, we borrowed the Term Loan B tranche of $16.5 million. Our ability to draw an additional $16.5 million under Term Loan C was subject to the satisfaction of one or more specified triggers related to the results of our Phase 2b clinical trial of TRV027. Although those triggers were not attained, in December 2016, we and the lenders modified the terms and conditions under which we could exercise an option to draw $10 million of Term Loan C. In March 2017, we borrowed the Term Loan C tranche of $10.0 million.

Borrowings under Terms Loans A and B accrue interest at a fixed rate of 6.50% per annum. Borrowings under Term Loan C accrue interest at a fixed rate of 6.98% per annum. We were required to make payments of interest only on borrowings under the loan agreement on a monthly basis through and including January 1, 2018; as of January 1, 2018, payments of principal in equal monthly installments and accrued interest have been and will be due until the loan matures on March 1, 2020. Upon the last payment date of the amounts borrowed under the agreement, we will be required to pay a final payment fee equal to 6.6% of the aggregate amounts borrowed. In addition, if we repay Term Loan A, Term Loan B, or Term Loan C prior to the applicable maturity date, we will pay the lenders a prepayment fee of 1.0% of Term Loans A and B respectively, and 3.0% of Term Loan C if the prepayment occurs on or before March 31, 2018, 2.0% of Term Loan C if the prepayment occurs on or between April 1, 2018 and March 31, 2019, and 1.0% of the Term Loan C if the prepayment occurs on or after April 1, 2019.

Our obligations are secured by a first priority security interest in substantially all of our assets, including our cash and cash equivalents and marketable securities, but excluding our intellectual property (together, the collateral). In addition, we have agreed not to pledge or otherwise encumber our intellectual property, with specified exceptions. Upon an event of default, the lenders have the right to foreclose upon the available collateral, including our existing cash and cash equivalents and marketable securities.

In connection with entering into the original agreement, we issued to the lenders and placement agent warrants to purchase an aggregate of 7,678 shares of our common stock, of which 5,728 shares remain outstanding as of December 31, 2017. 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. In connection with the draw of Term Loan B, we issued to the lenders and placement agent additional warrants to purchase an aggregate of 34,961 shares of our common stock. These warrants have substantially the same terms as those noted above, and have an exercise price of $10.6190 per share and an expiration date of December 23, 2025. In connection with the draw of Term Loan C, we issued to the lenders and placement agent additional warrants to purchase an aggregate of 62,241 shares of our common stock. These warrants have substantially the same terms as those noted above, and have an exercise price of $3.6150 per share and an expiration date of March 31, 2027. 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.

Option Agreement with Allergan plc

In May 2013, we entered into an agreement with Allergan, under which we granted to Allergan an exclusive option to license TRV027. We received no consideration upon the grant of the option to Allergan. In March 2015, we signed a letter agreement with Allergan pursuant to which Allergan paid us $10 million to fund the expansion of the Phase 2b trial of TRV027 in AHF from 500 patients to 620 patients. The $10 million received in March 2015 was recorded as deferred revenue. The collaboration revenue was recorded on a straight-line basis through the expected term of the trial and was fully recognized as of June 30, 2016. In August 2016, Allergan notified us of its decision to not exercise its option. As such, we have retained all rights to TRV027.

Critical Accounting Policies and Significant Judgments and Estimates

The preparation of our consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of our financial statements, as well as the reported revenues and expenses during the reported periods. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

A summary of our significant accounting policies appears in the notes to our audited consolidated financial statements for the year ended December 31, 2017 included in this annual report on Form 10-K. However, we believe that the following accounting policies are important to understanding and evaluating our reported financial results, and we have accordingly included them in this discussion.

Research and Development

In connection with our October 2017 restructuring, we announced an updated strategy to focus our resources on the potential approval and commercialization of OLINVO in the United States. With this strategic repositioning, we halted our investment in early stage research. We intend to complete the ongoing Phase 1 trial of TRV250 for acute migraine, after which we will assess options for further development of this asset, as well as for our series of novel S1P modulators for neuropathic pain.

Research and development cost are charged to expense as incurred. Research and development costs include, but are not limited to, personnel expenses, clinical trial supplies, fees for clinical trial services, manufacturing costs, consulting costs and allocated overhead, including rent, equipment, depreciation and utilities.

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 us by our 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.

As part of the process of preparing our financial statements, we are required to estimate our expenses resulting from our 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. Our objective is to reflect the appropriate trial expenses in our financial statements by matching those expenses with the period in which services are performed and efforts are expended. We may account for these expenses according to the progress of the trial as measured by subject progression and the timing of various aspects of the trial. We determine 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, we adjust our clinical expense recognition if actual results differ from estimates. We make estimates of our accrued expenses as of each balance sheet date based on the facts and circumstances known to us at that time. Our clinical trial accruals are dependent upon the timely and accurate reporting of contract research organizations and other third party vendors. Although we do not expect our estimates to be materially different from amounts actually incurred, our 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, 2017, 2016 and 2015, there were no material adjustments to our prior period estimates of accrued expenses for clinical trials.

Stock-Based Compensation

We have applied the fair value recognition provisions of Financial Accounting Standards Board Accounting Standards Codification Topic 718,*Compensation — Stock Compensation*, or ASC 718, to account for stock-based compensation for employees. We recognize compensation costs related to stock options granted to employees based on the estimated fair value of the awards on the date of grant.

We have equity incentive plans under which various types of equity-based awards including, but not limited to, incentive stock options, non-qualified stock options, and restricted stock awards, may be granted to employees, non-employee directors, and non-employee consultants.We also have an inducement plan under which various types of equity-based awards, including non-qualified stock options and restricted stock awards, may be granted to new employees.

For stock options granted to employees and directors, we recognize compensation expense for all stock-based awards based on the estimated grant-date fair values. For restricted stock awards to employees, the fair value is based on the closing price of the Company's common stock on the date of grant. The value of the portion of the award that is ultimately expected to vest is recognized as expense ratably over the requisite service period. The fair value of stock options is determined using the Black-Scholes option pricing model. We utilize a dividend yield of zero based on the fact that we have never paid cash dividends and have no current intention of paying cash dividends. In connection with the early adoption of ASU 2016-9 in the quarter ended December 31, 2016, we elected an accounting policy to record forfeitures as they occur.

See Note 7 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 all years presented.

Recent Accounting Pronouncements

See Note 2, *Summary of Significant Accounting Policies,* to the consolidated financial statements included in Part II of this annual report on Form 10-K for information on recent accounting pronouncements.

JOBS Act

The Jumpstart Our Business Startups Act of 2012, or 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
(in thousands, except per share data)

Comparison of Years Ended December 31, 2017 and 2016

	Year Ended December 31,		
	2017	2016	Change
Revenue:			
Collaboration revenue	$ —	$ 3,750	$ (3,750)
Total revenue	—	3,750	(3,750)
Operating expenses:			
General and administrative	19,639	16,077	3,562
Research and development	48,974	89,956	(40,982)
Restructuring	1,774	—	1,774
Total operating expenses	70,387	106,033	(35,646)
Loss from operations	(70,387)	(102,283)	31,896
Other income (expense):			
Change in fair value of warrant liability	65	78	(13)
Miscellaneous income	614	222	392
Net (loss) gain on asset disposals	(56)	(16)	(40)
Interest income	679	743	(64)
Interest expense	(2,780)	(1,738)	(1,042)
Total other (expense) income	(1,478)	(711)	(767)
Net loss attributable to common stockholders	$ (71,865)	$ (102,994)	$ 31,129

Revenue

To date, we have derived revenue principally from research grants and collaboration arrangements. In March 2015, we signed a letter agreement with Allergan plc pursuant to which it paid us $10.0 million to fund the expansion of our Phase 2b trial of TRV027 from 500 patients to 620 patients. The collaboration revenue was recorded on a straight-line basis over the remaining period of the trial and was fully recognized as of June 30, 2016.

General and administrative expense

General and administrative expenses consist principally of salaries and related costs for personnel in our executive, finance, commercial, and other administrative areas, including stock-based compensation and travel expenses. Other general and administrative expenses include professional fees for legal, market research, consulting, and accounting services.

General and administrative expenses increased by $3.6 million, or 22%, for the year endedDecember 31, 2017 compared to the same period in2016, primarily as a result of increased headcount and associated salary, bonus and stock compensation expenses, OLINVO market research expenditures, and increased facility expenditures associated with the relocation of our corporate headquarters to Chesterbrook, Pennsylvania, in July 2017.

Research and development expense

Research and development expenses consist primarily of costs incurred for research and the development of our product candidates. In addition, research and development expenses include salaries and related costs for our research and development personnel and stock-based compensation and travel expenses for such individuals.

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.

Research and development expenses decreased by $41.0 million, or 46%. The following table summarizes our research and development expenses (in thousands):

	Year Ended December 31,	
	2017	2016
Personnel-related costs	$ 12,115	$ 12,499
OLINVO	28,688	63,156
TRV027	99	6,890
TRV250	3,629	2,970
Other research and development	4,443	4,441
	$ 48,974	$ 89,956

The decrease in research and development expenses during the year endedDecember 31, 2017 was due to decreased expenditures upon completion of the OLINVO Phase 3 clinical program and the second quarter 2016 completion of a TRV027 Phase 2b clinical trial in AHF.

Restructuring Expense

On October 11, 2017, upon the approval of our board of directors, we announced a restructuring and reduction in force of approximately 30% of our workforce, or 21 employees, as well as other cost saving initiatives. The Company incurred pre-tax restructuring charges of $1.8 million during the year ended December 31, 2017, primarily related to severance and lease termination payments for our office and laboratory space in King of Prussia, PA and vivarium space in Exton, PA .

Other Income (Expense)

Other expense increased during the year ended December 31, 2017 primarily due to interest expense related to our Term Loan C tranche of $10.0 million that was drawn in December 2016.

Comparison of Years Ended December 31, 2016 and 2015

	Year Ended December 31,		
	2016	2015	Change
Revenue:			
Collaboration revenue	$ 3,750	$ 6,250	$ (2,500)
Total revenue	3,750	6,250	(2,500)
Operating expenses:			
General and administrative	16,077	12,797	3,280
Research and development	89,956	44,074	45,882
Total operating expenses	106,033	56,871	49,162
Loss from operations	(102,283)	(50,621)	(51,662)
Other income (expense):			
Change in fair value of warrant liability	78	(70)	148
Miscellaneous income	222	174	48
Net (loss) gain on asset disposals	(16)	(8)	(8)
Interest income	743	331	412
Interest expense	(1,738)	(334)	(1,404)
Total other (expense) income	(711)	93	(804)
Net loss	(102,994)	(50,528)	(52,466)

Revenue

The decrease in collaboration revenue was due to the March 2015 Allergan payment of $10.0 million, which was recognized on a straight-line basis and was fully recognized as of June 30, 2016.

General and administrative expense

General and administrative expenses increased by $3.3 million, or 26%, for the year endedDecember 31, 2016 compared to the same period in2015, primarily as a result of increased headcount and associated salary, bonus and stock compensation expenses, and market research expenditures.

Research and development expense

Research and development expenses increased by $45.9 million, or 104%, from $44.1 million for the year endedDecember 31, 2015 to $90.0 million for the year ended December 31, 2016. The following table summarizes our research and development expenses (in thousands):

	Year Ended December 31,	
	2016	2015
Personnel-related costs	$ 12,499	$ 9,646
OLINVO	63,156	16,916
TRV027	6,890	11,851
TRV250	2,970	1,014
Other research and development	4,441	4,647
	$ 89,956	$ 44,074

The increase for the year ended December 31, 2016 was primarily driven by (i) increased expenditures on the development of OLINVO including expenses associated with initiating our Phase 3 program in 2016 partially offset by a decrease in expenses primarily associated with the completion of the OLINVO Phase 2b abdominoplasty clinical trial in 2015, (ii) the initiation of the TRV250 IND-enabling studies during 2016, and (iii) increased headcount and associated salary, benefits, and stock based compensation expense, all partially offset by(iv) decreased expenditures on the development of TRV027 due to the completion of the Phase 2b study in June 2016.

Liquidity and Capital Resources
(in thousands, except per share data)

We incurred net losses of $71.9 million, $103.0 million, and $50.5 million for the years endedDecember 31, 2017, 2016, and 2015, respectively. Net cash used in operating activities was $71.3 million, $91.6 million, and $40.1 million for those same periods. At December 31, 2017, we had an accumulated deficit of $357.5 million, working capital of $49.3 million, cash and cash equivalents of $16.6 million, and marketable securities of $49.5 million.

Cash Flows

The following table summarizes our cash flows (in thousands):

	Year Ended December 31,		
	2017	2016	2015
Net cash (used in) provided by:			
Operating activities	$ (71,255)	$ (91,554)	$ (40,075)
Investing activities	32,780	37,798	(56,939)
Financing activities	30,986	32,329	107,582
Net (decrease) increase in cash and cash equivalents	$ (7,489)	$ (21,427)	$ 10,568

Net cash used in operating activities

Net cash used in operating activities was $71.3 million for the year endedDecember 31, 2017 and consisted primarily of a net loss of $71.9 million. Cash outflows were partially offset by non-cash expense for stock compensation of $6.4 million, a decrease in accounts payable and accrued expenses of $8.4 million primarily associated with the completion of the Phase 3 OLINVO clinical trials, and other non-cash adjustments.

Net cash used in operating activities was $91.6 million for the year endedDecember 31, 2016 and consisted primarily of a net loss of $103.0 million and net cash outflows from a decrease in deferred revenue of $3.8 million. These cash outflows were partially offset by non-cash expense for stock compensation of $5.9 million, an increase in accounts payable and accrued

expenses of $7.1 million primarily associated with the Phase 3 OLINVO clinical trials, and other non-cash adjustments in our net loss totaling $2.2 million.

Net cash used in operating activities was $40.1 million for the year endedDecember 31, 2015, consisting primarily of a net loss of $50.5 million partially offset by noncash adjustments of $5.1 million and changes in operating assets and liabilities of $5.3 million. Changes in operating assets and liabilities were primarily driven by an increase of deferred revenue of $3.8 million associated with the payment received from Allergan in March 2015 and an increase in accounts payable and accrued expenses of $2.8 million, partially offset by a decrease in prepaid expenses and other assets of $1.2 million.

Net cash provided by (used in) investing activities

Net cash provided by investing activities for the years endedDecember 31, 2017 and 2016 was $32.8 million and $37.8 million, respectively, and was primarily from the maturities of marketable securities. 2017 also included expenditures related to the July 2017 relocation of our corporate headquarters to Chesterbrook, Pennsylvania. Net cash used in investing activities for the year ended December 31, 2015 was $56.9 million and was primarily due to purchases of marketable securities.

Net cash provided by financing activities

Net cash provided by financing activities was $31.0 million for the year endedDecember 31, 2017, which was primarily due to net proceeds of $20.7 million from the sale of common stock through our at-the-market, or ATM, sales facility with Cowen and Company, LLC, or Cowen, and net proceeds of $9.9 million from the March 31, 2017 draw of Term Loan C.

Net cash provided by financing activities was $32.3 million for the year endedDecember 31, 2016, which was primarily due to net proceeds of $32.1 million from the sale of common stock in February and December 2016 through Cowen pursuant to our ATM sales facility.

Net cash provided by financing activities was $107.6 million for the year endedDecember 31, 2015, which was primarily due to net proceeds of $68.3 million from the public follow-on offering of common stock, net proceeds of $22.0 million from the sale of common stock through Cowen pursuant to our ATM sales facility and $16.4 million of net proceeds from our December 23, 2015 borrowing under our term loan agreement with Oxford Finance LLC and Pacific Western Bank.

All periods presented also include proceeds from exercises of common stock options.

Operating and Capital Expenditure Requirements

We have not achieved profitability since our inception and we expect to continue to incur net losses and negative cash flows from operations for the foreseeable future. We expect our cash expenditures to continue to be significant in the near term as we continue monthly principal and interest repayments on our existing loan facility until March 2020, prepare for future regulatory activities related to the OLINVO NDA, and continue activities in preparation for commercial operations, particularly with respect to expenses associated with the manufacturing, selling, and marketing of OLINVO, if approved by the FDA.

We believe that our cash and cash equivalents and marketable securities as ofDecember 31, 2017, together with interest thereon, and proceeds from the sale of shares of common stock under our ATM facility between January 1, 2018 and the date of this filing, will be sufficient to fund our operating expenses and capital expenditure requirements into the second quarter of 2019. In 2018, we have generated net proceeds of approximately $5.8 million from sales of common stock under the ATM through the date of this filing. We anticipate that we will need to raise substantial additional financing in the future to fund our operations. To meet these requirements, we may seek to sell equity or convertible securities in public or private transactions that may result in dilution to our stockholders. In December 2015, we filed a $250 million shelf registration statement that includes a $75 million ATM sales facility with Cowen acting as our sales agent. Approximately $14.6 million remains available under the ATM sales facility as of the date of this filing. We may offer and sell shares of our common stock under the existing registration statement (including under our ATM facility) or any registration statement we may file in the future. 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.

Ultimately, 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 timing and results of the FDA's review of the NDA submission for OLINVO and related regulatory activities;

- our ability to enter into collaborative agreements for the development and/or commercialization of our product candidates, including for OLINVO;
- the number and development requirements of any other product candidates that we may 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 ofDecember 31, 2017 (in thousands):

	Payments Due By Period				
	Total	Less than 1 year	1 - 3 years	3 - 5 years	More than 5 years
Operating lease obligations(1)	$ 14,385	$ 970	$ 2,627	$ 2,777	$ 8,011
Loans payable	28,500	12,667	15,833	—	—
Total	$ 42,885	$ 13,637	$ 18,460	$ 2,777	$ 8,011

(1) Operating lease obligations reflect our obligation to make payments in connection with the lease for our office spaces, including our current location Chesterbrook, Pennsylvania and our previous location in King of Prussia, Pennsylvania.

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. In December 2016 and October 2017, we entered into manufacturing agreements that are cancelable upon 24 months prior notice of cancellation.

License Agreements and Other Commitments

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 also could 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

Our marketable securities consist of U.S. Treasury and U.S. government agency securities. The market value of such instruments fluctuates with current market interest rates. In general, as rates increase, the market value of a debt instrument would be expected to decrease; the opposite also is true. To minimize market risk, we have in the past held and, to the extent possible, will continue in the future to hold, such debt instruments to maturity at which time the debt instrument will be redeemed at its stated, or face, value. Due to the relatively short duration and nature of these instruments, we do not believe that we have a material exposure to interest rate risk related to our investment portfolio. Our marketable securities at December 31, 2017 totaled $49.5 million, and the weighted-average yield-to-maturity was approximately 1.5% with maturities of investments ranging up to 12 months.

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 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 ofDecember 31, 2017. 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, 2017, our internal control over financial reporting is effective based on those criteria.

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Trevena, Inc.

Opinion on the Financial Statements

We have audited the accompanying balance sheets of Trevena, Inc. (the "Company") as of December 31, 2017 and 2016, the related statements of income and comprehensive loss, stockholders' equity, and cash flows, for each of the three years in the period ended December 31, 2017, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2017 and 2016, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, in conformity with US generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting 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 opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures include examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2007.

Philadelphia, Pennsylvania

March 7, 2018

TREVENA, INC.

Balance Sheets

(in thousands, except share and per share data)

	2017	2016
Assets		
Current assets:		
Cash and cash equivalents	$ 16,557	$ 24,266
Marketable securities	49,543	86,335
Prepaid expenses and other current assets	1,393	1,788
Total current assets	67,493	112,389
Restricted cash	1,413	1,193
Property and equipment, net	3,805	1,059
Intangible asset, net	11	13
Total assets	$ 72,722	$ 114,654
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 1,424	$ 8,749
Accrued expenses and other current liabilities	4,303	8,208
Current portion of loans payable, net	12,425	5,039
Deferred rent	61	52
Total current liabilities	18,213	22,048
Loans payable, net	15,725	13,270
Capital leases, net of current portion	31	18
Deferred rent, net of current portion	3,006	187
Warrant liability	10	75
Other long term liabilities	1,104	475
Total liabilities	38,089	36,073
Commitments and contingencies (Note 8)		
Stockholders' equity:		
Common stock—$0.001 par value; 100,000,000 shares authorized, 62,310,795 and 55,768,414 shares issued and outstanding at December 31, 2017 and December 31, 2016, respectively	62	56
Preferred stock—$0.001 par value; 5,000,000 shares authorized, none issued or outstanding at December 31, 2017 and December 31, 2016	—	—
Additional paid-in capital	392,103	364,148
Accumulated deficit	(357,490)	(285,625)
Accumulated other comprehensive income (loss)	(42)	2
Total stockholders' equity	34,633	78,581
Total liabilities and stockholders' equity	$ 72,722	$ 114,654

See accompanying notes to financial statements.

TREVENA, INC.

Statements of Operations and Comprehensive Loss
(in thousands, except share and per share data)

	Year Ended December 31,		
	2017	2016	2015
Revenue:			
Collaboration revenue	$ —	$ 3,750	$ 6,250
Total revenue	—	3,750	6,250
Operating expenses:			
General and administrative	19,639	16,077	12,797
Research and development	48,974	89,956	44,074
Restructuring charges	1,774	—	—
Total operating expenses	70,387	106,033	56,871
Loss from operations	(70,387)	(102,283)	(50,621)
Other income (expense):			
Change in fair value of warrant liability	65	78	(70)
Miscellaneous income	614	222	174
Net (loss) gain on asset disposals	(56)	(16)	(8)
Interest income	679	743	331
Interest expense	(2,780)	(1,738)	(334)
Total other (expense) income	(1,478)	(711)	93
Net loss attributable to common stockholders	$ (71,865)	$ (102,994)	$ (50,528)
Other comprehensive income (loss), net:			
Unrealized gain (loss) on marketable securities	(44)	208	(187)
Other comprehensive income (loss)	(44)	208	(187)
Comprehensive loss	$ (71,909)	$ (102,786)	$ (50,715)
Per share information:			
Net loss per share of common stock, basic and diluted	$ (1.21)	$ (1.97)	$ (1.15)
Weighted average common shares outstanding, basic and diluted	59,436,649	52,398,521	43,794,276

See accompanying notes to financial statements.

TREVENA, INC.
Statements of Stockholders' Equity
For the Period From January 1, 2015 to December 31, 2017
(in thousands, except share data)

	Stockholders' Equity					
	Common Stock					
	Number of Shares	0.001 Par Value	Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity
Balance, January 1, 2015	39,241,173	$ 39	$ 231,153	$ (131,970)	$ (19)	$ 99,203
Stock-based compensation expense	—	—	3,427	—	—	3,427
Exercise of stock options	384,033	1	905	—	—	906
Net exercise of common stock warrant	2,397	—	—	—	—	—
Issuance of common stock warrants	—	—	4	—	—	4
Issuance of common stock, net of issuance costs	11,175,000	11	90,295	—	—	90,306
Unrealized loss on marketable securities	—	—	—	—	(187)	(187)
Net loss	—	—	—	(50,528)	—	(50,528)
Balance, December 31, 2015	50,802,603	$ 51	$ 325,784	$ (182,498)	$ (206)	$ 143,131
Stock-based compensation expense	—	—	5,903	—	—	5,903
Exercise of stock options	149,622	—	256	—	—	256
Net exercise of common stock warrant	698	—	—	—	—	—
Issuance of common stock, net of issuance costs	4,815,491	5	32,072	—	—	32,077
Unrealized gain on marketable securities	—	—	—	—	208	208
Adjustment to accumulated deficit as a result of adoption of ASU 2016-09	—	—	133	(133)	—	—
Net loss	—	—	—	(102,994)	—	(102,994)
Balance, December 31, 2016	55,768,414	$ 56	$ 364,148	$ (285,625)	$ 2	$ 78,581
Stock-based compensation expense	—	—	6,387	—	—	6387
Exercise of stock options	293,809	—	361	—	—	361
Issuance of common stock warrants	—	—	501	—	—	501
Issuance of common stock, net of issuance costs	6,248,572	6	20,706	—	—	20,712
Unrealized loss on marketable securities	—	—	—	—	(44)	(44)
Net loss	—	—	—	(71,865)	—	(71,865)
Balance, December 31, 2017	62,310,795	$ 62	$ 392,103	$ (357,490)	$ (42)	$ 34,633

See accompanying notes to financial statements.

TREVENA, INC.

Statements of Cash Flows
(in thousands)

	Year Ended December 31,		
	2017	2016	2015
Operating activities:		(in thousands)	
Net loss	$ (71,865)	$ (102,994)	$ (50,528)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	490	246	208
Stock-based compensation	6,387	5,903	3,427
Noncash interest expense on loans	1,050	534	180
Loss on disposal of assets	70	17	11
Revaluation of warrant liability	(65)	(78)	70
Amortization of bond premiums on marketable securities	474	1,334	1,210
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	612	104	(1,224)
Accounts payable and accrued expenses	(8,408)	7,130	2,821
Deferred revenue	—	(3,750)	3,750
Net cash used in operating activities	(71,255)	(91,554)	(40,075)
Investing activities:			
Purchases of property and equipment	(3,495)	(605)	(361)
Purchase of intangible asset	—	—	(15)
Maturities of marketable securities	99,018	115,824	69,827
Purchases of marketable securities	(62,743)	(77,421)	(126,390)
Net cash provided by (used in) investing activities	32,780	37,798	(56,939)
Financing activities:			
Proceeds from exercise of common stock options	361	256	906
Proceeds from loans payable, net	9,921	—	16,368
Proceeds from issuance of common stock, net	20,712	32,077	90,311
Capital lease payments	(8)	(4)	(3)
Net cash provided by financing activities	30,986	32,329	107,582
Net (decrease) increase in cash and cash equivalents	(7,489)	(21,427)	10,568
Cash, cash equivalents, and restricted cash—beginning of period	25,459	46,886	36,318
Cash, cash equivalents, and restricted cash—end of period	$ 17,970	$ 25,459	$ 46,886
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ 1,730	$ 1,204	$ 155
Capital lease additions	$ 27	$ 18	$ —
Fair value of common stock warrants issued	$ 501	$ —	$ 4

See accompanying notes to financial statements.

TREVENA, INC.

Notes to Financial Statements

December 31, 2017

1. Organization and Description of the Business

Trevena, Inc., or 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 biopharmaceutical company developing innovative therapies based on breakthrough science to benefit patients and healthcare providers confronting serious medical conditions. The Company operates in one segment and has its principal office in Chesterbrook, Pennsylvania.

Since commencing operations in 2007, the Company has devoted substantially all of its financial resources and efforts to research and development, including preclinical studies and clinical trials. The Company has never been profitable and has not yet commenced commercial operations. In January 2018, the United States Food and Drug Administration, or FDA, accepted the NDA submission for OLINVO, the Company's lead product candidate. The FDA also indicated that the Prescription Drug User Fee Act, or PDUFA, review date for the OLINVO NDA is November 2, 2018 and that it plans to hold an advisory committee meeting to discuss the NDA. If OLINVO ultimately receives regulatory approval, the Company plans to commercialize it in the United States, either on its own or with a commercial partner, for use in acute care settings such as hospitals and ambulatory surgery centers; outside the United States, the Company plans to commercialize OLINVO in certain countries with commercial partners.

Since the Company's inception, the Company has incurred losses and negative cash flows from operations. At December 31, 2017, the Company had an accumulated deficit of $357.5 million. The Company's net loss was $71.9 million, $103.0 million and $50.5 million for the years ended December 31, 2017, 2016 and 2015, respectively. The Company expects its cash and cash equivalents of $16.6 million and marketable securities of $49.5 million as of December 31, 2017, together with interest thereon, to be sufficient to fund its operating expenses and capital expenditure requirements into the second quarter of 2019.

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, or U.S. 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, or ASC, and Accounting Standards Update, or ASU, of the Financial Accounting Standards Board, or FASB. The Company's functional currency is the U.S. dollar.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumption that affect the amounts reported in the financial statements and accompanying notes. 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 common stock warrants, the accounting for research and development costs, accrued expenses and the recoverability of the Company's net deferred tax assets and related valuation allowance. The financial data and other information disclosed in these notes are not necessarily indicative of the results to be expected for any future year or period. The Company bases its estimates on historical experience and also on assumptions that it believes are reasonable, however, actual results could significantly differ from those results.

Cash and Cash Equivalents and Marketable Securities

The Company considers all highly liquid investments that have maturities of three months or less when acquired to be cash equivalents. Cash equivalents are valued at cost, which approximates their fair market value. The Company maintains a portion of its cash and cash equivalent balances in money market mutual funds that may invest substantially all of their assets in U.S. government agency securities, U.S. Treasury securities or reverse repurchase agreements, or RRAs. RRAs are

collateralized by deposits in the form of 'Government Securities and Obligations' for an amount not less than102% of their value. The Company does not hold any RRAs as of December 31, 2017.

The Company classifies its marketable securities as "available-for-sale", pursuant to ASC Topic 320,*Investments—Debt and Equity Securities*, or ASC 320, carries them at fair market value and classifies them as current assets on its balance sheets. Unrealized gains and losses on marketable securities are recorded as a separate component of accumulated other comprehensive income/(loss) included in stockholders' equity. As of December 31, 2017 and 2016, the Company had $49.5 million and $86.3 million, respectively, in available-for-sale investments, all classified as current assets. See Note 3 for additional information.

The fair value of the Company's investments 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 (loss). If a decline in the fair value is considered other-than-temporary, based on available evidence, the unrealized loss is transferred from other comprehensive income (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. Realized gains (losses) are included in interest income (expense) in the statement of operations and comprehensive income (loss) on a specific identification basis.

Restricted Cash

The Company maintains $1.3 million as collateral under a letter of credit for the Company's facility lease obligations in Chesterbrook, Pennsylvania. The Company also maintains a letter of credit totaling $0.1 million as collateral for the Company's facility lease obligations in King of Prussia, Pennsylvania. The Company has recorded these deposits and accumulated interest thereon as restricted cash on its balance sheet.

Fair Value of Financial Instruments

The carrying amount of the Company's financial instruments, which include cash and cash equivalents, marketable securities, 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, 2017 and 2016 is the nominal value of the loan payable, which is the carrying value, net of debt discount and deferred charges. The nominal value approximates fair value because the interest rate is reflective of the rate the Company could obtain on debt with similar terms and conditions. Certain of the Company's common stock warrants are carried at fair value, as disclosed in Note 3.

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. See Note 3 for additional information.

Concentration of Credit 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'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 has no off-balance sheet concentrations of credit risk such as foreign currency exchange contracts, option contracts or other hedging arrangements.

Property and Equipment

Property and equipment consists of computer and laboratory equipment, software, office equipment, furniture, manufacturing equipment 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,

manufacturing equipment and software. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the asset.

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.

Intangible Asset

The intangible asset recorded in the Company's financial statements is associated with the acquisition of the domain name for the Company's website. Identifiable intangible assets are initially recorded at fair market value at the time of acquisition, utilizing a cost approach and the initial value is amortized over the expected useful life of the asset. The Company also capitalizes costs incurred to renew or extend the term of recognized intangible assets.

The determination of the value of intangible assets requires management to make estimates and assumptions that affect the Company’s consolidated financial statements. The Company assesses potential impairments to intangible assets when there is evidence of events or changes in circumstances that indicate the carrying amount of an asset may not be recovered. The Company’s judgements regarding the existence of impairment indicators and future cash flows related to intangible assets are based on operational performance of the Company, market conditions and other factors. If impairment is indicated, the Company will reduce the carrying value of the intangible assets to fair value. The Company believes the future cash flows to be received from its intangible asset will exceed the intangible asset carrying value, and accordingly, the Company has not recognized any impairment losses through December 31, 2017.

Common Stock Warrants

Freestanding warrants that are related to the purchase of 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. These 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. 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 warrants are classified as Level 3 liabilities. See Note 3 for additional information.

In addition, in connection with entering into loan agreements, the Company has issued warrants to purchase shares of the Company’s common stock. These detachable warrant instruments qualify for equity classification and have been allocated upon the relative fair value of the base instrument and the warrant. See Note 6 for additional information.

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 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 cost are charged to expense as incurred. Research and development costs include, but are not limited to, personnel expenses, clinical trial supplies, fees for clinical trial services, manufacturing costs, consulting costs and allocated overhead, including rent, equipment, depreciation and utilities.

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.

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 may account 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, 2017, 2016 and 2015, there were no material adjustments to the Company's prior period estimates of accrued expenses for clinical trials.

Stock-Based Compensation

At December 31, 2017, the Company had two stock-based compensation plans, which are more fully described in Note 7. The Company has applied the fair value recognition provisions of Financial Accounting Standards Board Accounting Standards Codification Topic 718, *Compensation — Stock Compensation*, to account for stock-based compensation for employees. The Company recognizes compensation costs related to stock options granted to employees based on the estimated fair value of the awards on the date of grant.

The Company has equity incentive plans under which various types of equity-based awards including, but not limited to, incentive stock options, non-qualified stock options, and restricted stock awards, may be granted to employees, non-employee directors, and non-employee consultants. The Company also has an inducement plan under which various types of equity-based awards, including non-qualified stock options and restricted stock awards, may be granted to new employees.

For stock options granted to employees and directors, the Company recognizes compensation expense for all stock-based awards based on the estimated grant-date fair values. For restricted stock awards to employees, the fair value is based on the closing price of the Company's common stock on the date of grant. The value of the portion of the award that is ultimately expected to vest is recognized as expense ratably over the requisite service period. The fair value of stock options is determined using the Black-Scholes option pricing model. The Company utilizes a dividend yield of zero based on the fact that the Company has never paid cash dividends and has no current intention of paying cash dividends. As of fiscal year ended December 31, 2016, the Company adopted the forfeiture rate methodology change in accordance with ASU 2016-9 to record forfeitures as they occur.

See Note 7 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 all years presented.

Income Taxes

Income taxes are recorded in accordance with ASC Topic 740,*Income Taxes*, or 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. To date, the Company has not taken any uncertain tax position or recorded any reserves, interest or penalties.

On December 22, 2017, the U.S. government enacted comprehensive tax legislation commonly referred to as the Tax Cuts and Jobs Act, or the Tax Act. Additionally, the SEC staff issued SAB 118, which provides guidance on accounting for the effects of the Tax Act. See Note 13.

Comprehensive Income (Loss)

Comprehensive income (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 income (loss) relates to unrealized investment gains or losses on the Company's marketable securities for all periods presented.

Basic and Diluted Net Loss Per Share of Common Stock

The Company's basic net loss per share is calculated by dividing the net loss by the weighted average number of shares of common stock outstanding for the period. The diluted net loss per common share is computed by giving effect to all potential dilutive common stock equivalents outstanding for the period. 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 all periods presented.

Recently Adopted Accounting Standards

In March 2016, the FASB issued ASU 2016-09,*Improvements to Employee Share-Based Payment Accounting,* or ASU 2016-09, which amends ASC Topic 718, *Compensation— Stock Compensation*. ASU 2016-09 is designed to simplify several aspects of accounting for share-based payment award transactions that include the income tax consequences, classification of awards as either equity or liabilities, and classification of excess tax benefits on the statement of cash flows. This guidance also permits an accounting policy election to either estimate the number of awards that are expected to vest or account for forfeitures when they occur. The Company elected to early adopt the standard during the three months ended December 31, 2016 and has elected to recognize forfeitures as they occur. The adoption did not have a material effect on the Company's interim and annual 2016 financial statements.

Recent Accounting Standards Not Yet Adopted

In February 2018, the FASB issued ASU 2018-02,*Reclassification of Certain Tax Effects from Accumulated Other Comprehensive Income*, which provides the option to reclassify stranded tax effects within accumulated other comprehensive income to retained earnings. This option would be available in each period in which the effect of the change in the U.S. federal corporate income tax rate in the Tax Cuts and Jobs Act (or a portion thereof) is recorded. This is effective for the Company beginning after December 15, 2018, with early adoption permitted. These amendments should be applied in the period of adoption or retrospectively to each period in which the effect of the change in the U.S federal corporate income tax rate in the Tax Cuts and Jobs Act is recognized. The Company is evaluating the effect this standard will have on its financial statements and related disclosures. See Note 13.

In May 2017, the FASB issued ASU No. 2017-09,*Stock Compensation - Scope of Modification Accounting,*which amends the scope of modification accounting for share-based payment arrangements. The amendment provides guidance about which changes to the terms or conditions of a share-based payment award require an entity to apply modification accounting.

The new standard is effective for fiscal years beginning after December 15, 2017. The Company is currently evaluating the effect that this guidance may have on its consolidated financial statements.

In August 2016, the FASB issued ASU 2016-15,*Statement of Cash Flows (Topic 230),* to clarify how certain cash receipts and payments should be presented in the statement of cash flows. The standard is effective for annual periods beginning after December 15, 2017 and interim periods within that reporting period. Early adoption is permitted. The Company is evaluating the effect this standard will have on its financial statements and related disclosures.

In February 2016, the FASB issued ASU 2016-02,*Leases (Topic 842*), which requires lessees to record most leases on their balance sheets and disclose key information about leasing arrangements in an effort to increase transparency and comparability among organizations. The standard is effective for annual periods beginning after December 15, 2018 and interim periods within that reporting period. Early adoption is permitted. The Company is evaluating the effect this standard will have on its financial statements and related disclosures.

In May 2014, the FASB issued ASU 2014-09,*Revenue from Contracts with Customers.* ASU 2014-09 is a comprehensive new revenue recognition model requiring a company to recognize revenue to depict the transfer of goods or services to a customer in an amount reflecting the consideration it expects to receive in exchange for those goods or services. Additionally, in March 2016, the FASB issued ASU 2016-08, *Revenue from Contracts with Customers, Principal versus Agent Considerations.* ASU 2016-08 amends the principal versus agent guidance in ASU 2014-09 to clarify how an entity should identify the unit of accounting for the principal versus agent evaluation and how it should apply the control principal to certain types of arrangements. The effective date for both standards is January 1, 2018, with an option that permits companies to adopt the standard as early as the January 1, 2017. Early application prior to the January 1, 2017 is not permitted. The Company has determined that they will elect the modified retrospective transition method, meaning the cumulative effect of applying the new guidance is recognized at the date of initial application as an adjustment to the opening accumulated deficit balance. Since the Company does not have any open contracts with customers as of December 31, 2017, the adoption of this standard is not expected to have a material impact on the Company's financial statements.

3. Fair Value of Financial Instruments

ASC Topic 820, *Fair Value Measurement,* or 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 measurements, ASC 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.

Cash, Cash Equivalents, Restricted Cash, and Marketable Securities

The following table presents the Company's cash, cash equivalents, restricted cash, and marketable securities as of December 31, 2017 and 2016 (in thousands):

	December 31, 2017						
	Adjusted Cost	Unrealized Gains	Unrealized Losses	Fair Value	Cash and Cash Equivalents	Restricted Cash	Marketable Securities
Cash	$ 6,783	$ —	$ —	$ 6,783	$ 5,370	$ 1,413	$ —
Level 1 (1):							
Money market funds	11,187	—	—	11,187	11,187	—	—
U.S. treasury securities	1,991	—	—	1,991	—	—	1,991
Subtotal	13,178	—	—	13,178	11,187	—	1,991
Level 2 (2):							
U.S. government agency securities	47,594	—	(42)	47,552	—	—	47,552
Total	$ 67,555	$ —	$ (42)	$ 67,513	$ 16,557	$ 1,413	$ 49,543

	December 31, 2016						
	Adjusted Cost	Unrealized Gains	Unrealized Losses	Fair Value	Cash and Cash Equivalents	Restricted Cash	Marketable Securities
Cash	$ 13,756	$ —	$ —	$ 13,756	$ 12,563	$ 1,193	$ —
Level 1 (1):							
Money market funds	10,043	—	—	10,043	10,043	—	—
Level 2 (2):							
Repurchase agreements	1,660			1,660	1,660		
U.S. government agency securities	86,333	19	(17)	86,335	—	—	86,335
Subtotal	87,993	19	(17)	87,995	1,660	—	86,335
Total	$ 111,792	$ 19	$ (17)	$ 111,794	$ 24,266	$ 1,193	$ 86,335

(1) The fair value of Level 1 securities is estimated based on quoted prices in active markets for identical assets or liabilities.

(2) The fair value of Level 2 securities is estimated based on observable inputs other than quoted prices in active markets for identical assets and liabilities, quoted prices for identical or similar assets or liabilities in inactive markets, or other inputs that are observable or can be corroborated by observable market data for substantially the full term on the assets or liabilities.

The Company classifies investments available to fund current operations as current assets on its balance sheets. As of December 31, 2017, the Company did not hold any investment securities exceeding a one-year maturity.

Unrealized gains and losses on marketable securities are recorded as a separate component of accumulated other comprehensive income (loss) included in stockholders' equity. Realized gains (losses) are included in interest income (expense) in the statement of operations and comprehensive income (loss) on a specific identification basis. The Company did not record any realized gains or losses during the years ended December 31, 2017 and 2016. To date, the Company has not recorded any impairment charges on marketable securities related to other-than-temporary declines in market value.

The Company recognizes transfers between levels of the fair value hierarchy as of the end of the reporting period. We do not hold Level 3 securities, and therefore, there were no transfers in or out of Level 3 in the hierarchy during the years ended December 31, 2017 or 2016.

Warrant Liability

At December 31, 2017, there is an outstanding warrant to purchase up to 20,161 shares of the Company's common stock with a fair value recorded as a liability as it contains a cash settlement feature upon certain strategic transactions. The following table sets forth a summary of changes in the fair value of this 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 (in thousands):

	Warrant Liability
Balance as of January 1, 2016	$ 153
Amounts acquired or issued	—
Changes in estimated fair value	(78)
Balance as of December 31, 2016	75
Amounts acquired or issued	—
Changes in estimated fair value	(65)
Balance as of December 31, 2017	$ 10

On each re-measurement date, the fair value of the warrant classified as a liability 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, 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, 2017 and 2016 to determine the warrant liability:

	December 31,	
	2017	2016
Estimated remaining term	4.3 years	5.3 years
Risk-free interest rate	2.1%	2.0%
Volatility	77.6%	77.2%
Dividend yield	—%	—%
Fair value of underlying instrument*	$ 1.60	$ 5.88

*Trevena, Inc. closing stock price.

The warrant liability is recorded on its own line item on the Company's balance sheets and is marked-to-market at each reporting period with the change in fair value recorded on its own line in the statements of operations and comprehensive loss.

In addition to the outstanding warrant to purchase 20,161 shares of common stock discussed above, the Company has outstanding warrants to purchase an aggregate of 102,930 shares of the Company's common stock. These warrants qualify for equity classification and have been allocated upon the relative fair value of the base instrument and the warrant. See Note 6 for additional information.

4. Property and Equipment, net

Property and equipment consisted of the following (in thousands):

	Estimated Useful Life in Years	December 31, 2017	December 31, 2016
Laboratory equipment	5	$ —	$ 1,935
Computers and software	3 - 5	749	521
Office equipment and furniture	5	872	314
Manufacturing equipment	5	242	242
Leasehold improvements	5 - 10	4,824	2,150
Leased assets	5	59	32
Total property and equipment		6,746	5,194
Less accumulated depreciation and amortization		(2,941)	(4,135)
Property and equipment, net		$ 3,805	$ 1,059

Depreciation and amortization expense was $0.5 million, $0.2 million, and $0.2 million for the years ended December 31, 2017, 2016 and 2015, respectively.

5. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following (in thousands):

	December 31, 2017	December 31, 2016
Compensation and benefits	$ 2,489	$ 2,680
Clinical trial expenses	—	5,479
Restructuring (severance)	1,077	—
Pharmaceutical development expenses	444	—
Accrued interest	158	—
Other accrued expenses and other current liabilities	135	49
Total accrued expenses and other current liabilities	$ 4,303	$ 8,208

6. Loans Payable

In September 2014, the Company entered into a loan and security agreement with Oxford Finance LLC and Pacific Western Bank (formerly Square 1Bank) (together, the lenders), pursuant to which the lenders agreed to lend the Company up to $35.0 million in a three-tranche series of term loans (Term Loans A, B, and C). Upon initially entering into the agreement, the Company borrowed $2.0 million under Term Loan A. In April 2015, the Company amended the agreement with the lenders to change the draw period for Term Loan B. In December 2015, the Company further amended the agreement with the lenders to, among other things, change the draw period for Term Loan C, modify the interest only period, and modify the maturity date of the loan. In December 2015, the Company borrowed the Term Loan B tranche of $16.5 million. The Company's ability to draw an additional $16.5 million under Term Loan C was subject to the satisfaction of one or more specified triggers related to the results of the Company's Phase 2b clinical trial of TRV027, which were announced in May 2016. Although those triggers were not attained, in December 2016, the Company and the lenders modified the terms and conditions under which the Company could exercise an option to draw $10.0 million of Term Loan C. In March 2017, the Company borrowed the Term Loan C tranche of $10.0 million.

Borrowings under Term Loans A and B accrue interest at a fixed rate of6.50% per annum. Borrowings under Term Loan C accrue interest at a fixed rate of6.98% per annum. The Company is required to make payments of interest only on borrowings under the loan agreement on a monthly basis through and including January 1, 2018, after which payments of principal in equal monthly installments and accrued interest will be due until the loan matures on March 1, 2020. Upon the last payment date of the amounts borrowed under the agreement, the Company will be required to pay a final payment fee equal to 6.6% of the aggregate amounts borrowed, which is recorded as interest expense over the term of the loans payable. In addition, if the Company repays Term Loan A, Term Loan B, or Term Loan C prior to the applicable maturity date, it will pay the lenders a prepayment fee of 1.0% of Term Loans A and B respectively, and 3.0% of Term Loan C if the prepayment occurs on or before March 31, 2018,2.0% of Term Loan C if the prepayment occurs on or between April 1, 2018 and March 31, 2019, and 1.0% of the Term Loan C if the prepayment occurs on or after April 1, 2019.

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, including the Company's cash, cash equivalents, and marketable securities but excluding the Company's intellectual property (together, the collateral). 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 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 Company's business, operations or condition (financial or otherwise), a material impairment in the value of the collateral or in the prospect of repayment of the Company's obligations to the lender, certain levies, attachments and other restraints on the Company's business, insolvency, defaults under other agreements and misrepresentations. Upon an event of default, the lenders have the right to foreclose upon the available collateral, including the Company's existing cash and cash equivalents and marketable securities.

In connection with entering into the agreement, the Company issued to the lenders and the placement agent warrants to purchase an aggregate of 7,678 shares of Trevena common stock, of which 5,728 shares remain outstanding as of December 31, 2017. 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. 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 the Company is not the surviving entity. In connection with the draw of Term Loan B, the Company issued to the lenders and the placement agent additional warrants to purchase an aggregate of 34,961 shares of Trevena common stock. These warrants have substantially the same terms as those noted above, have an exercise price of $10.6190 per share and an expiration date of December 23, 2025. In connection with draw of Term Loan C, the Company issued to the lenders and placement agent additional warrants to purchase an aggregate of 62,241 shares of our common stock. These warrants have substantially the same terms as those noted above, and have an exercise price of $3.6150 per share and an expiration date of March 31, 2027.

As of December 31, 2017, borrowings of $28.5 million attributable to Term Loans A, B and C are outstanding. Interest expense of $1.7 million, $1.2 million and $0.2 million was recorded during the years ended December 31, 2017, 2016 and 2015, respectively. The Company incurred lender and third party costs of $1.0 million, related to the issuance of our term loans. Per ASU 2015-3, *Interest-Imputation of Interest*, debt discount and debt issuance costs are to be presented as a contra-liability to the debt on the balance sheet. These costs will be amortized to interest expense over the life of the loans using the effective interest method. A total of $0.3 million, $0.1 million and $0.1 million of debt discount and debt issuance costs were amortized to interest expense during the years ended December 31, 2017, 2016, and 2015, respectively.

The following table summarizes how the issuance of Term Loans A, B, and C are reflected on the balance sheet at December 31, 2017 (in thousands):

	December 31, 2017
Gross proceeds	$ 28,500
Debt discount and debt issuance costs	(350)
Carrying value	28,150
Current portion of loans payable, net	12,425
Loans payable, net	$ 15,725

Aggregate maturities of long term debt as of December 31, 2017 are as follows (in thousands):

2018	$	12,667
2019		12,667
2020		3,166
2021		—
2022		—
	$	28,500
Debt Discount and deferred financing costs		(350)
	$	28,150

7. Stockholders' Equity

Equity Offerings

Under its certificate of incorporation, the Company was authorized to issue up to 100,000,000 shares of common stock as of December 31, 2017 and December 31, 2016, respectively. The Company also was authorized to issue up to 5,000,000 shares of preferred stock as of December 31, 2017 and December 31, 2016. 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.

On December 14, 2015, the Company entered into an at the market, or ATM, sales agreement with Cowen and Company, LLC, or Cowen, to offer and sell, from time to time at its sole discretion, shares of its common stock, par value $0.001 per share, having an aggregate offering price of up to $75.0 million through Cowen as its sales agent. Sales of the shares are deemed to be "at the market offerings", as defined in Rule 415 under the Securities Act of 1933, as amended. The Company will pay Cowen a commission of up to three percent of the gross sales proceeds and provided Cowen with customary indemnification rights. In 2017, the Company issued and sold 6,248,572 shares of common stock under this ATM facility at a weighted average price per share of $3.41 resulting in gross proceeds of $21.3 million. The net offering proceeds to the Company were approximately $20.7 million after deducting related expenses, including commissions. In 2016, the Company issued and sold 4,815,491 shares of common stock under this ATM facility at a weighted average price per share of $6.865 resulting in gross proceeds of $33.1 million. The net offering proceeds to the Company were approximately $32.1 million after deducting related expenses, including commissions.

On September 16, 2015, the Company issued and sold 7,475,000 shares of common stock in a public offering at a price of $9.75 per share, for gross proceeds of approximately $72.9 million. The net offering proceeds to the Company were approximately $68.3 million, after deducting underwriting discounts and commissions of approximately $4.4 million and offering costs of $0.2 million.

On April 3, 2015, the Company entered into an ATM agreement with Cowen to offer and sell, from time to time at the Company's sole discretion, shares of its common stock, par value $0.001 per share, having an aggregate offering price of up to $40.0 million through Cowen as its sales agent. The Company paid Cowen a commission of up to three percent of the gross sales proceeds and provided Cowen with customary indemnification rights. In 2015, the Company issued and sold an aggregate of 3,700,000 shares of common stock at a weighted average price per share of $6.0001 for aggregate gross proceeds of $22.9 million. The net offering proceeds to the Company were approximately $22.0 million after deducting related expenses, including commissions. This ATM agreement is no longer in effect.

Equity Incentive Plans

In 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 restricted stock and stock options to eligible employees, directors and consultants to the Company.

In 2013, the Company adopted the 2013 Equity Incentive Plan, as amended on May 14, 2014, collectively, 2013 Plan. The 2013 Plan became effective upon the Company's entry into the underwriting agreement related to its IPO in January 2014 and, as of such date, no further grants were permitted under the 2008 Plan. The 2013 Plan provides for the grant of incentive stock options, nonstatutory stock options, 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. The 2013 Plan contains an "evergreen" provision, pursuant

to which the number of shares of common stock available for issuance under the plan automatically increases on January 1 of each year beginning in 2015.

On December 15, 2016, the Company adopted the Trevena, Inc. Inducement Plan, or the Inducement Plan, effective January 1, 2017, pursuant to which the Company reserved 500,000 shares of the Company's common stock for issuance under the Inducement Plan. The Plan provides for nonstatutory stock options and restricted stock unit awards. The only persons eligible to receive grants of awards under the Inducement Plan are individuals who satisfy the standards for inducement grants under Nasdaq Marketplace Rule 5635(c)(4) and the related guidance under Nasdaq IM 5635-1, including individuals who were not previously an employee or director of the Company or are following a bona fide period of non-employment, in each case as an inducement material to such individual's agreement to enter into employment with the Company.

Under all 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 or its designee. Vesting generally occurs over a period of not greater than four years.

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 (in thousands):

	Year Ended December 31,		
	2017	2016	2015
Research and development	$ 1,954	$ 3,511	$ 1,460
General and administrative	4,433	2,392	1,967
Total stock-based compensation	$ 6,387	$ 5,903	$ 3,427

A summary of stock option activity and related information through December 31, 2017 follows:

	Options Outstanding		
	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)
Balance, December 31, 2015	4,630,073	$ 4.98	7.87
Granted	2,067,500	8.43	
Exercised	(149,622)	1.71	
Forfeitures	(177,373)	(7.47)	
Balance, December 31, 2016	6,370,578	$ 6.10	7.60
Granted	4,187,344	3.96	
Exercised	(293,809)	1.23	
Forfeited/canceled	(1,639,890)	(6.18)	
Balance, December 31, 2017	8,624,223	$ 5.22	7.17
Vested or expected to vest at December 31, 2017	8,624,223	$ 5.22	7.17
Exercisable at December 31, 2017	3,782,652	$ 5.18	5.04

The intrinsic value of the options exercisable as of December 31, 2017 was $0.4 million, based on the Company's closing stock price of $1.60 per share and a weighted average exercise price of $5.18 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, 2017, 2016 and 2015 was estimated at $2.68, $5.26 and $4.49 per share, respectively, on the date of grant using the Black-Scholes option-pricing model with the following weighted-average assumptions:

	Year Ended December 31,		
	2017	2016	2015
Expected term of options (in years)	6.2	6.2	6.2
Risk-free interest rate	2.0%	1.5%	1.7%
Expected volatility	75.6%	68.6%	68.5%
Dividend yield	—%	—%	—%

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 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: In 2016, upon adoption of ASU 2016-9, the Company elected to record forfeitures upon occurrence, rather than utilizing an estimate.

The fair value of the Company's common stock, prior to the IPO, 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.

As of December 31, 2017, there was $12.6 million of total unrecognized compensation expense related to unvested options that will be recognized over the weighted average remaining period of 2.64 years.

Shares Available for Future Grant

At December 31, 2017, the Company has the following shares available to be granted:

	2013 Plan	Inducement Plan
Available at December 31, 2016	1,101,331	500,000
Authorized	2,230,736	—
Granted	(3,966,844)	(220,500)
Forfeited/canceled	1,626,390	13,500
Available at December 31, 2017	991,613	293,000

Shares Reserved for Future Issuance

At December 31, 2017, the Company has reserved the following shares of common stock for issuance:

Stock options outstanding under 2013 Plan	8,417,223
Shares available for future grant under 2013 Plan	991,613
Stock options outstanding under Inducement Plan	207,000
Shares available for future grant under Inducement Plan	293,000
Employee stock purchase plan	225,806
Warrants outstanding	123,091
Total shares of common stock reserved for future issuance	10,257,733

8. Commitments and Contingencies

Licenses

On May 3, 2013, the Company entered into an agreement with Allergan plc (formerly Actavis plc and Forest Laboratories Holdings Limited) (“Allergan”), under which the Company granted to Allergan an exclusive option to license TRV027. Under the option agreement, the Company conducted, at its expense, a Phase 2b trial of TRV027 in acute heart failure. In March 2015, Allergan and the Company signed a letter agreement pursuant to which Allergan paid the Company $10.0 million to fund the expansion of the Phase 2b trial of TRV027 from 500 patients to 620 patients. Collaboration revenue was recognized on a straight-line basis over the study period and was fully recognized as of June 30, 2016. In August 2016, Allergan notified the Company of its decision not to exercise its option, and the Company therefore has retained all rights to TRV027.

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 December 2016, we entered into a 130-month office lease for approximately 40,565 square feet of space in Chesterbrook, Pennsylvania for the Company’s principal executive office; the term for this lease is commenced in July 2017. In June 2017, the Company exercised the option to lease an additional 8,321 square feet of space in the same building. The term for this lease amendment commenced in November 2017.

The Company's previous principal executive office was located in King of Prussia, Pennsylvania, pursuant to a lease that extends until September 2020. The Company had the option to terminate the lease after May 31, 2018 with a required termination payment of $0.15 million. In November 2017, in connection with our restructuring and reduction in force (see Note 10), the Company provided notice of its intent to terminate the facility lease of approximately 16,714 square feet of office and laboratory space in King of Prussia, Pennsylvania. The $0.15 million termination fee was paid to the landlord on the date the Company exercised the termination option. As a result, this lease will be deemed terminated on August 15, 2018.

The Company historically leased vivarium space in Exton, Pennsylvania. The vivarium lease was able to be terminated at any time upon 90 days’ written notice by the Company. In October 2017, in connection with the restructuring and reduction in force, the vivarium lease was terminated. Early termination fees totaling less than $0.1 million were incurred.

Rent expense under operating leases was $1.3 million, $0.6 million and $0.6 million in 2017, 2016 and 2015, respectively.

Future minimum lease payments under noncancelable lease agreements as of December 31, 2017, are as follows (in thousands):

	Operating Lease
2018	$ 970
2019	1,275
2020	1,352
2021	1,376
2022 and beyond	9,412
Total minimum lease payments	$ 14,385

The Company had deferred rent of $3.1 million and $0.2 million at December 31, 2017 and 2016, respectively, related to our facility leases.

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.

9. Revenue

For arrangements with multiple elements, the Company recognizes revenue in accordance with the FASB's Accounting Standards Update No. 2009-13, Multiple-Deliverable Revenue Arrangements, which provides guidance for separating and allocating consideration in a multiple element arrangement. Deliverables under the arrangement are separate units of accounting if the delivered item has value to the customer on a standalone basis and if the arrangement includes a general right of return relative to the delivery or performance of the undelivered item is considered probable and substantially within the Company's control. The consideration that is fixed or determinable at the inception of the arrangement is allocated to the separate units of accounting based on their relative selling prices. Management exercises significant judgment in determining whether a deliverable is a separate unit of accounting.

In determining the separate units of accounting, the Company evaluates whether the components have standalone value to the collaborator based on consideration of the relevant facts and circumstances for each arrangements. Whenever the Company determines that an element is delivered over a period of time, revenue is recognized using either a proportional performance model, if a pattern of performance can be determined, or a straight-line model over the period of performance, which is typically the research and development term.

The Company entered into a letter agreement with Allergan in March 2015 under which the Company received a nonrefundable upfront fee of $10.0 million. The terms of this agreement contained multiple deliverables which included (i) research and development activities and (ii) testing and analysis related to a Phase 2b trial of TRV027. Collaboration revenue is recognized only when the price is fixed or determinable, persuasive evidence of an arrangement exists, delivery has occurred or the services have been rendered and the Company has fulfilled its performance obligations under the contract. The Allergan collaboration revenue was recorded on a straight-line basis and was fully recognized as of June 30, 2016.

10. Restructuring Charges

On October 11, 2017, upon the approval of the Company's Board of Directors, the Company announced a restructuring and reduction in force of approximately 30% of the Company's workforce, or 21 employees. As part of this restructuring, the Company also halted its investment in early stage research.

The Company incurred pre-tax restructuring charges of $1.8 million during the year ended December 31, 2017, primarily related to severance and personnel related costs in addition to lease termination payments, as detailed below.

In October 2017, in connection with our restructuring and reduction in force, we terminated our lease related to vivarium space in Exton, Pennsylvania, under an agreement expiring on December 31, 2018. We incurred termination fees equivalent to three months rent, totaling less than $0.1 million, in relation to the early termination of this agreement.

Additionally, in November 2017, we provided notice of our intent to terminate our facility lease of approximately16,714 square feet of office and laboratory space in King of Prussia, Pennsylvania, under an agreement that expires in September 2020. We paid the landlord a $0.15 million termination fee on the date we exercised the termination option. As a result, this lease will be deemed terminated on August 15, 2018.

11. Net Loss Per Common Share

The following table sets forth the computation of basic and diluted net loss per share for the periods indicated (in thousands, except share and per share data):

	Year Ended December 31,		
	2017	2016	2015
Basic and diluted net loss per common share calculation:			
Net loss	$ (71,865)	$ (102,994)	$ (50,528)
Net loss attributable to common stockholders	$ (71,865)	$ (102,994)	$ (50,528)
Weighted average common shares outstanding	59,436,649	52,398,521	43,794,276
Net loss per share of common stock - basic and diluted	$ (1.21)	$ (1.97)	$ (1.15)

The following outstanding securities at December 31, 2017, 2016 and 2015 have been excluded from the computation of diluted weighted shares outstanding, as they would have been anti-dilutive:

	December 31,		
	2017	2016	2015
Options outstanding	8,624,223	6,370,578	4,630,073
Warrants	123,091	60,850	62,800
Total	8,747,314	6,431,428	4,692,873

12. Comprehensive Income (Loss)

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

Balance, January 1, 2016	$ (206)
Net unrealized loss arising during the period	208
Balance, December 31, 2016	$ 2
Net unrealized gains on marketable securities	(44)
Balance, December 31, 2017	$ (42)

There were no reclassifications out of accumulated other comprehensive income or loss as well as no tax effect for all periods presented.

13. Income Taxes

As the Company has historically incurred net operating losses, the Company has not recorded a provision for income taxes. Deferred tax assets and liabilities reflect the net effects of net operating loss and tax credit carryovers and temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. The Company maintains a full valuation allowance against its net deferred tax assets because significant utilization of such amounts is not presently expected in the foreseeable future.

On December 22, 2017, the U.S. government enacted comprehensive tax legislation , the Tax Act. The Tax Act makes broad and complex changes to the U.S. tax code that will affect 2017 including reducing the U.S. federal corporate tax rate to 21 percent. The following changes will affect 2018 (1) elimination of the corporate alternative minimum tax, or AMT, and changing how existing AMT credits can be realized; (2) a new limitation on deductible interest expense; (3) the repeal of the domestic production activity deduction; and (4) limitations on net operating losses , or NOLs, generated after December 31, 2017, to 80 percent of taxable income.

The SEC staff issued SAB 118, which provides guidance on accounting for the tax effects of the Tax Act. SAB 118 provides a measurement period that should not extend beyond one year from the Tax Act enactment date for companies to complete the accounting under ASC 740. The Tax Act reduced the corporate tax rate to 21 percent, effective January 1, 2018. Consequently, Trevena has recorded a decrease related to deferred tax assets, or DTAs, and deferred tax liabilities, or DTLs, with a corresponding net adjustment to deferred income tax of expense of $42.0 million for the year ended December 31, 2017. This expense is offset fully by a change in the valuation allowance. The Company's preliminary estimate of the Tax Act and the remeasurement of its deferred tax assets and liabilities is subject to the finalization of management's analysis related to certain matters, such as developing interpretations of the provisions of the Tax Act, changes to certain estimates and the filing of the Company's tax returns. U.S. Treasury regulations, administrative interpretations or court decisions interpreting the Tax Act may require further adjustments and changes in the Company's estimates. The final determination of the Tax Act and the remeasurement of the Company's deferred assets and liabilities will be completed as additional information becomes available, but no later than one year from the enactment of the Tax Act.

Significant components of the Company's net deferred tax assets as ofDecember 31, are as follows (in thousands):

	December 31,	
	2017	2016
Deferred tax assets:		
Net operating loss carryforwards	$ 16,042	$ 15,748
Research and development credits	12,239	11,020
Research and development expenses capitalized for tax purposes	83,707	97,495
Deferred rent	365	97
Depreciation	427	553
Other temporary differences	3,203	1,895
Total deferred tax assets	115,983	126,808
Deferred tax liabilities:		
Prepaid expenses	(65)	(105)
Total deferred tax liabilities	(65)	(105)
Net deferred tax assets	115,918	126,703
Less valuation allowance	(115,918)	(126,703)
Net deferred tax asset	$ —	$ —

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,		
	2017	2016	2015
Percent of pre-tax income:			
U.S. federal statutory income tax rate	34.0 %	34.0 %	34.0 %
Permanent Differences	0.1 %	— %	0.1 %
State taxes, net of federal benefit	6.7 %	6.6 %	6.6 %
Research and development credit	1.7 %	4.0 %	3.9 %
Rate change due to tax reform	(58.5)%	—	—
Other	1.0 %	— %	0.3 %
Change in valuation allowance	15.0 %	(44.6)%	(44.9)%
Effective income tax rate	— %	— %	— %

As of December 31, 2017, the Company had federal and state net operating loss carryforwards of $55.7 million and $4.4 million that begin to expire at various dates starting in 2027. As of December 31, 2017, the Company had federal research and development tax credit carryforwards of $12.2 million that begin to expire at various dates starting in 2027. The Company's ability to utilize net operating loss carryforwards, or NOLs, or tax credit carryforwards may be subject to annual limitations under certain provisions of the Internal Revenue Code related to "changes in ownership."

The Company files income tax returns in the U.S. and the Commonwealth of Pennsylvania. Tax years for fiscal 2014 through 2016 are open and potentially subject to examination by the federal and state taxing authorities. The Company is currently not under examination by the Internal Revenue Service or any other jurisdictions for any tax years. To the extent the Company utilizes in the future any tax attribute NOL carryforwards from a tax period that may otherwise be closed to examination, the Internal Revenue Service, state tax authorities, or other governing parties may still adjust the NOL carryforwards upon their examination of the future period in which the attribute was utilized.

14. 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 2017, 2016 and 2015, the Company provided matching contributions of $0.4 million, $0.4 million and $0.3 million, respectively.

15. Selected Quarterly Financial Data (Unaudited)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
	(in thousands, except share and per share amounts)			
2017				
Total revenue	$ —	$ —	$ —	$ —
Loss from operations	(20,975)	(19,884)	(15,413)	(14,115)
Net loss	$ (20,714)	$ (20,432)	$ (15,999)	$ (14,720)
Net loss per share of common, basic and diluted	$ (0.36)	$ (0.35)	$ (0.27)	$ (0.24)
Weighted average shares outstanding, basic and diluted	56,894,672	58,381,868	60,113,327	62,290,002
2016				
Total revenue	$ 1,875	$ 1,875	$ —	$ —
Loss from operations	(17,749)	(19,104)	(29,713)	(35,717)
Net loss	$ (17,732)	$ (19,295)	$ (29,985)	$ (35,982)
Net loss per share of common, basic and diluted	$ (0.35)	$ (0.37)	$ (0.57)	$ (0.67)
Weighted average shares outstanding, basic and diluted	51,350,365	52,174,569	52,205,156	53,850,166

The quarters presented above for 2017 have been adjusted to reflect the adoption of ASU 2016-09 and related impact, that is deemed immaterial, of electing to recognize forfeitures of share-based payment awards as they occur rather than using an estimate.

16. Subsequent Events

Equity Offerings

In 2018, the Company issued and sold 3,386,527 shares of common stock pursuant to the existing ATM facility with Cowen. The shares were sold at a weighted average price per share of $1.76. The net offering proceeds to the Company were approximately $5.8 million after deducting related expenses, including commissions. Approximately $14.6 million remained available under the ATM sales facility as of the date of this filing.

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, 2017.

Based on that evaluation, our management, including our CEO and CFO, concluded that as of December 31, 2017 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 into 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.

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 2018 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 2018 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 2018 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 2018 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 2018 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 2018 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 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 2018 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 2018 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.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) DOCUMENTS FILED AS PART OF THIS REPORT

The following is a list of our financial statements 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

(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 Warrant issued by Trevena, Inc. to Oxford Finance LLC, Pacific Western Bank and Three Point Capital, LLC (incorporated by reference to Exhibit 4.1 to Registrant's Current Report on Form 8-K, filed with the SEC on December 23, 2015).
10.1*	License Agreement, dated as of May 3, 2013, by and between the Registrant and Forest Laboratories Holdings Limited (now Allergan 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).
10.2*	Option Agreement, dated as of May 3, 2013, by and between the Registrant and Forest Laboratories Holdings Limited (now Allergan 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	Letter Agreement dated March 5, 2015 between Trevena, Inc. and Actavis plc (now Allergan plc) (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, filed with the SEC on March 10, 2015).
10.4	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).
10.5	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).
10.6	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).
10.7	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).

10.8	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).
10.9	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).
10.10	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).
10.11	4th Amendment to Commercial Lease Agreement dated as of January 30, 2015, by and between the Registrant and Pios Grande KOP Business Center, L.P. (successor-in-interest KOPBC, Inc.) (incorporated by reference to Exhibit 10.4 to Registrant's Quarterly Report on Form 10-Q, filed with the SEC on May 7, 2015).
10.12#	Agreement of Lease between Chesterbrook Partners, LP and Trevena, Inc. for 955 Chesterbrook Blvd., Suite 200, Wayne, PA, dated as of December 9, 2016 (incorporated by reference to Exhibit 10.12 to Registrat's Annual Report on Form 10-K filed with the SEC on March 8, 2017).
10.13+	First Amendment dated June 12, 2017 to Agreement of Lease between Chesterbrook Partners, LP and Trevena, Inc. for 955 Chesterbrook Blvd., Suite 200, Chesterbrook, PA as of December 9, 2016 (incorporated by reference to Exhibit 10.1 to Registrant's Quarterly Report on Form 10-Q filed with the SEC on August 3, 2017).
10.14+	2008 Equity Incentive Plan, as amended to date (incorporated by reference toExhibit 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).
10.15+	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).
10.16+	2013 Equity Incentive Plan (incorporated by reference toExhibit 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).
10.17+	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).

10.18+	Form of Stock Option Grant Notice and Stock Option Agreement under 2013 Equity Incentive Plan (incorporated by reference to Exhibit 10.5 to Registrant's Quarterly Report on Form 10-Q, filed with the SEC on May 7, 2015).
10.19+	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).
10.20+	Trevena, Inc. Inducement Plan, effective January 1, 2017 (incorporated by reference toExhibit 10.1 to Registrant's Current Report on Form 8-K, filed with the SEC on December 19, 2016).
10.21+	Form of Stock Option Grant Notice and Stock Option Agreement used in connection with the Trevena, Inc. Inducement Plan (incorporated by referenced to Exhibit 10.2 to Registrant's Current Report on Form 8-K, filed with the SEC on December 19, 2016).
10.22+	Form of Restricted Stock Unit Grant Notice and Restricted Stock Unit Award Agreement used in connection with Trevena, Inc. Inducement Plan (incorporated by reference to Exhibit 10.3 to Registrant's Current Report on Form 8-K, filed with the SEC on December 19, 2016).
10.23+	Trevena, Inc. Incentive Compensation Plan, effective as of January 1, 2015 (incorporated by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K, filed with the SEC on January 5, 2015).
10.24+	Non-Employee Director Compensation Plan (incorporated by reference toExhibit 10.1 to the Registrant's Current Report on Form 8-K filed with the SEC on July 1, 2014).
10.25+	Trevena, Inc. Non-Employee Director Compensation Policy, effective as of January 1, 2016 (incorporated by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K, filed with the SEC on December 11, 2015).
10.26+	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).
10.27+	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).
10.28+	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).
10.29+	Amendment to Executive Employment Agreement dated as of May 14, 2015 by and between Trevena, Inc. and Maxine Gowen, Ph.D. (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, originally filed with the SEC on May 5, 2015).
10.30+	Second Amendment to Executive Employment Agreement dated as of January 6, 2017 by and between Trevena, Inc. and Maxine Gowen, Ph.D. (incorporated by referenced to Exhibit 10.1 to Registrant's Current Report on Form 8-K, filed with the SEC on January 6, 2017).
10.31+	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).
10.32+	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).

10.33+	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).
10.34+	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).
10.35+	Omnibus Amendment to Employment Agreements dated as of May 4, 2015 by and between Trevena, Inc. and each of Roberto Cuca, Michael Lark, John M. Limongelli and David Soergel (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K, filed with the SEC on May 5, 2015).
10.36+	Omnibus Amendment to Employment Agreements dated January 6, 2017 by and between Trevena, Inc. and each of Carrie L. Bourdow, Roberto Cuca, Yacoub Habib, Michael Lark, John M. Limongelli and David Soergel (incorporated by reference to Exhibit 10.2 to Registrant's Current Report on Form 8-K, filed with the SEC on January 6, 2017).
10.37+	Executive Employment Agreement effective as of May 4, 2015 by Trevena, Inc. and Carrie L. Bourdow (incorporated by reference to Exhibit 10.3 to Registrant's Current Report on Form 8-K, originally filed with the SEC on May 5, 2015).
10.38+	Executive Employment Agreement effective as of July 20, 2015 by and between Trevena, Inc. and Yacoub Habib (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, originally filed with the SEC on July 21, 2015).
10.39	First Amendment to Executive Employment Agreement effective as of January 1, 2016 by and between Trevena, Inc. and Yacoub Habib (incorporated by reference to Exhibit 10.33 to the Registrant's Form 10-K filed with the SEC on March 9, 2016).
10.40	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).

10.41	First Amendment to Loan and Security Agreement, dated April 13, 2015, 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 Registrant's Current Report on Form 8-K, filed with the SEC on April 13, 2015).
10.42	Second Amendment to Loan and Security Agreement dated December 23, 2015, by and among Trevena, Inc., as borrower, Oxford Finance LLC, as collateral agent and lender, and Pacific Western Bank (as the successor to Square 1 Bank), as lender (incorporated by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K, filed with the SEC on December 23, 2015).
10.43	Third Amendment to Loan and Security Agreement dated December 30, 2016, by and between Trevena, Inc., as borrower, Oxford Finance LLC, as collateral agent and lender, and Pacific Western Bank (as successor to Square 1 Bank), as lender (incorporated by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K, filed with the SEC on January 4, 2017).
10.44	Common Stock Sales Agreement, dated December 14, 2015, by and between Trevena, Inc. and Cowen and Company, LLC (incorporated by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K, filed with the SEC on December 14, 2015).
10.45#*	Master Commercial Supply Agreement dated October 20, 2017 by and between Alcami Corporation and Trevena, Inc.
10.46#*	Development and Supply Agreement by and between Pfizer, Inc. and Trevena, Inc. dated as of December 15, 2016
12.1#	Statement Regarding Computation of Ratios.
23.1#	Consent of Independent Registered Public Accounting Firm.
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, 2016 and 2015, formatted in XBRL (eXtensible Business Reporting Language): (i) Balance Sheets as of December 31, 2016 and 2015, (ii) Statements of Operations and Comprehensive Loss for the years ended December 31, 2016, 2015 and 2014, (iii) Statement of Redeemable Convertible Preferred Stock and Stockholders' Equity as of December 31, 2016, 2015 and 2014, (iv) Statements of Cash Flows for the years ended December 31, 2016, 2015 and 2014 and (v) Notes to Financial Statements, tagged as blocks of text.

Filed herewith.

+ Indicates management contract or compensatory plan.

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

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 7, 2018

TREVENA, INC.

By: /s/ Maxine Gowen

Maxine Gowen

President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and 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 7, 2018
/s/ Roberto Cuca Roberto Cuca	Senior Vice President and Chief Financial Officer (Principal Financial and Accounting Officer)	March 7, 2018
/s/ Leon O. Moulder, Jr. Leon O. Moulder, Jr	Chairman, Board of Directors	March 7, 2018
/s/ Michael R. Dougherty Michael R. Dougherty	Director	March 7, 2018
/s/ Adam M. Koppel Adam M. Koppel, M.D., Ph.D.	Director	March 7, 2018
/s/ Julie H. McHugh Julie H. McHugh	Director	March 7, 2018
/s/ Jake R. Nunn Jake R. Nunn	Director	March 7, 2018
/s/ Anne M. Phillips Anne M. Phillips, M.D.	Director	March 7, 2018
/s/ Barbara Yanni Barbara Yanni	Director	March 7, 2018

EXHIBIT INDEX

Exhibit Number	Description
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10.46*	Development and Supply Agreement by and between Pfizer, Inc. and Trevena, Inc. dated as of December 15, 2016.
12.1	Statement Regarding Computation of Ratios.
23.1	Consent of Independent Registered Public Accounting Firm.
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.
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[*] = Certain confidential information contained in this document, marked by brackets, has been omitted and filed separately with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934, as amended.

Exhibit 10.45

MASTER COMMERCIAL SUPPLY AGREEMENT

THIS MASTER COMMERCIAL SUPPLY AGREEMENT (the "Agreement") is made and entered into this 20th day of October, 2017 (the "Effective Date"), by and between **Alcami Corporation**, having a place of business at 2320 Scientific Park Drive, Wilmington, NC 28405 (including its wholly-owned subsidiaries, collectively, "Company"), and **Trevena, Inc.**, having a place of business at 955 Chesterbrook Blvd, Suite 200, Chesterbrook, PA 19087 ("Client"). Company and Client, as used herein, may be referred to, collectively, as "Parties" and individually as a "Party".

Recitals

WHEREAS, the Parties entered into a certain Master Services Agreement dated on or about July 2, 2014, as amended on March 1, 2015, and August 10, 2016, and as may be amended from time-to-time in the future (the "MSA").

WHEREAS, the MSA governs the pre-commercial supply of Drug Product and API (both as defined below) for Client's clinical trial programs.

WHEREAS, subject to the terms and conditions contained in this Agreement, Client desires to engage Company to perform Services (as defined below) to address some of Client's commercial Drug Product and API supply needs.

WHEREAS, Company is willing to perform such Services for Client according to the terms and conditions provided for in this Agreement.

NOW, THEREFORE, for and in consideration of the foregoing premises and of the mutual covenants of the Parties hereinafter set forth, the Parties hereto agree as follows:

ARTICLE 1
DEFINITIONS

The following words, terms and phrases, when used herein, shall have the following respective meanings:

1.1 **"Act"** shall mean the United States Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), as amended from time to time, and the regulations promulgated thereunder.

1.2 **"Affiliate"** shall mean, with respect to a Party, a company, whether a corporation or other business entity, that is Controlling, Controlled by or under common Control with such Party.

1.3 **"API"** shall mean the active pharmaceutical ingredient with respect to the Drug Product.

1.4 **"API Firm Commitment"** shall have the meaning set forth in Section 4.2(b).

1.5 **"API Firm Order"** shall have the meaning set forth in Section 4.2(d).

1.6 **"API Long-Term Forecast"** shall have the meaning set forth in Section 4.1.

1.7 **"API Minimum Order Requirement"** shall have the meaning set forth in Section 4.2(a).

1.8 **"API Yield"** shall have the meaning set forth in Section 4.4.

1.9 **"Applicable Law(s)"** shall mean applicable federal, state, provincial and local laws applicable to the activities of a Party and all rules and regulations promulgated thereunder, including, without limitation, regulations promulgated by the FDA, DEA and/or other regulatory authorities.

1.10 **"Arising Intellectual Property"** means rights in all intellectual property which are made, developed or generated through the performance of the Services.

1.11 **"Batch"** shall mean a specific quantity of material produced in a contiguous process or series of processes that is expected to be homogeneous within specified limits.

1.12 **"Cancellation Fee"** shall have the meaning set forth in Section 4.3 for API and Section 5.3 for Drug Product.

1.13 **"cGMP"** or **"GMP"** shall mean the recognized pharmaceutical regulations and requirements of regulatory authorities such as those defined by the FDA's regulations at 21CFR Parts 210 and 211, those defined by Eudralex, "The Rules Governing Medicinal Products in the European Union," and specifically Volume 4, "Guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use" and applicable Annexes (Directives 2001/83/EC and amendments including Directives 2003/94/EC dated October 2003 and 2004/27/EC dated March 2004 and/or others that may be appropriate for the particular project)and as may be amended from time to time.

1.14 **"Client"** shall have the meaning set forth in the preamble.

1.15 **"Client Arising Intellectual Property"** shall have the meaning set forth in Section 15.2.

1.16 **"Client Indemnified Parties"** shall have the meaning set forth in Section 11.1.

1.17 **"Client Information"** shall have the meaning set forth in Section 14.1.

1.18 **[*]**

1.19 **"CML-474 Yield"** shall have the meaning set forth in Section 4.4.

1.20 **"Commercial Year**" means each period of twelve (12) consecutive calendar months during the Term of this Agreement beginning on January 1st and ending December 31st, except for the first Commercial Year, which shall commence upon [*] The first Commercial Year is expected to commence [*].

1.21 **"Commercialize"** or **"Commercialization"** shall mean, with respect to the Drug Product, the marketing, promotion, sale and distribution of such Drug Product.

1.22 **"Company"** shall have the meaning set forth in the preamble.

1.23 **"Company Arising Intellectual Property"** shall have the meaning set forth in Section 15.3.

1.24 **"Company Indemnified Parties"** shall have the meaning set forth in Section 11.2.

1.25 **"Company Information"** shall have the meaning set forth in Section 14.2.

1.26 **"Confidential Information"** shall have the meaning set forth in Section 14.3.

1.27 **"Control"** shall mean the direct or indirect ownership of more than fifty percent (50%) of the equity interest in such corporation or business entity, or the ability in fact to control the management decisions of a corporation or other business entity.

1.28 **"DEA"** means the United States Drug Enforcement Agency and any successor agency thereto.

1.29 **"Deliverables"** shall have the meaning set forth in Section 2.3.

1.30 **"Dispute"** shall have the meaning set forth in Section 16.14(a).

1.31 **"DMF"** shall have the meaning set forth in Section 8.8.

1.32 **"Documentation"** shall have the meaning set forth in Section 8.4.

1.33 **"Drug Product"** shall mean Oliceridine, a finished dosage form of human pharmaceutical product containing API.

1.33.1 **"Drug Product – Bulk"** shall mean Oliceridine in filled, unlabeled vials, packaged in appropriate bulk packaging suitable for shipment to a third party for further processing/packaging.

1.33.2 **"Drug Product – Finished"** shall mean Oliceridine fully packaged for commercial distribution.

1.34 **"Drug Product Firm Commitment"** shall have the meaning set forth in Section 5.2(b).

1.35 **"Drug Product Firm Order"** shall have the meaning set forth in Section 5.2(c).

1.36 **"Drug Product Long-Term Forecast"** shall have the meaning set forth in Section 5.1.

1.37 **"Drug Product Minimum Order Requirement"** shall have the meaning set forth in Section 5.2(a).

1.38 **"ERP"** or **"Tail Coverage"** shall mean Extended Reporting Period.

1.39 **"Facility"** shall mean Company's facility(ies) where the Services are performed, as reflected in more detail on Appendix C hereto.

1.40 **"FDA"** shall mean the U.S. Food and Drug Administration and any successor agency thereto.

1.41 **"Force Majeure"** is an event described in Section 16.12.

1.42 **"Indemnification Claim"** shall have the meaning set forth in Section 11.3(a).

1.43 **"Initial Term"** shall have the meaning set forth in Section 13.1.

1.44 **"Inspection Period"** shall have the meaning set forth in Section 6.2(a).

1.45 **"Intellectual Property"** means collectively, patents, patent applications, trademarks, copyright, trade secrets, inventions, know-how and any other intellectual property whether statutory or non-statutory.

1.46 **"Latent Defect"** shall have the meaning set forth in Section 6.2(a).

1.47 **"Losses"** shall have the meaning set forth in Section 11.1.

1.48 **"Manufacture"** or **"Manufacturing"** shall mean the manufacture, processing, packaging and labeling if such packaging and labeling is performed by Company, quality control and testing of CML-474, API and/or Drug Product performed prior to their Release To The Client by Company in accordance with the terms of this Agreement and the Quality Agreement.

1.49 **"Marketing Authorizations"** shall mean the United States new drug application or abbreviated new drug application, as applicable, for the Drug Product(s).

1.50 **"Material Change"** shall have the meaning set forth in Section 3.2.

1.51 **"Nonconforming Product"** shall have the meaning set forth in Section 6.2(a)(ii).

1.52 **"Other Changes"** shall have the meaning set forth in Section 3.4.

1.53 **"Out of Specification"** shall mean a result that is not within the Specifications, whether these are qualitative or quantitative.

1.54 **"Pre-Existing Intellectual Property"** means all Intellectual Property owned, conceived, developed, first reduced to practice or otherwise made or acquired by a Party prior to the Effective Date hereof *or* outside of the Services performed under this Agreement or any Work Order, including all modifications, adjustments or improvements thereto.

1.55 "**Program Manager**" shall have the meaning set forth in Section 3.14(b).

1.56 **"Project Team"** shall have the meaning set forth in Section 3.14(b).

1.57 **"Purchase Prices"** shall have the meaning set forth in Section 7.1.

1.58 **"Quality Agreement"** shall have the meaning set forth in Section 8.3.

1.59 **"Raw Material Costs"** shall have the meaning set forth in Section 7.2(a).

1.60 **"Raw Materials"** shall mean any starting and reagent materials used to Manufacture the API or Drug Product.

1.61 **"Recall"** shall have the meaning set forth in Section 12.1(b).

1.62 **[*]**

1.63 **"Renewal Period"** shall have the meaning set forth in Section 13.1.

1.64 "**Replacement Product**" shall have the meaning set forth in Section 6.2(d).

1.65 "**Rolling Forecast**" shall have the meaning set forth in Section 4.1 for API and Section 5.1 for Drug Product.

1.66 **"Services"** shall mean the Manufacturing services described herein.

1.67 "**SMF**" shall have the meaning set forth in Section 8.8.

1.68 **"Specifications"** means the release specifications for the Manufacture, processing, bulk packaging, testing and testing procedures, shipping, storage and supply of the API, CML-474 intermediate and/or Drug Product, any Raw Materials requirements, analytical procedures and standards of quality control and quality assurance, agreed upon and maintained in Company's controlled documents for the API, CML-474 intermediate, and/or Drug Product. The API, CML-474 intermediate and Drug Product release Specifications as of the Effective Date shall be attached hereto as Appendix D-1, D-2 and D-3 below and updated from time to time. Current API, CML-474 intermediate and Drug Product Release Specifications shall be maintained in Company's controlled document system.

1.69 **"Steering Committee**" shall have the meaning set forth in section 3.14(a).

1.70 **"Technology Transfer"** shall have the meaning set forth in Section 13.4(d).

1.71 **"Term"** shall have the meaning set forth in Section 13.1.

1.72 **"Territory"** shall mean the United States, its territories and possessions, or other jurisdictions agreed upon in writing by the Parties.

1.73 **"Third Party Claims"** shall have the meaning set forth in Section 11.1.

1.74 **"Work Order"** shall have the meaning set forth in Section 2.3.

ARTICLE 2
SCOPE OF AGREEMENT

2.1 **Agreement.** As a master form of contract, this Agreement together with all Appendices (all of which are incorporated herein by reference) and any written amendments to any of the foregoing executed by the Parties allows the Parties to set forth the terms, conditions and administrative procedures generally applicable to Services

provided by Company or any of its wholly-owned subsidiaries to Client or any of its Affiliates.

2.2 Appendices. The attached Appendices are incorporated herein by reference and form part of this Agreement:

APPENDIX A: Sample Work Order Template
APPENDIX B-1: API Batch Sizes and Cost
APPENDIX B-2: Drug Product - Finished, Batch Sizes and Cost
APPENDIX B-3: Drug Product - Bulk, Batch Sizes and Cost
APPENDIX C: Facilities
APPENDIX D-1: Initial API Release Specifications (for reference)
APPENDIX D-2: Initial Drug Product Release Specifications (for reference)
APPENDIX D-3: Initial CML-474 Release Specifications (for reference)

2.3 Work Orders. This Agreement may provide for the issuance of multiple work orders or a work order may be issued hereunder for non-Manufacturing Services, or other Services more fully described in the work order, substantially in the form of Appendix A to this Agreement (each, a "Work Order"). The Work Order shall set forth the scope of Services to be provided, the deliverables ("Deliverables") and budget and payment schedule. Client's execution of each Work Order will be deemed its authorization for Company to proceed with the Services. All Work Orders and Deliverables hereunder shall be governed by the terms of this Agreement. Additions to or modifications of a Work Order must be made in writing and signed by both Parties.

2.4 Grant. Client hereby grants to Company during the Term of this Agreement, on a product-by-product basis, a nonexclusive, royalty-free right to Manufacture the API, Drug Product and CML-474 in the Territory and to use, if reasonable and necessary, any and all of Client's licenses, trademarks, regulatory data and/or technical information, know-how and Confidential Information of Client related to the API and Drug Product for the purpose of Company carrying out its obligations hereunder, subject to the conditions of this Agreement. Upon termination of this Agreement, the grant provided in this Section 2.4 shall immediately terminate.

2.5 Engagement.

(a) During the Term of this Agreement and subject to the terms and conditions set forth herein, Client agrees to purchase from Company, and Company agrees to Manufacture and supply, the number of Batches of API, Drug Product – Finished (if any), Drug Product – Bulk and CML-474 per calendar year specified in the applicable purchase order in accordance with Sections 4.2 and 5.2 at the effective Purchase Price (initial prices outlined in Appendices B-1, B-2 and B-3). Notwithstanding the foregoing, Client shall be entitled, at its sole cost and expense, to qualify other manufacturer(s) to manufacture CML-474, Drug Product and API at any time to supply quantities of CML-474, Drug Product and API that Company is unable or unwilling to supply in accordance with this Agreement. In the event Company is unable to accommodate Client's Drug Product or API requirements as set forth herein and in accordance with Article 3, Client, at its discretion, may have a third party manufacture such quantities of CML-474, Drug Product or API that Company is unable or unwilling to supply.

(b) Notwithstanding the foregoing, to the extent Client intends to Commercialize API or Drug Product in a jurisdiction outside the Territory and desires, in its sole discretion, to engage Company to Manufacture such API or Drug Product the Parties shall, upon written notice from Client to Company, use reasonable efforts to negotiate in good faith an agreement, or amendment to this Agreement, as necessary.

2.6 Marketing Authorizations. Client shall use commercially reasonable efforts to maintain the Marketing Authorizations in full force and effect at all times. Upon request by Client, Company shall use commercially reasonable efforts to assist Client in connection therewith as may be outlined in a separate statement of work or other related agreement, the terms of which shall be governed by this Agreement.

2.7 Additional API or Drug Product. The Parties covenant and agree that additional products may be added to this Agreement upon Client's written request and such additional products shall be governed by the general conditions hereof with any special terms (including, without limitation, price) governed by an addendum hereto signed by both Parties.

ARTICLE 3
MANUFACTURING SERVICES

3.1 Manufacture of API and Drug Product. Subject to the terms and conditions contained herein, Company shall Manufacture, handle and prepare for shipment all API and Drug Product Manufactured pursuant to this Agreement (a) in accordance with this Agreement and the Quality Agreement, and (b) in material compliance with cGMP applicable to the Manufacturing of the API and Drug Product.

3.2 Company Changes to Manufacturing Process. Except as required by Applicable Law(s), or cGMP, Company shall not Materially Change the Manufacturing process of API or Drug Product or change the Facility where the API or Drug Product is Manufactured without the prior written consent of Client, which consent shall not be unreasonably withheld, conditioned, or delayed. Company shall notify Client of all Material Changes, including Material Changes required by Applicable Law(s), as soon as practicable after Company learns of such change. A "Material Change" is one that requires a submission to the applicable regulatory authority(ies) for the Territory or is a change to the Manufacturing process, as set forth in the Manufacturing Batch record.

3.3 Client Requested Changes. Client shall inform Company in writing of any proposed modifications to the Specifications or the Manufacturing process. Unless required by Applicable Law(s), cGMP and/or the Marketing Authorizations, any proposed change that will materially impact Company's Manufacturing process shall require Company's prior written consent, which consent shall not be unreasonably withheld, conditioned, or delayed. Company shall make changes required by Applicable Law(s), as well as those to which it consents, which consent shall not be unreasonably withheld, conditioned or delayed, as promptly as practicable; provided, however, that such changes comply with Applicable Law(s), cGMP and the Marketing Authorizations.

3.4 Costs of Changes. Unless otherwise agreed by the Parties, any and all direct costs associated with changes requested by Company and/or changes required by Applicable Law(s) that apply generally to Company's Facility where the applicable Manufacturing occurs shall be borne by Company; provided, however, in the event Applicable Law(s) imposes a registration fee (such as GDUFA or PDUFA) or similar user fee, and the fee relates to Company's Services hereunder, the Parties shall determine in good faith an equitable portion of such fee to be paid by Client. The Parties understand and agree that Company shall Manufacture the Drug Product in accordance with Applicable Law(s) and regulations, as the same may be amended from time to time. Each Party shall keep the other promptly and fully advised of any new instructions or specifications required by regulatory authority or Applicable Law(s) and shall discuss the cost of implementing such requirements, including by way of example, implementation of serialization.

Unless otherwise agreed by the Parties, or otherwise necessitated by Company's gross negligence and/or intentional acts or omissions, any and all direct costs associated with other changes, including, without limitation, changes requested by Client, changes required by Applicable Law(s) that apply specifically to API or Drug Product, and changes required by a change to a Marketing Authorization, shall be borne by Client (collectively, the "Other Changes"). If the change is an Other Change, (i) the Purchase Prices shall be adjusted by the change in Company's cost of Manufacture of the API or Drug Product caused by such Other Change, and (ii) Client shall reimburse Company for costs, expenses or losses associated with write-offs, obsolescence and/or destruction of any work in process or finished inventory resulting from any such Other Change. If permitted by Applicable Law(s) and cGMP, any work in process and/or finished inventory resulting from any Other Change may be made available for delivery or pickup by Client, at Client's sole cost and expense. The Parties agree to use good faith efforts to discuss changes to the Purchase Prices due to any Other Change, or otherwise, prior to any Purchase Price increase taking effect.

Client may be required to make changes to the proposed API or Drug Product presentations based on clinical data and/or FDA feedback. In such instances, both Parties will work in good faith to identify and implement these changes expeditiously and agree on any adjustments in pricing or cost as appropriate.

Both Parties shall use reasonable efforts to identify and evaluate process improvements for quality and cost improvement opportunities. Such changes may include, but are not limited to, larger Batch sizes, alternative components, or otherwise. The cost savings and reductions to unit pricing achieved by such process improvements and/or cost improvements will be shared in the same proportion as which the cost-savings activities were funded by each of the Parties.

3.5 Notification and Approval of Changes. Client shall have sole responsibility for obtaining any and all necessary regulatory approvals from the relevant regulatory agencies in the Territory for changes to the Specifications and the Marketing Authorizations and for reporting any changes to such Specifications and the Marketing Authorizations to the relevant regulatory agencies in the Territory as appropriate. Upon request by Client, Company shall use commercially reasonable efforts to assist Client in obtaining any such approvals; provided that Client will pay Company in accordance with the terms of a separate statement of work or similar agreement which is governed by the terms of this Agreement. Client will provide to Company for its files a final copy of the CMC section related to Company activities of any such applications and/or submissions for regulatory approval unless otherwise prohibited by Applicable Law(s).

3.6 Retesting of Materials. In the event an analytical test results in Out of Specification or aberrant data, the Parties agree that appropriate re-testing may be performed to confirm the initial test result. [*], unless such re-testing demonstrates that the Out of Specification or aberrant data was due to Company's failure to perform the Services in accordance with the Work Order or related to an assignable laboratory error or otherwise attributable to Company's gross negligence or intentional acts or omissions.

3.7 Labeling. Client shall be responsible for the labeling to be used on each Drug Product and the packaging thereof, including any changes to such labels, and Client shall ensure that all such labeling complies with Applicable Law(s). Company shall use the specified labeling (and only such labeling) on the Drug Product, and shall not use such labeling on any other product unless approved by Client and permitted by Applicable Law(s). Any Client-directed change to a Drug Product label shall be implemented by Company as soon as reasonably practicable following Company's receipt of written notification of such label changes. [*] any materials acquired from a third-party that are required for Company to perform the Services.

3.8 Finished Drug Product Release. Company will provide Client with Manufacturing documents as are necessary for Client to release each lot of Drug Product for human use. Client shall be responsible for the final release of Drug Product for human use and other approved commercial purposes.

3.9 Raw Materials and Client Supplied Materials Company shall purchase at its own expense and for its own account all Raw Materials and packaging components not supplied by Client that Company may use to Manufacture the API and Drug Product. Except as otherwise agreed to between the Parties, all right, title, and interest in and to these items shall remain the sole property of Company until API and/or Drug Product incorporating such items are Manufactured and prepared for shipment to Company's alternate Manufacturing Facility or Released To The Client, as applicable. However, [*]. Company shall obtain Client's written consent prior to changing the source/and or type of Raw Material if such change will impact the Client's Marketing Authorizations. Client may supply to Company at its own expense and for its own account Raw Materials to be used in the Manufacture of API and Drug Product hereunder, and such Raw Materials shall remain the sole property of Client. Company shall have no liability for lost or damaged Raw Materials [*].

3.10 Delivery Schedule; Project Delay. The scheduled dates for the performance of the Services as defined by the Parties represent the Parties' best estimates of the timing for the various activities to be performed; however, both Parties agree that unforeseen delays may occur. If such delays occur, both Parties will use good faith efforts to minimize the timing disruption to the scope of work and shall agree upon an appropriate adjustment in the lead times or delivery schedules, as needed, for the API and/or Drug Product(s). Except in the event of a Force Majeure event, delay in Raw Material delivery not due to Company error, or delay in delivery of Client supplied Raw Materials, Company shall not be entitled to invoke this Section 3.10 to excuse any delay in performance of obligations under this Agreement. If a Party believes the performance of any obligations under this Agreement will be delayed it shall immediately notify the other Party of the delay and cause and shall provide a good faith estimate of when performance will resume. When the affected Party is able to recommence the performance of obligations hereunder, it shall notify the other Party, and unless otherwise agreed, shall immediately resume performing its obligations. In the event Company anticipates delivery of API or Drug Product will not meet the scheduled delivery date [*], Company shall provide notice to Client and propose a remedy plan to the Steering Committee within [*] thereafter. The Steering Committee shall discuss and mutually agree upon a timeline for execution of the remedy plan.

For API orders [*].

For Drug Product orders [*].

Subject to Client's rights under Section 6.2(a), no delay in the shipment or delivery of any API or Drug Product shall relieve Client of its obligations under this Agreement, including arranging for shipment and accepting delivery of API and Drug Product.

3.11 Client Delays/Rescheduling. Client or its designee must provide on time, in the right quantity and within Specification, any Raw Materials (including starting materials) agreed to be supplied by Client. In a timely manner after execution of this Agreement, the Steering Committee shall agree to a supply strategy for Client supplied Raw Materials, to include lead time required for receipt by Company and minimum stock levels to be maintained. If required Raw Materials are not supplied by Client to Company as and when needed, all dates quoted by Company for delivery and completion of any stage of the Services may be extended if necessary. Client shall propose a remedy plan to the Steering Committee within [*] from the date Client recognizes the delay. The Steering Committee shall discuss and mutually agree upon a revised timeline for delivery of a delayed Client order. In the event of a Force Majeure event, Client shall not be liable for any delay fees or expenses that Company may incur. If the delivery of any Client-supplied Raw Materials (including RM1023) is delayed, other than due to a Force Majeure event, Company may charge Client for the reasonable and necessary cost and expenses directly resulting from such Client delay, which are not otherwise avoidable, including idle capacity cost which cannot be filled with new, unplanned work for another client, [*]. Company shall not be held liable for any delay, supply deficiency or supply failure caused solely by Client.

[*] Client shall also be responsible for the cost of any Raw Materials that may expire as a result of the request to delay. Notwithstanding anything to the contrary contained herein, Client shall have no liability for a delay caused by Company's gross negligence or intentional acts or omissions or caused by a Force Majeure event. Client shall not be charged [*] if Company can avoid idle capacity costs by successfully re-allocating the designated resource with new, unplanned work for another client.

3.12 Changes to Firm Orders. Any Firm Order may be amended only by mutual agreement of the Parties and such amendments shall not affect the Minimum Order Requirement. Client may submit purchase orders for volumes of API or Drug Product in excess of any Firm Order subject to the limitations herein. Company shall exercise commercially reasonable efforts to comply with any proposed amendments to accepted Firm Orders or accommodate additional purchase orders, but shall not be liable for its inability to do so. Client acknowledges that Company will rely on the Rolling Forecast and Firm Orders submitted pursuant to Articles 4 and 5 herein in ordering or producing the Raw Materials required for production, including the Manufacture of intermediate CML-474. To accommodate changes in orders, Company shall order or produce Raw Materials sufficient to meet Client's excess order requirements. If Raw Materials ordered or produced to support Client's excess order requirements are not included in API or Drug Product Manufactured [*], or if such Raw Materials have expired (subject to a cGMP compliant inventory rotation such as "First-in First-Out"), [*].

API: [*], provided the purchase order is issued no later than six (6) months prior to the scheduled Manufacture start date. Any request is subject to DEA quota and Raw Materials availability. [*].

Drug Product: [*], provided the purchase order is issued no later than three (3) months prior to the scheduled Manufacture start date. Any request is subject to available capacity, DEA quota, and Raw Materials availability. [*]

3 . 1 3 Stability Study Cancellation. [*], as defined in the approved stability protocol, [*], as defined in the approved stability protocol, [*], as defined in the approved stability protocol, [*]. Upon cancellation, Client shall pay any fees associated with the removal and disposition of samples from the stability chambers, if any, and all Services completed through the effective date of cancellation.

3.14 Steering Committee; Project Management.

(a) Steering Committee. Company and Client will jointly constitute a team ("Steering Committee") including at a minimum, senior representatives from Operations, Commercial and Quality from each Party (or such representatives as the Parties mutually agree) to oversee the work under each Work Order as well as commercial Manufacturing with one (1) representative from each of Client and Company having the authority to make decisions on behalf of such Party. The Steering Committee representatives may invite other employees, consultants or advisors of the Parties or their Affiliates to the Steering Committee meetings, to serve in an advisory capacity as relevant to the matters at hand. The Steering Committee will be considered as a working committee that will have as its goal the prompt and mutually agreeable resolution of any financial, technical or quality issues that may arise in order to advance and preserve a harmonious relationship established by and between Company and Client. Either Party may change its representatives on the Steering Committee at any time by written notice to the other Party.

The Steering Committee shall meet at least quarterly or as otherwise as may be necessary or agreed by the Steering Committee, which meetings shall occur by teleconference, videoconference or in person and may address any relevant issue a Party wishes to call to the attention of the Steering Committee, to review past performance on mutually agreed upon metrics, discuss future partnership objectives, and to oversee the relationship between Client and Company. The Steering Committee shall be responsible for performing the following functions:

(i) reviewing business strategy;

(ii) ensuring goal alignment by establishing and reviewing agreed upon KPI's;

(iii) assessing and developing risk mitigations and/or redundancies;

(iv) discussing market dynamics and impact to supply/demand;

(v) reviewing Client's Long-Term Forecast and Company's anticipated capacity at least annually; and

(vi) implementing procedures for project governance and the resolution of questions or disputes that may arise under this Agreement or a Work Order.

(b) Project Management. Promptly upon execution of this Agreement, Company and Client shall each designate such of their respective employees to sufficiently represent process development, quality assurance, analytical services, manufacturing, and project management to form a team ("Project Team").The project team has the responsibility to direct and oversee the activities to be carried out per this Agreement. Each Party shall also designate one of its employees to act as its project manager (each, a "Program Manager"), who will be primarily responsible for communicating all instructions and information concerning the project to the members of the Project Team. The Project Team and/or the Program Managers shall consult periodically during the performance of the Services, through face-to-face meetings, telephone conferences and/or videoconferences, at times to be mutually agreed upon by the Program Managers. Each Party may appoint a substitute or replacement Program Manager or a member(s) of the Project Team in the absence of its original Program Manager or original member(s) of the Project Team by notifying the other Party in writing of such substitution or replacement. Neither the Program Managers nor the Project Team shall have the right to modify, amend or waive any provision of this Agreement.

ARTICLE 4
SPECIFIC API MANUFACTURING TERMS

In addition to the foregoing, the following provisions will apply to API Manufacturing Services. For clarification, "API Manufacturing Services" shall mean services performed in Company's GMP manufacturing suites and in-process testing directly supporting those activities. The terms contained in this Article 4 shall not apply to Drug Product Manufacturing Services (as defined in Article 5 below).

4.1 Forecasting. [*], unless otherwise agreed by the Parties, Client shall provide to Company a written non-binding delivery forecast estimating Client's annual requirements [*] (each such forecast, the "API Long-Term Forecast").

Concurrent with the placing of its first API order with Company and during the first month of each calendar quarter thereafter, [*], specifying the requested delivery dates by calendar quarter (each, a "Rolling Forecast"). Notwithstanding anything contained in this Section 4.1, Client shall provide the first API order under this Agreement at least [*] prior to the expected delivery date.

In response to each Rolling Forecast, Company shall provide Client with an estimated schedule of Manufacturing start and delivery dates, including a schedule for Manufacture of CML-474, if required to meet Client's Rolling Forecast requirements. The first [*] shall show specific dates and the [*] shall be shown by quarter.

4.2 Firm Commitments.

(a) Provided Company is not in default of this Agreement, [*].

(b) Except as provided in Section 2.5(a) above, [*], as determined by the Manufacturing start dates, shall be [*] for Company to produce such quantities on the delivery dates described therein and for Client to purchase the quantities of API specified therein (the "API Firm Commitment"); [*] shall be [*] upon the Parties.

(c) Client understands that to ensure a timely supply of API and Drug Product, it is necessary for Company to Manufacture CML-474 in sufficient volumes to meet the forecasted production requirements for API in Client's Rolling Forecast. Client understands and agrees that Company shall rely upon the Rolling Forecast to produce such quantities of CML-474 as required to meet the forecasted quantities of API in Client's Firm Commitment. Client will review plans for CML-474 Manufacturing and the Parties shall agree to the plan to support API supply.

(d) With respect to each API Firm Commitment, Client shall submit to Company binding written purchase orders (an "API Firm Order") confirming the quantity of API ordered and CML-474 as required by Company (which shall be in full Batch quantities), the requested delivery dates, and such other information as Company may find reasonably necessary to Manufacture the API and CML-474, if applicable. Company will confirm acceptance of any API Firm Order (consistent with this Agreement) within [*] of receipt and respond with a schedule of estimated Manufacture start dates and estimated delivery dates. Except as provided in Section 3.10 of this Agreement, the Parties expressly agree that any requested delivery dates shall not be binding on Company and that any timelines represent the Parties' best estimates of the timing for the various activities or Services to be performed.

(e) All purchase orders shall be placed in accordance with this Section 4.2 and no later than nine (9) months prior to the planned Manufacturing start date. Company shall Manufacture and prepare for shipment the quantity of API specified in the API Firm Order and related purchase orders. If requested by Client, Company shall use its commercially reasonable and good faith efforts to deliver quantities in excess of [*] of the applicable API Firm Order subject to available capacity. The API Firm Order shall be made available for shipment in accordance with Section 6.1 (Delivery/Shipment).

(f) Company's acceptance of any API Firm Commitment or purchase order is contingent upon Company's ability to obtain a DEA quota. Further, Company's ability to Manufacture designated quantities of API for Client shall be contingent upon Company obtaining a DEA quota sufficient to meet Client's commercial API demand. Company reserves the right to modify any API Firm Order, as needed, to comply with regulatory requirements, including DEA quota. At the time Company is required by DEA to submit request for controlled substance quota (currently in the month of May of the current year for the following year) Company shall use commercially reasonable efforts to obtain necessary DEA quotas using the most current Rolling Forecast. Additional requests will be made as required based on increases to the API Firm Order.

4.3 Cancellation. Company, at its sole discretion, [*] (or Batch Manufacture start date if Company is not manufacturing a series of Batches in a campaign) (a "Cancellation Fee"). Such Cancellation Fee will be [*]. Client is responsible for [*].

4.4 API and CML-474 Process Yield Company shall use commercially reasonable efforts to maximize the API process yield (the "API Yield") and the [*] for each commercial Batch. The [*] the respective commercial Manufacturing process, or as may be agreed to by the Steering Committee. [*]. Manufacturing line losses for RM1023 will be calculated based on [*] during the Commercial Year, after reconciling all Batches produced during the calendar year. Within [*] the previous Commercial Year, [*]. Client shall provide documentation of the RM1023 acquisition cost on an annual basis.

ARTICLE 5
SPECIFIC DRUG PRODUCT MANUFACTURING TERMS

In addition to the foregoing, the following provisions will apply to Drug Product Manufacturing Services. For clarification, "Drug Product Manufacturing Services" shall mean services performed in Company's GMP manufacturing, inspection or packaging suites and in-process testing directly supporting those activities. All other services are defined as non-Manufacturing. The terms contained in this Article 5 shall not apply to API Manufacturing Services.

5.1 Forecasting. [*], unless otherwise agreed by the Parties, [*].

[*] (each, a "Rolling Forecast") specifying by quarter the requested delivery dates. Notwithstanding anything contained in this Section 5.1, [*]

In response to each Rolling Forecast, Company shall provide Client with an estimated schedule of Manufacture start and corresponding delivery dates, the first [*] of which shall be displayed by week, and the remainder shall be shown by quarter.

5.2 Firm Commitments.

(a) [*]

(b) [*] Company to produce and deliver such quantities on the delivery dates described therein, and for Client to accept such Batches delivered per the terms of this Agreement (the "Drug Product Firm Commitment"). [*].

(c) With respect to each Drug Product Firm Commitment, Client shall submit to Company binding written purchase orders (a "Drug Product Firm Order") confirming the quantity of each Drug Product ordered (which shall be in full Batch quantities), the requested delivery dates, and such other information as Company may find reasonably necessary to Manufacture the ordered Drug Product. Company will confirm acceptance of any Drug Product Firm Order (consistent with this Agreement) within [*] of receipt and respond with a schedule of estimated Manufacture start dates and estimated delivery dates. Except as provided in Section 3.10 of this Agreement, the Parties expressly agree that any requested delivery dates shall not be binding on Company and that any timelines represent the Parties' best estimates of the timing for the various activities or Services to be performed.

(d) [*]

(e) [*] Company shall Manufacture and prepare for shipment the quantity of a Drug Product specified in the Drug Product Firm Order and related purchase orders. Notwithstanding the foregoing, with respect to a Drug Product, in no event shall Company be required in any calendar quarter to deliver more than [*] of the quantities in the applicable Drug Product Firm Order applicable to that quarter but Company shall use its commercially reasonable and good faith efforts to deliver quantities in excess of [*] of the applicable Drug Product Firm Order, subject to available capacity. The Drug Product Firm Order shall be made available for shipment in accordance with Section 6.1 (Delivery/Shipment).

(f) Company's acceptance of any Drug Product Firm Commitment or purchase order is contingent upon Company's ability to obtain a DEA quota. Further, Company's ability to Manufacture designated quantities of Drug Product for Client shall be contingent upon Company obtaining a DEA quota sufficient to meet Client's commercial Drug Product demand. Company reserves the right to modify any Drug Product Firm Order, as needed, to comply with regulatory requirements, including DEA quota. At the time Company is required to submit the necessary request for controlled substance quota to DEA (currently, due in the month of April, for quota for the following year) Company shall use commercially reasonable efforts to obtain necessary DEA quotas using the current Rolling Forecast. Company shall make additional requests as required, based on increases to the Drug Product Firm Order.

5.3 Cancellation. Company, at its sole discretion, reserves the right to charge [*] for any Batch or campaign that is [*] Manufacture start date (or Batch Manufacture start date if Company is not Manufacturing a series of Batches), [*]. Such Cancellation Fee will be [*]. Client is responsible for [*].

5.4 API Consumption Factor. Company shall use commercially reasonable efforts to maximize the API Yield for each commercial Batch of Drug Product. A maximum API consumption target, or Drug Product per API ratio, shall be [*] using the commercial Manufacturing process or as may be agreed to by the Steering Committee. Within [*] following the end of each Commercial Year, Company shall prepare an annual reconciliation of Drug Product Batches to calculate the annual Drug Product yield. For any API consumption above the API consumption target [*].

ARTICLE 6
DELIVERY; ACCEPTANCE AND REJECTION

6.1 Delivery/Shipment. Company shall use commercially reasonable efforts to make API and Drug Product available for shipment by the delivery date requested in the applicable Firm Order. All API and Drug Product(s) shall be delivered [*] (Incoterms 2010) Company's Manufacturing Facility. Client shall pay all crating, skidding, rigging, customs, freight, shipping, insurance and common carrier charges on all shipments in connection with Client's chosen method of shipment. Unless otherwise agreed or due to Company's gross negligence or intentional acts or omissions, Company shall have no liability for loss or damage to API or Drug Product(s) that occurs during shipment.

In the case of scheduled Drug Product, prior to pick-up by the carrier Client must provide Company with reasonable evidence (e.g. a copy of the current DEA registration for the destination, when applicable) that the destination for the Drug Product is authorized to receive the Drug Product. Notwithstanding anything to the contrary in this Agreement or any Work Order, Client acknowledges and agrees that Company shall have no obligation to release Drug Product for shipment to any destination for which

Client has not provided adequate evidence of authorization as required in this Section 6.1. [*]. [*]

Should Client not take delivery of API or Drug Product(s) within [*]. Company shall store API or Drug Product for up to [*], after which time, Company shall invoice Client [*] for storage fees at Company's then-current rates. Company shall store all API and Drug Product at proper temperatures, in proper conditions and in accordance with applicable Specifications, cGMP and as may be required by Applicable Law(s). [*]. Notwithstanding anything to the contrary in this Section 6.1, the time periods noted above shall automatically extend and Client shall not be charged for storage fees if Client either requests additional information as part of its inspection of API and/or Drug Product, or rejects API and/or Drug Product that was Released To The Client as noted in Section 6.2 below.

Notwithstanding the foregoing, where Company Manufactures API to be used in production of the Drug Product at a Facility, [*] until the API shelf life expires or such API is used in the Manufacture of Drug Product. Company shall arrange for shipment on behalf of the Client upon Release To The Client of Batch documentation. Title to API used in production of the Drug Product shall remain with Client at all times while in Company's possession or stored on Client's behalf. [*] all required insurance in amounts necessary to insure all API and Drug Product while maintained at any Facility or shipped between Company's Facilities.

6.2 Inspection, Acceptance and Rejection of Delivered API or Drug Product.

(a) Upon [*], Client shall have the right, but not the obligation, to inspect and test the API and Drug Product. Client may, [*] (the "Inspection Period"), reject any API and Drug Product that:

i. was not in compliance with the applicable API and Drug Product Specifications or such API and Drug Product's Certificate of Analysis at the time of [*]; or

ii. is recalled by any regulatory authority or by Company due to Company's negligence, intentional acts or omissions or breach of this Agreement (collectively, "Nonconforming Product").

In the event that any API or Drug Product is rejected or if additional information regarding Batch release documentation was requested by Client, by written notice to Company [*], then such API or Drug Product shall be deemed accepted. This shall not include API or Drug Product that later is found to have had Latent Defect(s) which were not reasonably discoverable [*]. As used herein, "Latent Defect" shall mean any defect in any Batch of API or Drug Product that subsequently becomes evident, provided that the defect is attributable to Company and was not reasonably discernible during the Inspection Period. Following confirmation or substantiation by a mutually agreeable independent expert, Company will only be responsible for Latent Defects to the extent such defect is directly attributable to Company's breach of warranties set forth in Section 10.1 herein or breach of any of its obligations in Manufacturing API and/or Drug Product as provided in this Agreement. Notwithstanding any other provision contained herein, Company shall not be responsible for any Latent Defect discovered [*].

(b) Company will only be responsible for Batch(es) of API or Drug Product rejected after the Inspection Period to the extent that Company is responsible for said non-conformity. Notwithstanding anything to the contrary herein, in no event shall Company be responsible for noncompliance with Specifications for API or Drug Product that met Specifications at time of Release To The Client or from non-conformities that result from a deficiency or change in the Client supplied materials utilized in such Batch(es) of API or Drug Product(s) or a defect in the Specifications for the API or Drug Product(s).

(c) In the event that Client rejects API or Drug Product(s) as provided in this Agreement, Company shall use commercially reasonable efforts to replace the Nonconforming Product(s) or give notice that it disagrees with the rejection. If Client and Company do not agree whether the API or Drug Product met Specifications at the time of Release To The Client, such API or Drug Product(s) shall be submitted for testing to an independent laboratory acceptable to both Parties for the purpose of determining the results. Any determination by such authority with respect to compliance to Specification shall be final and binding upon the Parties. If it is determined that such API or Drug Product(s) failed to meet applicable Specifications [*] due to Company's breach of its warranties contained in Section 10.1 herein, or if due to Company's gross negligence and/or intentional acts or omissions, Company shall pay the expenses associated with such analyses; otherwise, Client shall pay such expenses and purchase the API or Drug Product in accordance with this Agreement.

(d) If it is determined that Company is directly responsible for the nonconformance, Company shall as soon as it is commercially practicable to do so, replace such Nonconforming Product with conforming API or Drug Product (the "Replacement Product") at its sole cost and expense, not including the price for any Client supplied materials in excess of insurance limits. All Replacement Product shall be subject to Client's testing and approval as provided in this Section 6.2 and the Quality Agreement. If Client previously paid the Purchase Price for the Nonconforming Product(s), then, Company shall Manufacture the Replacement Product and prepare Replacement Product for shipment in accordance with Section 6.1 (Delivery/Shipment).

ARTICLE 7
PRICE, TERMS OF PAYMENT

7.1 Purchase of API and Drug Product(s). The Batch size and the initial prices to be paid for the API, CML-474, and Drug Product – Finished, if any, and Drug Product – Bulk by Client to Company shall be set forth in Appendix B-1, B-2, and B-3 respectively, attached hereto and incorporated herein by reference (the "Purchase Prices"). The Purchase Prices are in United States Dollars, and are exclusive of applicable taxes. Client shall be responsible for the payment of any and all taxes applicable to the API, CML-474, Drug Product(s) and Services described herein.

7.2 Price Change; Notice.

(a) [*], subject to Section 7.2 (b) below, [*] such increased prices pertain ("Raw Material Costs"), and (ii) [*], for API or Drug Product to be delivered after January 1st for each year during the Term. Upon Client's request, Company shall provide reasonable documentation that reflects the increase in cost of Raw Material Costs. Company may also increase the Purchase Price to reflect any material change in an environmental, safety or regulatory standard that impacts Company's costs or its ability to perform the Services. Upon request, Company shall provide written evidence of this material change prior to any change in the Purchase Price. Company shall provide written notification, and written, supporting evidence upon request, of any annual increase in the Purchase Prices prior to the January 1st effective date of the increase in Purchase Prices, or as increases in the cost of Raw Materials occur, as applicable.

(b) In the event the first Commercial Year does not commence on or before the Commercial Year Outside Date, then Purchase Price increases permitted by Section 7.2(a) shall apply beginning on January 1st of the year immediately following the Commercial Year Outside Date. In such event, until [*]

7.3 Invoices.

(a) **Intermediate**. Company shall provide invoices to Client for CML-474 upon each Release To The Client of Batch Documentation.

(b) **API.** Company shall provide invoices to Client for API upon [*]. Where Company Manufactures API to be used in production of Drug Product at another Facility, Company shall arrange for shipment and provide invoices to Client upon [*].

(c) **Drug Product.** Company shall provide invoices to Client for Drug Product upon [*] (e.g. finished bulk, finished packaged, or finished packaged and labeled, including serialization).

(d) Client shall pay each such invoice [*], regardless of when or whether Client has arranged for shipment of the API or Drug Product(s) to its final destination.

Client shall pay each undisputed invoice, in United States Dollars by business check, Client wired funds or Client ACH transfers (unless otherwise agreed upon in writing by the Parties), [*]. Invoice receipt shall be defined as date of electronic verification of invoice communication via fax or email to a Client contact designee. Company reserves the right to charge administrative fees when Client's payment preferences deviate from Company's standard practices. Client shall make no setoff or deduction of any kind from any payments due to Company unless Client receives written authorization from Company authorizing such setoff or deduction. Undisputed invoice balances not remitted [*]. Should any part of the invoice be in dispute, Client shall pay the balance of the undisputed amount according to the terms and conditions described herein while said dispute is being resolved. Should payment of undisputed amounts not be received within [*] of Client's receipt of an invoice, after [*] notice to Client the payment shall be deemed in default and Company reserves the right to cease all work and pursue collection activities. In such event, Client shall be responsible for all collection fees and expenses incurred by Company, including reasonable attorney's fees.

7.4 Taxes and Duties. Client shall be responsible for all taxes imposed on the sale of API, Drug Product or Services by operation of law and Purchase Prices are exclusive of applicable taxes. The consideration stated under any Work Order or otherwise is net of any taxes imposed on the amounts payable to Company hereunder.

ARTICLE 8
REGULATORY MATTERS; RECORDS

8.1 Access to Company's Facilities by Client Representatives. During regular business hours and mutually agreed upon times, Client may review the records of Company relating to the Services performed and expenses incurred to assure compliance with all provisions of this Agreement. Such review [*], unless otherwise agreed, and shall be offered to Client by Company not more than [*]. Subsequent reviews during the same calendar year or such reviews that cannot be completed in [*] will be at Client's sole cost and expense, at Company's then current rates [*]. Client shall also be provided an invoice for any incidental expenses Company incurs resulting from such review. While Services are being performed for Client, [*], or more if agreed upon by the Parties in writing, shall be permitted to be on-site at Company's Facility as reasonably required to monitor such Services. Client's rights in this Section 8.1 shall be subject to compliance with Company's reasonable measures for purposes of confidentiality, safety, and security, and will be further subject to Client's compliance with Company's premises rules that are generally applicable to all persons at Company's Facilities. Company reserves the right to require an independent third party to audit on behalf of any client deemed by Company in its reasonable discretion to be a direct competitor of Company. Should Client utilize one or more third party(ies) in exercising its rights in this paragraph, Client certifies that such party(ies) shall be subject to an obligation of confidentiality consistent with the obligations of confidentiality required of Client hereunder and such third party(ies) shall be subject to any and all conditions upon Client's rights that are set forth in this Section.

At all times, Company shall be solely responsible for obtaining, maintaining and paying for all necessary approvals, licenses and permits to perform the Services provided in this Agreement at each of its Facilities.

Any 'for cause' audits shall be conducted in accordance with the Quality Agreement (defined below).

8.2 Inspections by Governmental or Regulatory Authority. Company shall be responsible for handling and responding to any FDA or other governmental body inspections or inquiries received by Client or Company regarding the Services during the Term of this Agreement. Company shall prepare for preapproval inspection at its own cost (not including out-of-pocket expenses incurred) and allow audits and inspections by the Pharmaceuticals and Medical Devices Agency (PMDA), European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA), and the FDA. All out-of-pocket costs incurred by Company for regulatory agency inspections directly related to the API and/or Drug Product being Manufactured at the Facility shall be charged to Client. In cases where Company is required to provide significant Client or Drug Product specific support to such inspections or inquiries, or allow audits or inspections by regulatory agencies other than those listed above, Client agrees to pay Company for the time required, at Company's then current regulatory support rate.

Each Party shall notify the other regarding any such inquiries and provide the other Party copies of any pertinent correspondence from such authorities related to the API, Drug Product or Services covered in this Agreement. Company shall provide to Client and any governmental body any information reasonably requested by Client and/or such governmental body concerning any governmental inspection related to any API or Drug Product (with all information provided to Client being subject to the confidentiality provisions in Article 14 herein and with Company being able to redact any information provided to Client to remove third party confidential information that does not relate to the Client's API or Drug Product). Client agrees to fully cooperate with and assist Company in fulfilling its obligations pursuant to this Section 8.2. Client shall have the right to review and comment on any communication to any regulatory authority which is related to or involves API or Drug Product

8.3 Quality Agreement. The Parties have entered into a quality agreement, effective November 4, 2016 (the "Quality Agreement") which shall be maintained in the controlled documents of the Parties. The Quality Agreement details the quality and regulatory responsibilities of the Parties with respect to the API and Drug Product; provided, however, that in the event of conflict between the terms of this Agreement and the Quality Agreement, (i) the provisions of the Quality Agreement will prevail with respect to all matters pertaining to, or governed by, GMP and (ii) in all other respects, the provisions of this Agreement will prevail.

8.4 Retention of Documentation. Raw data, documentation, Batch records, source documents and reports (collectively, "Documentation") shall be retained by Company for the period of time set forth in the Quality Agreement, with the exception of Documentation that supports validations, which will be maintained for the duration of the utilization of the method or process validated. If specifically requested by Client, longer term storage may be arranged at Client's expense. Otherwise, Documentation may be destroyed following the retention period.

During the above-described retention periods, Documentation shall be available for inspection by Client, its authorized agents and authorized government agencies.

8.5 Retention of Materials. Samples retained by Company shall be held according to the Quality Agreement.

Analytical test samples are retained for [*] and then destroyed. Prior arrangements must be made to retain samples [*].

Upon request, Client may arrange longer term storage at its expense. Documentation, Drug Product retains or other materials shall be held by Company for longer periods of time if required by Applicable Law(s).

8.6 Safety Information. Client shall provide all necessary safety information concerning chemical entities it supplies to Company to ensure safe handling, storage, usage, shipment and disposal. Company may refuse, without liability, substances that Company cannot handle safely or which lack, in Company's assessment, sufficient information such that Company can determine that such substances do not pose a risk to health or safety while in Company's possession.

8.7 Waste. Company will be responsible for the removal and disposal of all waste resulting from Company's Manufacturing of the API and/or Drug Product, consistent with the Material Safety Data Sheet and DEA guidelines.

8.8 Access to Drug Master Files. Where applicable, Company will grant Client reference rights to all Drug Master Files (the "DMF") and Site Master Files (the "SMF") necessary to support Client's regulatory filings for the API and/or Drug Product. To affect this, Company will execute certain letters of authorization, which will be delivered to the appropriate regulatory authorities to permit them to consult Company's DMF and SMF in their review of Client's API and/or Drug Product regulatory submissions. Company will send copies of such authorization letters to Client. Company will update its DMF and SMF annually and will inform Client prior to making any modifications thereto in order to permit Client to amend or supplement any affected regulatory submissions and filings for API and/or Drug Product.

8.9 Ownership of Regulatory Approvals. The Parties agree that Client will be the sole and exclusive owner of all right, title and interest in and to all regulatory approvals related to the API and Drug Product and any submissions for such regulatory approvals. Company will reasonably assist Client in the preparation of all documents necessary to affect Client's rights in such regulatory approval applications and submissions, at the expense of Client.

ARTICLE 9
INSURANCE

9.1 Client Insurance. At all times while this Agreement is in effect Client shall maintain the following insurance:

a. Products Liability Insurance (including coverage for Clinical Trials) in an amount of not less than [*]; or, if outside the US at compulsory limits (whichever is greater).
b. General Liability (Premises Operations) in the amount of not less than [*] per occurrence and in the annual aggregate.
c. Automobile Liability in the amount of not less than [*] combined single limit;
d. Workers' Compensation (or equivalent outside the U.S) – Statutory limits;
e. Employer's Liability in an amount not less than:
   (i) [*] – Each Accident
   (ii) [*] – Disease Each Employee
   (iii) [*] – Disease Policy Limit.

Client may utilize its Umbrella Liability policy to satisfy the above insurance requirements.To the extent that any of the above coverages are underwritten on a claims-made basis, Client shall agree to maintain coverage, or procure an Extended Reporting Period ("ERP" or "Tail Coverage") for a period of [*].

Coverage should be placed with an insurance carrier with an A.M. Best rating of not less than A-VII. Evidence of the above coverage shall be provided prior to the Effective Date of this Agreement and annually thereafter during the Term.

Client shall cause its insurers to name Company as additional insured for the following lines of coverage:

x. Products Liability/Clinical Trials;
and
y. Commercial General Liability;
and
z. Umbrella Liability.

9.2 Company Insurance. At all times while this Agreement is in effect Company shall maintain the following insurance:

a. Products and Professional Liability Insurance (including coverage for Clinical Trials) in an amount of not less than [*].

   Such Professional Liability Insurance shall include third-party insurance coverage and shall be at Client's expense, with a limit of [*], to cover loss or damage to Client supplied Raw Materials, API or Drug Product arising from Company's negligence in the Manufacturing or handling of any API, CML-474, Client supplied Raw Materials or Drug Product as further provided in Sections 6.2(d), 11.4 and 12.1(b). In the event of an actual loss, Company shall reimburse Client for the premium and pay any applicable deductible attributable to the policy and such policy shall pay covered amounts in excess of the deductible. At Client's option and expense, Company shall renew the third-party insurance policy annually.
b. General Liability (Premises Operations) in the amount of not less than [*] and in the annual aggregate.
c. Automobile Liability in the amount of [*];
d. Workers' Compensation (or equivalent outside the U.S) – Statutory limits;
e. Employer's Liability in an amount not less than:
   (i) [*] – Each Accident
   (ii) [*] – Disease Each Employee
   (iii) [*] – Disease Policy Limit.

To the extent that any of the above coverages are underwritten on a claims-made basis, Company shall agree to maintain coverage, or procure an ERP or Tail Coverage for a period of [*].

Coverage should be placed with an insurance carrier with an A.M. Best rating of not less than A-VII. Evidence of the above coverage shall be provided prior to the Effective Date of this Agreement and annually thereafter during the Term.

Company shall cause its insurers to name Client as additional insured for the following lines of coverage:

x. Products Liability/Clinical Trials;
and
y. Commercial General Liability;
and
z. Umbrella Liability.

Company and Client shall each cause its respective insurers to waive all right of subrogation and shall cause insurers to agree that they shall act as primary and not require contribution from any valid and collectible insurance which may be available to Company for liability arising from Client's negligence or to Client for liability arising from Company's negligence.

ARTICLE 10
REPRESENTATIONS, WARRANTIES AND COVENANTS

10.1 Representations, Warranties and Covenants of Company. Company hereby represents and warrants as follows:

(a) The execution, delivery and performance of this Agreement and the consummation of the transactions contemplated hereby are within Company's powers and have been duly authorized by all necessary action on the part of Company. This Agreement has been duly executed and delivered by Company and constitutes legal, valid and binding obligations of Company, enforceable against Company in accordance with its terms.

(b) The execution, delivery and performance by Company of this Agreement does not and will not (i) contravene or conflict with the organizational documents of Company, (ii) contravene or conflict with or constitute a violation of any Applicable Law(s), or (iii) breach or constitute a default under the provisions of any material contract, agreement or instrument to which it is a party or by which it is bound.

(c) Company shall perform its obligations hereunder in conformance with Applicable Law(s) (and cGMP if applicable).

(d) Company is not debarred and has not and shall not knowingly and intentionally use in any capacity the services of any employee or third party debarred under subsections 306(a) or (b) of the Generic Drug Enforcement Act of 1992.

(e) As of Release To The Client, all API and Drug Product(s) delivered to Client during the Term of this Agreement: (i) shall have been Manufactured by Company in material compliance with this Agreement, the Quality Agreement, and cGMP, in each case, as in effect at the time of Manufacture, (ii) assuming compliance by Client with Section 3.7 (Labeling), shall not be adulterated or misbranded within the meaning of the Act, and (iii) shall not have been Manufactured by Company in violation of any Applicable Law(s) in any material respect.

(f) [*], Company shall convey good title to all API and Drug Product(s) so delivered to Client or its designee.

(g) Company has all necessary and proper licenses, permits, approvals and expertise to perform its Manufacturing and related duties under this Agreement and any Work Order, and all Facilities have all necessary licenses, permits, and approvals necessary to perform the Manufacturing and related duties provided in this Agreement.

(h) Under no circumstances shall Company transfer any API and/ or Drug Product to any third parties, including any generic drug manufacturers, without first obtaining Client's prior written approval, which approval may be withheld in Client's sole discretion.

(i) There are no suits, claims, or proceedings pending, or to its best knowledge and belief, after due inquiry, threatened against it or any of its Affiliates in any court or by or before any governmental body or agency which would affect its ability to perform its obligations under this Agreement.

(j) Company represents and warrants to Client that, to the best of Company's knowledge, Company's Intellectual Property, that Company may license to Client under this Agreement or use in performing Services under this Agreement, does not infringe any patents of a third party. In performance of its obligations under this Agreement, Company will not knowingly incorporate into the Manufacturing process any third party Intellectual Property except with Client's consent.

EXCEPT AS SET FORTH IN THIS SECTION 10.1, COMPANY MAKES NO REPRESENTATIONS OR WARRANTIES, EXPRESS OR IMPLIED, AND SPECIFICALLY DISCLAIMS ALL SUCH REPRESENTATIONS AND WARRANTIES, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTIES OF MERCHANTABILITY, INFRINGEMENT, TITLE OR FITNESS FOR A PARTICULAR PURPOSE OR USE.

10.2 Representations, Warranties and Covenants of Client. Client hereby represents and warrants as follows:

(a) The execution, delivery and performance of this Agreement and the consummation of the transactions contemplated hereby are within Client's powers and have been duly authorized by all necessary action on the part of Client. This Agreement has been duly executed and delivered by Client and constitutes legal, valid and binding obligations of Client, enforceable against Client in accordance with its terms.

(b) The execution, delivery and performance by Client of this Agreement does not and will not (i) contravene or conflict with the organizational documents of Client, (ii) contravene or conflict with or constitute a violation of any Applicable Law(s), or (iii) breach or constitute a default under the provisions of any material contract, agreement or instrument to which it is a party or by which it is bound.

(c) Client shall comply in all material respects with all Applicable Law(s) relating to its Commercialization of the Drug Product(s).

(d) To the extent that Client supplies any Raw Materials or other information to Company (including packaging and labeling requirements) or engages in manufacturing with respect to any of the API or Drug Product (either directly or indirectly through a third party), all such Raw Materials or other information and formulas will comply with the Specifications and Applicable Law(s), including GMP.

(e) Client represents that to the best of its knowledge, the manufacture or the sale of the API or Drug Product(s) does not and will not infringe any third party intellectual property rights or other rights and that it is not aware of any patents existing in the Territory in which Client markets or distributes such Drug Product relating in any manner to the Drug Product or any use, method, activity or application relating thereto which could adversely impact upon or prevent Company from Manufacturing the API or Drug Product as contemplated by the terms hereof.

ARTICLE 11
INDEMNIFICATION

11.1 By Company. Company hereby indemnifies Client and its directors, officers, employees, Affiliates, stockholders, agents, attorneys, representatives, successors and permitted assigns (collectively, the "Client Indemnified Parties") against and agrees to hold each of them harmless from any and all claims relating to (i) product liability associated with the Client's API or Drug Product, (ii) losses, liabilities, obligations, damages, costs and expenses ("Losses") incurred by any Client Indemnified Party as a result of third party claims, actions or proceedings (collectively, "Third Party Claims") to the extent based upon, attributable to or resulting from the gross negligence, willful misconduct or intentional acts or omissions by a Company Indemnified Party in connection with this Agreement, (iii) intentional or willful infringement or alleged infringement of any Intellectual Property (except in either case if such Third Party Claims are directed at Client Intellectual Property), (iv) breach of any representations, warranties or covenants of Company under this Agreement, (v) personal injury or property damage to the extent that the injury or damage is the result of a material breach of any representations, warranties or covenants of Company under this Agreement; except in each case, to the extent such Losses are attributable to Client's material breach of this Agreement or arising from the gross negligence or willful misconduct of a Client Indemnified Party.

11.2 By Client. Client hereby indemnifies Company and its directors, officers, employees, wholly-owned subsidiaries, stockholders, agents, attorneys, representatives, successors and assigns (collectively, the "Company Indemnified Parties") against and agrees to hold each of them harmless from any and all Third Party Claims, including Losses incurred by any Company Indemnified Party to the extent based upon, attributable to or resulting from (i) intentional or willful infringement or alleged infringement of any third party Intellectual Property in the API or Drug Product (except in the case if such Third Party Claims are directed at Company Intellectual Property), (ii) any claim of personal injury or property damage to the extent that the injury or damage arises from the safety or efficacy of the Drug Product or is the result of a breach of this Agreement by Client, including, without limitation, any representation or warranty contained herein, (iii) any products liability claims related to Client API or Drug Product or claims arising directly or indirectly from the manufacture (but only to the extent caused by Client supplied Raw Materials), promotion, marketing, distribution or sale of, or use of or exposure to, the API or Drug Product, or Client supplied Raw Materials; except in each case, to the extent such Losses are attributable to Company's material breach of this Agreement, or arising from the gross negligence or willful misconduct of a Company Indemnified Party.

11.3 Indemnification Procedures.

(a) The indemnified Party shall give the indemnifying Party prompt notice of any such claim or lawsuit ("Indemnification Claim") (including a copy thereof) served upon it and shall fully cooperate with the indemnifying Party and its legal representatives in the investigation of any matter the subject of indemnification. The indemnifying Party may enter into a settlement agreement with a claimant but shall not admit liability to a claimant, purport to impose any obligation on the indemnified Party or fail to obtain a complete release of the indemnified Party without the prior written permission of the Party or Parties seeking indemnification, which permission shall not be unreasonably withheld. The indemnifying Party shall be responsible for all actual losses in the form of reimbursement for any Indemnification Claim.

(b) The failure of the indemnified Party to give reasonably prompt notice of any Indemnification Claim shall not release, waive or otherwise affect the indemnifying Party's obligations with respect thereto except to the extent that the indemnifying Party can demonstrate actual loss and prejudice as a result of such failure.

(c) The indemnified Party shall have no liability for any settlement entered into by an indemnified Party without the indemnifying Party's prior written consent.

11.4 Limitation on Liability. Except where arising from breach of Article 14 or gross negligence or willful misconduct, neither Party shall be liable, whether in contract, tort (including negligence) or otherwise, for any punitive, special, indirect, incidental, consequential or exemplary damages (including lost profit or business interruption even if notified in advance of such possibility) arising out of or pertaining to the subject matter of this Agreement, or performance of the Services.

In the event of a failed Manufacturing Batch due to Company's sole negligence, [*] Company will be liable for the cost of the insurance premium and deductible as set forth in Section 9.1 of this Agreement as well as re-working, re-processing or Manufacturing a replacement Batch of Drug Product and/or API and/or CML-474 (as applicable), at no additional charge to Client, including components, manufacturing supplies and testing.

11.5 Aggregate Cap. Except where arising from breach of Article 14 or gross negligence or willful misconduct, the total aggregate liability of either Party to this Agreement arising out of the Services performed hereunder shall be [*]. Except as specifically stated in this Agreement, Company shall not be liable for Client-supplied materials. Such liability cap amount does not alter each Party's insurance obligations under Article 9 (Insurance).

ARTICLE 12
COMPLAINTS; RECALL PROCEDURES

12.1 Complaints and Recalls.

(a) Complaints. Drug Product complaints received by Client with respect to Drug Product Manufactured by Company hereunder shall be sent to Company within the time period set forth in the Quality Agreement, after receipt to:

Alcami Corporation
Attention: Corporate Quality
2320 Scientific Park Drive
Wilmington, NC 28405
Facsimile No.: (910) 815-2387
Email: product.complaints@alcaminow.com

As more fully described in the Quality Agreement, Company shall investigate all complaints directly associated with the Manufacture of Drug Product(s) and shall provide an update every [*] and a report to Client regarding its investigation and any conclusions. Client shall investigate all other complaints associated with the Drug Product(s).

(b) Recall Procedures. As further set forth in the Quality Agreement, in the event that a recall, withdrawal or field correction of any Drug Product (a "Recall") is initiated, whether by a statutory or regulatory authority in any jurisdiction or by Client, Client shall notify Company promptly and in any event within [*] of receipt of written notice. Company shall reasonably cooperate with Client in connection with any Recall. Client shall (i) bear the cost of and be responsible for conducting all Recalls or market withdrawals of Drug Product, and (ii) purchase the Drug Product that was Recalled or incorporated into any final product that was Recalled, and (iii) reimburse Company for any out-of-pocket expenses related to the Recall. Notwithstanding the foregoing, to the extent such Recall or market withdrawal is directly attributable to Company's breach of warranties set forth in Section 10.1 herein, or Company's gross negligence or intentional acts or omissions, upon confirmation or substantiation by a mutually agreeable independent expert, Company shall Manufacture Replacement Product to replace any Nonconforming Product, including API (but not including any Client supplied materials in excess of insurance limits). Subject to Section 11.5, Company also shall be responsible to pay for the administrative expenses of such Recall, limited to reasonable expenses of notification of customers, the return and destruction of the recalled Nonconforming Product and any costs associated with delivery of Replacement API and/or Drug Product, but will not include any exceptional testing or investigations not required by Applicable Law(s). The foregoing constitutes Client's sole remedy and shall be Company's sole liability with respect to Recalls under this Agreement.

ARTICLE 13
TERM AND TERMINATION

13.1 Term of the Agreement. Unless earlier terminated in accordance with this Article 13, this Agreement shall take effect and commence on the Effective Date and continue in effect for eight (8) years (the "Initial Term"). In addition, after the expiration of the Initial Term, this Agreement will automatically renew for consecutive two (2) year terms (each, a "Renewal Period") unless either of the Parties terminates this Agreement at the end of the Initial Term or any applicable Renewal Period by providing the other Party with written notice, at least twelve (12) months prior to the end of the Initial Term or Renewal Period. The Initial Term and all Renewal Periods shall be collectively referred to herein as the "Term".

Notwithstanding the foregoing, unless the Parties agree or otherwise terminate the Services under Article 4 or Article 5 and all Work Orders in process, the provisions of this Agreement will continue to be effective for so long as Services are being performed under this Agreement, an API Firm Order, Drug Product Firm Order or any purchase order executed prior to expiration or termination of this Agreement. Termination of any Services or Drug Product under this Agreement shall not terminate this Agreement in its entirety unless so directed by the terminating Party and permitted under the terms of this Agreement.

13.2 Termination of the Agreement. Notwithstanding Section 13.1 herein, this Agreement may be terminated as follows:

(a) immediately upon the delivery of written notice by one Party, if the other Party is in material breach of any of the provisions of this Agreement and such breach is capable of being cured and is not cured within [*] after receipt of written notice identifying such breach (or if the breach is not capable of being remedied in such time period, if such cure has been commenced but is not diligently pursued and prosecuted to completion within a commercially reasonable time); or

(b) immediately upon the delivery of written notice by one Party, if the other Party has been unable to perform its obligations hereunder for [*] by reason of Force Majeure; or

(c) either Party at its sole option may immediately terminate this Agreement upon written notice, but without prior advance notice, to the other Party in the event that (i) the other Party is declared insolvent or bankrupt by a court of competent jurisdiction; (ii) a voluntary petition of bankruptcy is filed in any court of competent jurisdiction by such other Party; (iii) the other Party ceases or threatens to cease to carry on business; (iv) this Agreement is assigned by such other Party for the benefit of creditors; (v) there is a complete market withdrawal of a Drug Product; or (vi) in the event Client does not obtain appropriate regulatory authorization or approval to manufacture, market, sell and/or otherwise Commercialize a Drug Product in the Territory (including, but not limited to, failure to obtain FDA and/or DEA approvals); or

(d) either Party may terminate this Agreement as to any Drug Product upon [*] written notice in the event that any governmental agency takes any action that prevents Client from importing, exporting, purchasing or selling such Drug Product; or

(e) either Party at its sole option may terminate this Agreement by providing not less than [*] advance written notice of request to terminate this Agreement in its entirety.

13.3 Termination of Services, Products, or a Work Order. Unless otherwise agreed upon by the Parties, either Party may terminate the API Manufacturing Services under Article 4, or the Drug Product Manufacturing Services under Article 5, in whole or in part, as follows:

(a) on [*] written notice; or

(b) immediately upon the delivery of written notice by one Party, if the other Party is in material breach of any of the provisions of this Agreement and such breach is not cured within [*] after receipt of written notice identifying such breach (or if the breach is not capable of being remedied in such time period, if such cure has been commenced but is not diligently pursued and prosecuted to completion within a commercially reasonable time); or

(c) immediately upon the delivery of written notice by one Party, if the other Party has been unable to perform its obligations under this Agreement, or any Work Order for [*] by reason of Force Majeure; or

(d) either Party at its sole option may immediately terminate this Agreement or Services performed under Article 4 or Article 5 herein, upon written notice, but without prior advance notice to the other Party, in the event that (i) the other Party is declared insolvent or bankrupt by a court of competent jurisdiction; (ii) a voluntary petition of bankruptcy is filed in any court of competent jurisdiction by such other Party; (iii) the other Party ceases or threatens to cease to carry on business; or (iv) this Agreement is assigned by such other Party for the benefit of creditors; or

(e) either Party may terminate this Agreement as to any Drug Product upon [*] written notice in the event that any governmental agency takes any action that prevents Client from importing, exporting, purchasing or selling such Drug Product; or

(f) either Party may terminate the Services performed under Article 4 or Article 5 of this Agreement if: (i) an individual Drug Product is withdrawn from the market; or (ii) an individual Drug Product is found to infringe a third party's intellectual property. Termination of a Service under this Section 13.3(f) shall result in the termination of only API Manufacturing under Article 4 or only Drug Product Manufacturing under Article 5 and shall not affect or terminate the remaining Manufacturing Services of this Agreement.

(g) Client may terminate any Work Order, if activities or Services have not yet commenced, on [*] written notice.

(h) In the event Client, in its sole discretion, changes the final packaging presentation of Finished Drug Product and Company is unable or unwilling (without costs or charges to Client) to accommodate changes, and/or if Client consolidates packaging services under a single vendor, Client may terminate Drug Product packaging services upon [*] notice. Termination will take effect upon completion of all binding Firm Orders outstanding at the time notification is provided. Changes in packaging shall not be deemed or considered Other Changes as contemplated in Section 3.4 above.

Termination pursuant to Section 13.3(b) may be effected only with respect to the API or Drug Product and related Article of this Agreement to which the material breach relates and shall be effected by delivering written notice of such termination to the other Party. Termination shall be effective upon the date of such written notice unless a later date is specified in such written notice.

13.4 Effect of Termination. Upon termination or expiration of this Agreement in its entirety or with respect to any particular Services or Drug Product(s):

(a) Cessation of Activities. Upon termination or expiration of this Agreement, or any Services or Drug Product(s), Company shall stop performing Services and each Party shall return to the other any Confidential Information of such other Party subject to such termination or expiration. Client shall pay for the cost of work, materials used for the project and Services performed through the effective date of the termination, reasonable project shut down costs, and Company's cost of all materials and Services irrevocably incurred which cannot be reallocated and any applicable Cancellation Fees. Any unconsumed materials may be returned to Client at Client's sole cost and expense, or credited toward future Services, where permissible.

(b) Payment of Minimum Order Requirement; Client to Take API or Drug Product. In the event of termination of this Agreement or any Services or Drug Product(s) pursuant to Section 13.3(a) or 13.3(h) above by Client, Client shall pay Company any balance remaining of any Minimum Order Requirement (as set forth in Section 4 for API and Section 5 for Drug Product) in the same manner as set forth herein. Further, Client shall, at its option and with respect to any API or Drug Product that are subject to termination, be permitted to take delivery for any Raw Materials with applicable cost and handling, work-in-process or finished API or Drug Product (at prices then in effect under Appendix B-1, B-2 or B-3).

(c) Firm Orders. In the event of termination of this Agreement or any Services, pursuant to the terms set forth herein, Firm Orders (as set forth in Section 4.2(d) for API and Section 5.2(c) for Drug Product) with respect to API and/or Drug Product(s) not yet started, may be cancelled at Client's option. Provided, if requested by Client in writing, Company will complete the Manufacture of any work-in-process or scheduled work that is subject to a valid and effective Firm Order on the date on which the termination is effective. Once such work-in-process or scheduled work is completed, the resulting API and/or Drug Product(s) shall be delivered in accordance with Client's Firm Orders and paid for by Client in accordance with the Purchase Prices initially set forth in Appendix B-1, B-2 or B-3.

(d) Technical Transfer. In the event of expiration or earlier termination of this Agreement, Client may, at its sole expense and by written notice to Company, seek reasonable assistance from Company with respect to the transfer to another manufacturer or third party of the then-current process for Manufacturing API and/or Drug Product ("Technology Transfer"). Following Company's receipt of this notice, the Parties will establish, in good faith, a schedule and plan to effect the Technology Transfer and Company will thereafter reasonably cooperate with Client in implementing the plan. Upon written approval of the project plan by the Parties and agreed payment schedule to Company by Client, Company shall perform the related activities reasonably necessary to effect such Technology Transfer in a timely manner. As part of the Technology Transfer, Company will make available for collection one (1) copy of all Documentation (to the extent not previously delivered to Client) generated pursuant to the Manufacturing Services up to the date of termination or expiration of this Agreement including Batch records, development reports and production process documentation.

13.5 Survival. Notwithstanding anything else contained herein, the Parties agree that the provisions which by their nature should survive termination or expiration of this Agreement, including any Work Order entered hereunder, shall survive expiration or earlier termination of this Agreement and specifically agree that the following provisions shall survive the termination of this Agreement: the definitions of Article 1 to the extent such definitions pertain to terms in surviving provisions, Articles 6, 7, 8, 9, 11, 12, 13, 14, 15 in their entirety, and Sections 2.3, 3.4 through 3.13, 4.2, 4.3, 5.2, 5.3, 10.1(f), 10.1(j), 16.9, 16.14, 16.15, and 16.16.

ARTICLE 14
CONFIDENTIALITY AND PUBLIC DISCLOSURE

14.1 Company will hold in strict confidence, and shall not disclose to any third party without Client's prior written consent, all proprietary or confidential information concerning all materials and information provided by Client (collectively, "Client Information"). Company further agrees that it shall not use Client Information for

any purpose other than providing Services for Client under this Agreement and any Work Order issued hereunder.

14.2 Client will hold in strict confidence, and shall not disclose to any third party without Company's prior written consent, all proprietary or confidential information and materials belonging to Company ("Company Information").

14.3 **"**Confidential Information" shall mean Client Information and Company Information. Confidential Information also shall include all of a Party's written or oral information, disclosed by, or made available to the other Party (whether or not it has been identified as confidential) that by the nature of the information or the circumstances surrounding disclosure ought reasonably to be treated as confidential and/or proprietary, including, but not limited to, any oral, written, graphic or machine-readable information including any software code, trade secret, patent application, drawing, or claim, information, data, and data results, price, technique, protocol, invention, idea, process, formula, sample, compound, extract, media, vector and/or cell line and procedures and formulations for producing any such sample, compound, extract, media, vector and/or cell line, any process, formula or data relating to any research project, work in process, future development, engineering, manufacturing, marketing, servicing, financing or personnel matter relating to a Party, its present or future products, sales, suppliers, clients, customers, employees, investors, or business. Without limiting the generality of the foregoing, any non-public information regarding or related to a Party's business, products, drugs, compounds or chemical structures shall be deemed such Party's Confidential Information. Each Party may disclose Confidential Information only to its, and its subsidiaries' and Affiliates', directors, officers and employees who have need to know Confidential Information for the purposes of this Agreement, and each Party will be responsible for ensuring that all its, and its subsidiaries' and Affiliates', directors, officers, and employees to whom Confidential Information is disclosed will also observe such obligations of confidentiality and non-use as provided herein.

14.4 The above confidentiality obligation shall not apply or shall cease to apply to any information which the receiving Party can demonstrate by documentary proof:

(a) is already in the possession of the receiving Party at the time it is disclosed by the disclosing Party and not subject to a prior confidentiality agreement, or confidentiality protection contained in a separate, pre-existing agreement;

(b) is in the public domain at the time it is disclosed by the disclosing Party;

(c) enters the public domain through sources independent of the receiving Party and through no fault of the receiving Party;

(d) is lawfully obtained by the receiving Party without any confidentiality restrictions from a third party who has a right to disclose such information to the receiving Party;

(e) has been at any time developed by the receiving Party independently of disclosure from the disclosing Party; or

(f) to the limited extent necessary in order to comply with Applicable Law(s) or the order or requirement of a court, administrative agency, or other governmental body; provided, however, that the receiving Party shall provide prompt notice of such court order or requirement to the disclosing Party to enable the disclosing Party to seek a protective order or otherwise prevent or restrict such disclosure.

14.5 Neither Party (nor any of their respective subsidiaries and Affiliates) shall issue any press release or make any public announcement with respect to this Agreement and the transactions contemplated hereby without obtaining the prior written consent of the other Party (such consent not to be unreasonably withheld or delayed), except as may be required by Applicable Law(s) upon the advice of counsel and only if the disclosing Party provides the non-disclosing Party with a reasonable opportunity to first review the release or other public announcement, to the extent practicable.

14.6 These confidentiality obligations shall survive termination or expiration of this Agreement for a period of [*]. Any trade secrets shall remain protected by the confidentiality obligations contained in this Article 14 in perpetuity.

ARTICLE 15
INTELLECTUAL PROPERTY

15.1 Company acknowledges that Client Information, Client's Pre-Existing Intellectual Property, and Client-supplied materials provided to Company pursuant to this Agreement shall be and remain the sole and exclusive property of Client. Likewise, Client acknowledges that Company's Pre-Existing Intellectual Property utilized pursuant to this Agreement shall be and remain the sole and exclusive property of Company.

15.2 All rights, title, and interest to any Arising Intellectual Property shall be the exclusive property of Client to the extent such Arising Intellectual Property is directly related to the Client API or Drug Product(s) or in any way incorporates or relies upon Client Information, Client Confidential Information or Client's Pre-Existing Intellectual property ("Client Arising Intellectual Property"). Company hereby assigns to Client all rights, title and interest in and to Client Arising Intellectual Property. Company will, at Client's request and expense, do all reasonable acts and things and execute all documents as Client may reasonably request, to transfer and vest in Client the ownership and registration of Client Arising Intellectual Property rights, and thereafter Client shall be responsible for and shall control, at its sole expense, the preparation, prosecution, maintenance and enforcement of all patent applications, resulting patents, and any other forms of Client Arising Intellectual Property.

15.3 Client agrees that, as between Company and Client, Company shall own all Arising Intellectual Property that (i) is not derived from, reliant upon, based upon or otherwise incorporate any Client Information, Client's Confidential Information, Client's Pre-Existing Intellectual Property, Client Arising Intellectual Property, or Client-supplied materials, and (ii) is not directly related to the API or Drug Product(s) ("Company Arising Intellectual Property"). The Parties acknowledge and agree that Company may develop Company Arising Intellectual Property, in the course of fulfilling its obligations under this Agreement, which improvements are a result of Company's expertise and are of general applicability to Company's business of providing services for a variety of organizations other than Client. Company shall not incorporate any Company Pre-Existing Intellectual Property or Company Arising Intellectual Property into the Drug Product without (a) Client's written consent and (b) the grant of a license on commercially reasonable terms, with the right to grant and authorize sublicenses, by Company to Client under any and all such Company Pre-Existing Intellectual Property or Company Arising Intellectual Property incorporated into or used in the Manufacturing of the API and/or Drug Product, to manufacture, market, develop, sell, and otherwise Commercialize the Drug Product, which such license shall be fully-paid, perpetual and royalty free during the period Company Manufactures API and/or Drug Product on behalf of Client. To the extent that any Company Pre-Existing Intellectual Property or Company Arising Intellectual Property is incorporated into the API and/or Drug Product, Company hereby grants Client a fully-paid, perpetual and royalty free license to market, develop, sell, and otherwise Commercialize the API and/or Drug Product.

ARTICLE 16
MISCELLANEOUS

16.1 **Successors and Assigns**. This Agreement shall be binding upon and shall inure to the benefit of the Parties hereto and their respective successors and permitted assigns. No assignment by either Party of this Agreement or any of its rights or obligations hereunder shall be permitted, nor shall it be effective as between the Parties, unless and until the assignee shall have executed and delivered to the other Party an instrument in writing reasonably satisfactory to the other Party pursuant to which the assignee covenants in writing to be bound by all the obligations of the assigning Party hereunder. No assignment shall relieve the assignor of any of its obligations hereunder. Client shall not be prevented from or otherwise required to obtain Company consent or provide any other covenants to Company to the extent that Client provides written notice to Company prior to any assignment of this Agreement to a parent, subsidiary or Controlled Affiliate.

Except in the case of the sale of all of Client's outstanding shares of stock and/or assets or a Client merger with another entity, in the event any Drug Product is sold, Client shall require as a condition of the sale that the purchaser honor all of Client's outstanding purchase orders, any pending Client Minimum Order Requirements and the termination notice requirements in this Agreement.

16.2 **Notices**. Any notice required or permitted under this Agreement shall be in writing, shall specifically refer to this Agreement, and shall be sent by hand,

recognized overnight courier, confirmed facsimile transmission, or registered or certified mail service, postage prepaid, return receipt requested, to the following addresses or facsimile numbers of the Parties:

Client:

Trevena, Inc.
955 Chesterbrook Blvd.
Suite 200
Chesterbrook, PA 19087
Attn: Michael Lark
Fax: (610) 354-8850

With a copy to: General Counsel, located at the above address and fax number

Company:

Alcami Corporation
2320 Scientific Park Drive
Wilmington, NC 28405
Attn: Legal Department
Fax: (910) 815-2340

With a copy to: Chief Commercial Officer, located at the above address and fax number

All notices shall be deemed received (a) upon receipt when hand-delivered, (b) two (2) business days after deposit with a recognized overnight courier, (c) upon confirmation of delivery when sent by facsimile, and (d) five (5) business days after deposit in registered or certified mail service. A Party may change its contact information immediately upon written notice to the other Party in the manner provided in this Section.

16.3 Waiver. No delay on the part of Company or Client in exercising any right, power or privilege hereunder shall operate as a waiver thereof, nor shall any waiver on the part of either Party of any right, power or privilege hereunder operate as a waiver of any other right, power or privilege hereunder, nor shall any single or partial exercise of any right, power or privilege hereunder preclude any other or further exercise thereof or the exercise of any other right, power or privilege hereunder. Any provision of this Agreement may be waived if, and only if, such waiver is in writing and signed by the Party against whom the waiver is to be effective.

16.4 Entire Agreement. This Agreement, the Quality Agreement, and Work Orders constitute the entire agreement between the Parties with respect to the Manufacture of API and Drug Product(s) by Company for Client from the Effective Date and supersede all prior agreements, understanding and negotiations, both written and oral, between the Parties with respect to the subject matter of this Agreement.

16.5 Amendment. This Agreement, the Quality Agreement and any Work Order may be modified or amended only by written agreement of the Parties hereto.

16.6 Cooperation. Each Party will execute and deliver all such instruments and perform all such other acts as the other Party may reasonably request to carry out the transactions contemplated by this Agreement.

16.7 Headings. All headings herein are for convenience only and shall not be construed as a limitation of the scope of the particular sections to which they refer.

16.8 Counterparts. This Agreement may be executed by facsimile or email and in any number of counterparts, each of which shall be deemed an original but all of which together shall constitute a single instrument.

16.9 Governing Law; Jurisdiction. This Agreement shall be governed and construed in accordance with the laws of the State of Delaware excluding any choice of law rules which may direct the application of the law of another state.

16.10 Severability. If any provision of this Agreement is held to be illegal, invalid or unenforceable under any present or future law, and if the rights or obligations of any Party hereto under this Agreement will not be materially and adversely affected thereby, (a) such provision will be fully severable, (b) this Agreement will be construed and enforced as if such illegal, invalid or unenforceable provision had never comprised a part hereof, (c) the remaining provisions of this Agreement will remain in full force and effect and will not be affected by the illegal, invalid or unenforceable provision or by its severance herefrom, and (d) in lieu of such illegal, invalid or unenforceable provision, there will be added automatically as a part of this Agreement a legal, valid and enforceable provision as similar to the terms to such illegal, invalid or unenforceable provision as may be possible and reasonably acceptable to the Parties herein.

16.11 No Third Party Rights. Except as otherwise expressly set forth herein, no provision of this Agreement shall be deemed or construed in any way to result in the creation of any rights or obligations in any person not a Party to this Agreement.

16.12 Force Majeure. If either Party is prevented from complying, either totally or in part, with any of the terms or provisions set forth herein by reason of force majeure, including, by way of example and not of limitation, fire, flood, explosion, storm, hurricane, riot, war, rebellion, accidents, equipment failure, acts of God, or acts of governmental agencies or instrumentalities, in each case to the extent beyond its control despite its commercially reasonable efforts to avoid, minimize, and resolve such cause as promptly as possible, said Party shall (a) provide written notice of same to the other Party, and (b) subject to the obligations set forth above with respect to said Party's efforts to remove the disability, its obligations that are prevented from compliance by such force majeure are suspended, without liability, during such period of force majeure. Said notice shall be provided within ten (10) business days of the occurrence of such event and shall identify the requirements of this Agreement or such of its obligations as may be affected. The Party so affected shall give to the other Party a good faith estimate of the continuing effect of the force majeure condition and the duration of the affected Party's nonperformance.

16.13 No Other Relationship. It is expressly agreed that Company, on the one hand, and Client, on the other hand, shall be independent contractors and that nothing contained herein shall be deemed to create any joint venture or partnership between the Parties hereto, and, except as is expressly set forth herein, neither Party shall have any right by virtue of this Agreement to bind the other Party in any manner whatsoever.

16.14 Dispute Resolution.

(a) Negotiated Settlement. In the event of a dispute regarding payment or the performance of Services pursuant to this Agreement (each, a "Dispute"), the Parties shall endeavor to negotiate in good faith an agreeable solution. If after [*] following receipt of a Party's written notification of a Dispute such Dispute has not been resolved, the Dispute shall be brought to the attention of the senior management of each Party and such senior manager or his/her designee will negotiate in good faith to define and implement a final resolution. The intent of this Section 16.14(a) is to encourage the Parties to work together to resolve any Dispute without having to rely on arbitration or any other legal proceeding. However, nothing in this Section 16.14(a) shall prevent or inhibit either Party to institute any other action to resolve such Dispute(s).

(b) Binding Arbitration. If not resolved in accordance with the preceding paragraph (a), then any controversy or claim arising out of or relating to this Agreement, or the breach thereof, shall be settled by arbitration administered by the American Arbitration Association in accordance with its Commercial Arbitration Rules, and judgment on the award rendered by the arbitrator(s) may be entered in any court having jurisdiction thereof.

16.15 Destruction of API or Drug Product. Subject to the provisions of Section 6.2, notwithstanding any other provisions of this Agreement, the Quality Agreement or any Work Order, Client agrees to dispose of any API or Drug Product(s) at Company's direction that are nonconforming, fail to meet Specifications, are determined by the Parties or any third party not to meet quality standards, and otherwise are not usable due to a potential risk to health or safety. If such API and/or Drug Product is usable then return or destruction shall be at Client's discretion, provided that Client agrees to provide a statement or other reasonable documentation requested by Company regarding Client's intended use for the API and/or Drug Products. Any API or Drug Product(s) subject to a dispute shall not be disposed of, or otherwise used or distributed prior to resolution by the Parties. Each Party shall act in good faith and shall cooperate with the other Party and with any qualified independent expert in connection with an investigation or resolution of a dispute. At Client's direction, Company shall dispose of any Nonconforming Product(s) returned by Client in accordance with Applicable Law(s) at Company's cost if the nonconformity is directly attributable to Company's gross negligence or willful misconduct or Company's breach of this Agreement, otherwise at Client's cost.

16.16 No Solicitation of Employees. Company and Client agree that neither Party will directly nor indirectly recruit a current or former employee of the other Party who has performed any work in connection with this Agreement provided that newspaper, internet or other advertisements to fill job openings shall be deemed not to be "solicitation" hereunder. This provision shall remain in effect during the Initial Term and any Renewal Period of this Agreement and for [*] thereafter. Any exceptions to this provision must be in writing and signed by an authorized representative of each Party.

16.17 English Language. The Parties to this Agreement have agreed that this Agreement and all related documents shall be drafted in the English language only.

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement as of the Effective Date.

Trevena, Inc.	**Alcami Corporation**
_____	_____
Name: _____	Name: Syed T. Husain
Title: _____	Title: Chief Commercial Officer
Date: _____	Date: _____

Appendix A
Sample Work Order Template

WORK ORDER # __
Dated _____

The services described herein will be provided in accordance with the terms and conditions of the Master Commercial Supply Agreement dated October 20, 2017 (the "Agreement") between Trevena, Inc. (hereinafter referred to as "Client") and Alcami Corporation ("Company").

The following documents are attached to this Work Order and shall be incorporated herein:

ATTACHMENT I DESCRIPTION OF SERVICES AND BUDGET
ATTACHMENT II PAYMENT SCHEDULE AND TERMS

The Agreement and this Work Order together constitute the entire agreement with respect to the Services to be provided hereunder. In the event a Client purchase order or Company quotation or invoice contains any terms or conditions which are different from those contained in the Agreement and this Work Order, the terms of the Agreement and this Work Order shall control. In the event of a conflict between any provision of the Agreement and any provision of this Work Order, this Work Order shall control with respect to any inconsistencies over pricing, payments, budgets, pass-through expenses (and any sourcing or handling fees), shipping terms or the description of Services, and the Agreement shall control in all other respects.

All terms and conditions provided in the Agreement executed by the parties referenced above remain unmodified and in full force and effect.

ACKNOWLEDGED, ACCEPTED AND AGREED TO:

Trevena, Inc.	**Alcami Corporation**
_____	_____
Name: _____	Name: _____
Title: _____	Title: _____
Date: _____	Date: _____

Appendix B-1
API Batch Sizes and Cost

[*]

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Appendix B-2
Drug Product - Finished

Batch Sizes and Cost

[*]

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Appendix B-3
Drug Product - Bulk

Batch Sizes and Cost

[*]

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Appendix C
Facilities

[*]

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Appendix D-1
Initial API Release Specifications (for reference)*
**Parties agree to negotiate in good faith an Amendment to replace this Appendix D-1 with final Specifications upon approval of Client's Marketing Authorization.*

[*]

Appendix D-2
Initial Drug Product Release Specifications (for reference)*
**Parties agree to negotiate in good faith an Amendment to replace this Appendix D-2 with final Specifications upon approval of Client's Marketing Authorization*

[*]

Appendix D-3
Initial CML-474 Release Specifications (for reference)*
**Parties agree to negotiate in good faith an Amendment to replace this Appendix D-3 with final Specifications upon approval of Client's Marketing Authorization*

[*]

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[*] = Certain confidential information contained in this document, marked by brackets, has been omitted and filed separately with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934, as amended.

Exhibit 10.46

DEVELOPMENT AND SUPPLY AGREEMENT

by and between

PFIZER, INC.

and

TREVENA, INC.

Dated as of December 15, 2016

TABLE OF CONTENTS

DEVELOPMENT AND SUPPLY AGREEMENT

THIS DEVELOPMENT AND SUPPLY AGREEMENT (***"Agreement"***) is made as of this 15th day of December, 2016 (the ***"Effective Date"***) by and between Trevena, Inc., a company formed under the laws of Delaware and having its principal offices at 1018 West 8th Avenue, Suite A, King of Prussia, Pennsylvania 19406 (***"Trevena"***) and the Pfizer CentreOne group of Pfizer, Inc., a corporation formed under the laws of Delaware and doing business at 275 North Field Drive, Lake Forest, Illinois 60045, on behalf of itself and any one or more of its Affiliates (collectively, ***"Pfizer"***). Pfizer and Trevena collectively shall be referred to as the "Parties" and each as a "Party."

RECITALS

WHEREAS, Trevena owns rights to the pharmaceutical compound known as Oliceridine (TRV130) in development for the treatment of moderate to severe acute pain, and, upon receiving Regulatory Approval (as defined below), wishes to develop and market the Oliceridine (TRV130) product in standard glass vials with flip-off caps or as may otherwise be directed by Trevena;

WHEREAS, Trevena and Pfizer desire that Pfizer assist Trevena in the development of the Oliceridine (TRV130) product for commercial distribution;

WHEREAS, to govern the initial development of Oliceridine (TRV 130), on or about May 26, 2016, Trevena and Pfizer executed a certain Letter of Engagement for the Development and Manufacture of Trevena's Proprietary Pharmaceutical Compound, Oliceridine (TRV 130) (the "***LOE***") a copy of which is attached hereto and incorporated herein as Annex 1; and

WHEREAS, after Trevena has received all necessary Regulatory Approval (as defined herein) for Oliceridine (TRV130) product, the Parties desire that Pfizer manufacture and sell to Trevena certain of its commercial requirements for the Oliceridine (TRV130) product as set forth herein.

AGREEMENT

NOW THEREFORE, in consideration of the mutual covenants and representations contained in this Agreement and for other good and valuable consideration, the receipt and adequacy of which are hereby acknowledged, the Parties agree as follows:

ARTICLE 1
DEFINITIONS

Certain Defined Terms

As used in this Agreement:

1.1 ***"Active Pharmaceutical Ingredient"*** or ***"API"*** means the active pharmaceutical ingredient of the Drug in bulk form that Trevena will provide to Pfizer for incorporation into the Products, as specified in the Statement of Work.

1.2 ***"Active Pharmaceutical Ingredient Specifications"*** means the detailed description and parameters of the API, as set forth on Schedule 1.2.

1.3 ***"Adverse Drug Experience(s)"*** has the meaning as set forth in 21 CFR 310.305 or the substantial equivalent provisions of other Applicable Laws.

1.4 ***"Affiliate"*** means any corporation, firm, partnership or other legal entity, which directly or indirectly controls, is controlled by or is under common control with a Party to this Agreement. A Party will be deemed to "control" another entity if it (a) owns at least fifty percent (50%) of the equity (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or (b) has the power by contract or otherwise to direct the management and policies of the entity.

1.5 ***"Applicable Law"*** means all laws applicable to the manufacture, processing, distribution, sale and use of the Product as may be amended and in effect from time to time, including the FD&C Act and all applicable federal, state and local laws and regulations, all applicable cGMP and all other applicable laws and regulations, of any other applicable jurisdiction.

1.6 ***"Business Day"*** means any day of the week which is not a Saturday, Sunday or legal holiday observed by the United States Federal Government or the State governments of Illinois, Kansas, New York and Pennsylvania.

1.7 ***"Certificate of Analysis"*** means a document, signed by an authorized representative of Pfizer, describing the Product Specifications of and testing methods applied to the Product, and the results thereof.

1.8 ***"Certificate of Compliance"*** means a document signed by an authorized representative of Pfizer attesting that a particular lot, batch or run was manufactured in accordance with cGMP, Applicable Law, and the Product Specifications. The Certificate of Compliance may be included within the Certificate of Analysis, or separately, if required by Trevena for regulatory purposes or Applicable Law.

1.9 ***"cGMP"*** means those principles and guidelines of good manufacturing practices as current Good Manufacturing Practices is defined in the FDA rules and regulations, including the United States regulations set forth at 21 CFR Parts 210-211, as appropriate and as the same may be amended from time to time, and the corresponding requirements of any other applicable jurisdiction.

1.10 ***"Commercial Year"*** means each period of twelve (12) consecutive calendar months during this Agreement beginning on January 1st and ending December 31st, except for the first Commercial Year, which shall commence on the first day of the month after the month in which Trevena makes its first *bona fide* commercial sale of a Product to a non-Affiliate customer and ends on December 31st of the following year.

1.11 ***"Components"*** means the excipients, the vials and the component parts of the vials into which the Drug will be filled, and the labeling, packaging, ancillary goods, shipping materials and other items to be procured by Pfizer from various components supplier(s) to manufacture the Products in accordance with the Product Specifications.

1.12 ***"Confidential Information"*** has the meaning set forth in Section 11.1.

1.13 ***"Controlled Substance"*** means a drug or other substance, or immediate precursor, included in schedule I, II, III, IV, or V of part B of 21 U.S.C., §802(6).

1.14 ***"Drug"*** means Trevena's proprietary human pharmaceutical compound known as TRV130 (Oliceridine), an intravenous G Protein-biased ligand of the μ-opioid receptor used in the treatment of moderate to severe acute pain.

1.15 ***"Drug Master File"*** or ***"DMF"*** as used in Section 4.3, means the drug master file (as such term is defined in 21 C.F.R. Part 314.420) that may be used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of drug products intended for human use.

1.16 ***"DEA"*** means the United States Drug Enforcement Agency.

1.17 "***Facility***" means Pfizer's pharmaceutical manufacturing plant at McPherson, Kansas, or such other manufacturing facility mutually agreed to by the Parties in writing.

1.18 ***"FDA"*** means the United States Food and Drug Administration or any successor entity thereto.

1.19 ***"FD&C Act"*** means the United States Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301), as amended from time to time.

1.20 ***"Intellectual Property"*** or ***"IP"*** means all inventions, formulations, processes, works of authorship, and any and all rights under U.S. and/or foreign patents, trade secrets, know-how, copyrights, trademarks and other industrial or intangible property rights of a similar nature and moral rights; all rights pursuant to grants and/or registrations worldwide in connection with the foregoing and all other rights with respect thereto; all rights under applications for any such grant or registration, all rights of priority under international conventions to make such applications and the right to control their prosecution, and all rights under amendments, continuations, divisions and continuations-in-part of such application; and all rights under corrections, reissues, patents of addition, extensions and renewals of any such grant, registration and/or right.

1.21 ***"Manufacturing Process"*** means any and all processes (or any step in any process) that is provided to Pfizer by Trevena and that will be used to manufacture the Product, as evidenced in the batch documentation and/or development reports.

1.22 ***"Master Batch Record"*** shall mean the document that defines the manufacturing methods, materials, and other procedures, directions and controls associated with the manufacture and testing of the Product, which may be amended in writing from time to time by mutual agreement of the Parties.

1.23 ***"MSDS"*** means the Material Safety Data Sheet for the Product or the API containing such information as may be required by applicable government agencies.

1.24 ***"Product"*** means the Drug in final dosage form, filled, finished and packaged in standard glass vials with flip-top seals, or as otherwise mutually agreed by the Parties.

1.25 ***"Product Specifications"*** means those product, labeling and performance specifications for the Product filed with and approved by the relevant Regulatory Authority, including Product formulae, labeling, and materials required for the manufacture of the Product that is to be purchased and supplied under this Agreement, as such are set forth on Schedule 1.25, which specifications may be amended by the Parties from time to time in accordance with this Agreement.

1.26 ***"Quality & Technical Agreement"*** means the quality agreement that will be negotiated and signed by authorized representatives of the Parties and which will govern the essential quality obligations of them in the manufacture, testing and release of the Products hereunder. The Quality & Technical Agreement may be amended or revised from time to time by the mutual written agreement of the Parties. A copy of the Quality & Technical Agreement is attached hereto and incorporated herein as Schedule 7.2.

1.27 ***"Regulatory Approval"*** means the pre- and post-approval, licenses, registrations or authorizations of any relevant Regulatory Authority, including the FDA and DEA, necessary for the manufacture, distribution, sale or use of the Product in any relevant jurisdiction in accordance with Applicable Law.

1.28 ***"Regulatory Authority"*** means any federal, state or local or other regulatory agency, department, bureau or other governmental entity (including the FDA and DEA), which is responsible for issuing approvals, licenses, registrations or authorizations necessary for the manufacture, import, sale and use of the Product in any relevant jurisdiction.

1.29 ***"Term"*** means, individually the Initial Term of this Agreement, or collectively the Initial Term and any Renewal Term, as those defined terms are used herein.

1.30 ***"Territory"*** means the United States of America, including the District of Columbia, the Commonwealth of Puerto Rico, all territories and possessions of the United States of America, United States military bases, and any other location over which the FDA has jurisdiction to regulate medicinal products intended for human use.

1.31 ***"Third Party"*** means any party other than Pfizer or Trevena and their respective Affiliates.

1.32 ***"Waste"*** means all rejects, improper goods, garbage, refuse, remainder, residue, waste water or other discarded material, including solid, liquid, semisolid, or contained gaseous material that arises from the manufacture of the Product, including rejected, excess or unsuitable materials, API and Products.

ARTICLE 2
PROJECT OVERVIEW

2.1 General Principles

The Parties shall undertake a product development project (***"Project"***) consisting of the development activities and applicable timelines set forth on Schedule 2.1 (***"Statement of Work"***). Under the Project, Pfizer shall assist Trevena to develop the Product and to obtain any required Regulatory Approval(s) in the Territory. Subject to the successful completion of the Project in accordance with the Statement of Work, and following receipt by Trevena of all necessary Regulatory Approvals, Pfizer then shall manufacture and deliver Product to Trevena for sale by Trevena as a human pharmaceutical product.

2.2 Commercially Reasonable Efforts

Each Party shall use all commercially reasonable efforts successfully to complete the Project. However, the Parties acknowledge and agree that neither of them can guarantee that the Project will be successful, nor warrants that a marketable product will result from the Project.

ARTICLE 3
SERVICE FEES; SCOPE CHANGES; PROJECT MANAGEMENT

3.1 Development Fees

Trevena shall pay Pfizer a non-refundable development fee (the ***"Development Fee"***) for its work under the Project in accordance with the payment schedule set forth in the tables on Schedule 3.1.

3.2 Stability Studies

In accordance with requirements of the Statement of Work, Pfizer will prepare pre-market, and if requested by Trevena, market-life stability batches of Products and perform stability studies (***"Stability Work"***). The essential obligations of the Parties regarding Stability Work and the charges therefor are set forth on Schedule 3.2.

3.3 Changes in Project Scope

(a) ***Changes; Proposal*** In the event (i) Trevena requests that changes be made to any material aspect of the Project or the Product Specifications, or (ii) technical difficulties require that Pfizer perform either additional work or repeat work, and such additional work is required not because of Pfizer's fault or negligence, or (iii) the Parties mutually agree to conduct additional work related to the subject matter of this Agreement, Pfizer shall provide Trevena with terms and conditions of any such additional, repeat or new work, including the scope of work, pricing, timeframes and responsibilities in a proposal to be mutually agreed upon in writing and signed by both Parties (each, a ***"Proposal"***). Pfizer's pricing will include professional and other employees service fees quoted at its customary per/hour, per/person rates then in effect, relative to the work to be performed, consistent with its charges to other similarly-situated customers. Each Proposal shall reference this Agreement, shall be implemented as a change order when signed by the Parties, and the terms and conditions of this Agreement shall govern and control any and all such additional, repeat or new work; *provided, however*, that if any provision of any Proposal conflicts with this Agreement, the terms of this Agreement shall prevail with respect to all terms except pricing terms. Pfizer shall bear the costs and expenses of any changes to the Proposal or delays to the Project which are caused by Pfizer's requirement for Regulatory Authority approval or other authorizations (specifically, Drug Enforcement Agency (***"DEA"***) quotas) which are not requirements of Applicable Law or occur as a result of Pfizer-specific policies that are not otherwise required by Applicable Law.

(b) ***Expansion of Territory***. Trevena shall give Pfizer reasonable prior notice in the event that it desires to pursue marketing and sales activities for the Product in countries or geographic regions outside of the Territory. The Parties will then determine the preparatory work that may be required (if any) and upon agreement, Pfizer shall provide Trevena with all necessary additional technical/developmental and regulatory support, including, for example, regulatory support for Trevena's supplemental regulatory filings, packaging and product development, labeling, and relevant Regulatory Authority inspections. Any additional technical/developmental and regulatory support for such

other countries or geographic regions shall be considered a change in Project scope and the Parties will agree to the reasonable incremental costs of such additional support in accordance with Section 3.3(a). Any additional pre-approval inspections of the Facility that may be required by relevant Regulatory Authorities as a result shall be reimbursed in accordance with Section 7.5(b). If Trevena chooses to engage Pfizer to manufacture the Product for marketing and sale outside of the Territory, such batches which are produced shall be applied to any and all of Trevena's Minimum Purchase Requirement as defined in Section 6.8. Except as provided herein, nothing contained in this Section 3.3(b) shall grant any right to Pfizer, or obligate Trevena in any way to engage Pfizer to manufacture the Product for sale outside of the Territory.

(c) ***Assignment Fee***. In the event that Trevena assigns or otherwise transfers substantially all of its rights and obligations under this Agreement to a Third Party pursuant to Section 12.5, either to a commercial licensing partner or an acquirer of Trevena's business, [*] If a technology transfer is associated with the assignment, the specific technology transfer scope, activities and associated costs will be defined in a project plan.

3.4 Steering Committee; Project Manager

(a) ***Steering Committee***. Pfizer and Trevena will jointly constitute a team (***"Steering Committee"***) comprised of not less than [*] members from each Party (or such number as the Parties mutually agree) to oversee the work under the Statement of Work as well as commercial manufacturing with [*] representative from each of Trevena and Pfizer having the authority to make decisions on behalf of such Party. The Steering Committee representatives may invite other employees of the Parties or their Affiliates to the Steering Committee meetings, to serve in an advisory capacity as relevant to the matters at hand. The Steering Committee will be considered as a working committee that will have as its goal the prompt and mutually agreeable resolution of any financial, technical or quality issues that may arise in order to advance and preserve a harmonious relationship established by and between Pfizer and Trevena. Either Party may change its representatives on the Steering Committee at any time by written notice to the other Party.

The Steering Committee shall meet at least quarterly or as otherwise may be necessary or agreed by the Steering Committee, which meetings shall occur by teleconference, videoconference or in person and may address any relevant issue a party wishes to call to the attention of the Steering Committee, to review past performance on mutually agreed upon metrics, discuss future partnership objectives, and to oversee the relationship between Trevena and Pfizer. The Steering Committee shall be responsible for performing the following functions:

(i) reviewing business strategy;

(ii) ensuring goal alignment;

(iii) assessing and developing risk mitigations and/or redundancies;

(iv) discussing market dynamics and impact to supply/demand; and

(v) implementing procedures for project governance and the resolution of questions or disputes that may arise under this Agreement or the Project Statement of Work

(b) ***Project Team; Project Manager***. Promptly upon execution of this Agreement, Pfizer and Trevena shall each designate such of their respective employees from product development, quality assurance, manufacturing, and project management to form a team (***"Project Team"***) to direct the activities to be carried out under the Statement of Work. Each Party shall also designate one of its employees to act as its project manager (each, a ***"Project Manager"***), who will be primarily responsible for communicating all instructions and information concerning the Project to the members of the Project Team. The Project Team and/or the Project Managers shall consult periodically during the performance of the Services, through face-to-face meetings, telephone conferences and/or videoconferences, at times to be mutually agreed upon by the Project Managers. Each Party may appoint a substitute or replacement Project Manager or a member(s) of the Project Team in the absence of its original Project Manager or original member(s) of the Project Team by notifying the other Party in writing of such substitution or replacement. Neither the Project Managers nor the Project Team shall have the right to modify, amend or waive any provision of this Agreement.

3.5 Development Supplies

Based on Trevena's final Product formulations, concentration and fill volume and the Parties' agreement to the final Product Specifications, Pfizer will manufacture the Products as engineering batches, validation batches and stability batches (collectively, the ***"Development Supplies"***) at the prices set forth in the Statement of Work. The Parties acknowledge that Development Supplies may include products utilized for development purposes only (*e.g.*, in media fills, engineering runs, or as stability testing materials), which are not intended for commercial sale in the market; *provided, however*, that Pfizer will manufacture all validation batches of Product in accordance with cGMP, which, if permitted by Applicable Law, would allow Trevena to use such validation batches as part of its commercial supply. In accordance with a schedule to be mutually agreed by the Parties, Trevena shall issue its purchase order(s) for such Development Supplies at least [*] days before any requested delivery date. For the sake of clarity, all relevant provisions of Articles 5, 7, 8 and 9 also shall apply to the manufacture and delivery of the Development Supplies.

ARTICLE 4
REGULATORY SUBMISSIONS; APPROVALS

4.1 Regulatory Assistance

Except as otherwise provided herein, Trevena will be solely responsible for obtaining and maintaining any Regulatory Approvals, licences, registrations or authorizations of any relevant Regulatory Authority required for the manufacture, distribution, sale and use of the Product in the Territory.

(a) ***General Review***. In consideration of the Development Fees that Trevena will pay under the Statement of Work, upon Trevena's request, Pfizer will review those portions of Trevena's proposed regulatory submissions as relate to Pfizer's manufacturing, packaging and quality control, quality assurance, facilities, personnel, procedures and organization before the submissions are filed with relevant Regulatory Authorities. Pfizer will use its commercially reasonable efforts to complete its review of Trevena's submissions within [*] calendar days (but in any event, no later than [*] calendar days) after receipt and will promptly inform Trevena of any anticipated delays.

(b) ***Responses to Regulatory Authorities***. At Trevena's request, Pfizer shall consult with and advise Trevena in responding to questions from a Regulatory Authority regarding Trevena's regulatory submission for the Product, *provided, however,* that Trevena shall have the final control over such submissions. Pfizer shall provide Trevena with cost estimates based on Pfizer's customary per/hour, per/person rates for professional and other employees then in effect, relative to the work to be performed, consistent with its charges to other similarly-situated customers for any additional review and consultation as may be required by the Regulatory Authority (for example, for technical responses to an FDA finding of deficiency, should one arise). If Trevena approves such costs in writing, Trevena shall reimburse Pfizer for such approved costs upon completion of the work and within [*] days of receipt of Pfizer's invoice.

4.2 Facility Approvals

Pfizer will secure and maintain in good order, at its sole cost and expense, such current governmental registrations, licences, permits and approvals as are required by Regulatory Authorities in order for Pfizer to perform all of its obligations under this Agreement and to manufacture the Products at the Facility.

4.3 Access to Drug Master Files

Where applicable, Pfizer will grant Trevena reference rights to all Drug Master Files and Site Master Files necessary to support Trevena's regulatory filings for the Product. To affect this, Pfizer will execute certain letters of authorization, which will be delivered to the appropriate Regulatory Authorities to permit them to consult Pfizer's DMFs and SMFs in their review of Trevena's Product regulatory submissions. Pfizer will send copies of such authorization letters to Trevena. Pfizer will update its DMFs and SMFs annually and will inform Trevena prior to making any modifications thereto in order to permit Trevena to amend or supplement any affected regulatory submissions and filings for Product.

4.4 User Fees

Trevena will pay any Regulatory Authority user fees, if any, which may become payable for the Product.

4.5 Ownership of Regulatory Approvals

The Parties agree that Trevena will be the sole and exclusive owner of all right, title and interest in and to all Regulatory Approvals related to the API and Product and any submissions for such Regulatory Approvals. Pfizer will reasonably assist Trevena in the preparation of all documents necessary to affect Trevena's rights in such Regulatory Approval applications and submissions, at the expense of Trevena. Trevena will provide to Pfizer for its files a final copy of the CMC section related to Pfizer activities of any such applications and/or submissions for Regulatory Approval unless otherwise prohibited by Applicable Law.

ARTICLE 5
PRODUCT MANUFACTURING

5.1 Purchase and Sale of Products

Upon Trevena's receipt of all necessary Regulatory Approvals pursuant to the terms and conditions of this Agreement and for the term of this Agreement, Pfizer shall manufacture, sell and deliver to Trevena and Trevena will purchase from Pfizer certain of its requirements for the Product for sale in the Territory at the prices set forth herein. Trevena agrees that [*] to be marketed, distributed and sold in the Territory. Beginning with [*], and thereafter, throughout remainder of the Term, provided that Pfizer is not in material default of its obligations under this Agreement, Trevena agrees that [*].

5.2 Manufacturing Standards; Changes

(a) ***Product Specifications***. The Product Specifications are set forth on Schedule 1.25. Pfizer will manufacture the Product in accordance with the Specifications, cGMP and all Applicable Laws, as then in effect. The Product Specifications may be modified from time

to time in accordance with the provisions of Section 5.2(b) and Section 7.7.

(b) ***Changes.*** The Parties agree that if Trevena wishes to amend any aspect of its Manufacturing Process or the Product Specifications (***"Discretionary Changes"***), Trevena will provide written notice thereof to Pfizer for Pfizer's review and approval, which approval Pfizer will not unreasonably withhold, except where such change would have a material adverse impact on Pfizer's manufacturing operations in the area of the Facility where the Product is to be manufactured. Furthermore, each Party will promptly notify the other of any new instructions or changes to the Product Specifications that are required by any Regulatory Authority, change in Applicable Laws or other regulatory requirements, or by medical concerns related to the toxicity, safety and/or efficacy of the Products (***"Required Changes"***). The Parties will confer with respect to the best means to comply with such instructions or change requirements; *provided, however*, that Pfizer will comply with any reasonable instructions issued by Trevena with respect to implementing any Required Changes. An analytical improvement will be considered to be a Discretionary Change unless requested or required by a Regulatory Authority, in which case such improvement will be considered a Required Change.

(c) ***Costs of Changes.*** Except as may otherwise be agreed in the Statement of Work, [*] any and all costs with respect to Required Changes that are required to bring its manufacturing operations into compliance with Applicable Laws, and [*] any and all other costs related to Required Changes affecting the Product, which are unrelated to bringing Pfizer's manufacturing operations into compliance with Applicable Laws. Any Discretionary Changes to the Product Specifications or the Manufacturing Process initiated by either Party will be agreed to by the Parties, including which Party or Parties will be responsible for the funding of such Discretionary Changes. All Discretionary or Required Changes will be implemented in accordance with the change control provisions of the Quality & Technical Agreement.

(d) ***Cost Reduction Changes Prior to Commercialization***. The Steering Committee and the Project team shall undertake good faith discussions to consider measures to reduce the cost/pricing of the Product resulting from business, manufacturing and/or other changes which may be necessitated due to phase III clinical data and/or regulatory feedback. These changes could include, among other things:

(i) Different fill volume and vial size combinations [*];

(ii) [*]; and

(iii) [*]

Any such measures to be undertaken must be first approved by the Steering Committee and will be implemented in accordance with the scope change provisions of Section 3.3(a),

5.3 Pre-Approval Manufacture

Pfizer agrees to manufacture and supply those quantities of Product requested in firm Purchase Orders by Trevena that are necessary to validate Pfizer's manufacturing Facilities, obtain the necessary Regulatory Approval for Pfizer's production of the Product and build Trevena's pre-Regulatory Approval inventory as may be requested by Trevena. Trevena will pay for such Products in accordance with the terms and conditions of this Agreement, irrespective of whether the Products ultimately receive Regulatory Approval.

5.4 Active Pharmaceutical Ingredient

(a) ***API Supply***. Unless otherwise provided in the Project Statement of Work or this Agreement, the following provisions will apply to supplies of API by Trevena to Pfizer.

(i) ***Trevena API Supply***. Pfizer will manufacture the Product for Trevena from API that Trevena shall supply to Pfizer [*]. Trevena will supply API to Pfizer in quantities sufficient to satisfy Pfizer's gross manufacturing requirements of the Product, as specified in [*] purchase orders submitted by Pfizer and on lead times discussed and agreed by the Project Managers, but in no event later than [*] days prior to the scheduled start of manufacture. Pfizer will use the API received from Trevena only for the development activities contemplated by this Agreement and the manufacture of Product for Trevena and for no other purpose. Pfizer agrees that it will not acquire any right, title or interest in or to the API and will not distribute, sell or otherwise transfer the API to any Third Party or generic manufacturer or otherwise use the API for the manufacture of any generic version of the Product unless otherwise directed by Trevena in writing. Trevena will deliver the API, [*], the Facility pursuant to [*] purchase orders that Pfizer issues to Trevena. Pfizer shall be solely responsible, at its own cost and expense, for the proper storage and handling of all API once it has been accepted into the Facility, including separate storage as a Controlled Substance if and as required by the DEA. In accordance with DEA regulations, Pfizer will produce and maintain complete and accurate records regarding the receipt, storage and use of the API under this Agreement and will provide to Trevena a copy of its year-end Controlled Substance reconciliation report pertaining to the API. Any API, which is not used as provided in this Agreement shall be returned to Trevena or otherwise disposed as directed by Trevena in writing in accordance with Section 10.6(b).

(ii) ***API Documentation; Samples***. With each delivery of API, Trevena will include a certificate of analysis, signed by an authorized individual of Trevena (or its designated API supplier) containing basic information regarding the API, including (A) the manufacturing date of the batch/lot delivered, (B) the batch/lot number, and (C) the quantity of API in such batch/lot as shipped to Pfizer (will be provided on the certificate of analysis or an equivalent document such as a bill of lading or packing slip).

(iii) ***Incoming Testing***. Within [*] days of Pfizer's receipt of any API supplied by Trevena, Pfizer will (A) perform an identification test on the API and confirm the shipment quantity and (B) notify Trevena in writing of any inaccuracies with respect to quantity or certificate of analysis or of any claim that any portion of the shipment fails the identification test. Subject to the provisions of Section 5.4(a)(iv), in the event Pfizer notifies Trevena of any deficiency in the quantity or quality of API received, Trevena will promptly ship to Pfizer, [*], the quantity of API necessary to complete the API shipment. In the event Pfizer notifies Trevena that the API shipment does not conform to the Active Pharmaceutical Ingredient Specifications, Trevena will have the right to confirm such findings at the Facility.

(iv) ***API Dispute Resolution***. If Trevena contends that such shipment of API conforms to the API Specifications and Pfizer does not concur, the Parties will submit samples of such shipment to a mutually acceptable independent laboratory for testing. If such independent laboratory determines that the shipment conforms to the API Specifications, Pfizer will bear all expenses of shipping and testing such shipment samples. If such independent laboratory confirms that such shipment does not meet the API Specifications, Trevena will replace, at no cost to Pfizer, the portion of the API shipment which does not conform to the API Specifications and reimburse Pfizer for all expenses of shipping and testing the shipment samples. Pfizer will dispose of any nonconforming portion of any API shipment as directed by Trevena, at Trevena's expense.

(b) ***Title***. Notwithstanding [*] Trevena will retain title to the API while it is in the Facility. [*] and accepted by Pfizer, subject to the limitation in Section 5.4(c). Pfizer will mark the API as the property of Trevena and not permit any lien to be placed upon the API arising out of any act or omission of Pfizer.

(c) ***Loss and Replacement of API***. In the event of loss or damage of any API delivered hereunder or the failure of Product to meet Product Specifications, Trevena will supply to Pfizer replacement API according to the terms set forth in Section 5.4(a), except as otherwise provided herein. If the need for replacement of such API results from a material breach of any obligation of Pfizer under this Agreement or any negligent or intentional act or willful omission by Pfizer in the manufacture, handling or storage of Product or API, Trevena will supply to Pfizer replacement API and Pfizer will be responsible for the cost of the replacement API equal to Trevena's purchase cost/kg (as evidenced by Trevena's invoices) plus all related shipping and handling charges.

(d) ***Maximum Liability***. In no event shall Pfizer's liability for API replacement costs exceed [*] This Section 5.4(d) states Trevena's sole remedy, and Pfizer's sole liability, with respect to any claim arising under Sections 5.4(c), 5.4(e), 5.8(h) and 7.10(b). For purposes of this Section 5.4(d), the term "Occurrence" shall mean any incident involving (A) the handling and storage of Trevena's API prior to the start of compounding operations, (B) storage of the Product after completion of filling, testing and release operations, but (C) explicitly excludes any and all aspects of compounding, filling, finishing, testing and releasing the API and/or Product. Pfizer shall not be responsible for replacement of the API beyond the limitations of liability stated herein. However, this limitation of liability shall not apply if any API losses are caused by Pfizer's gross negligence or willful misconduct or if Pfizer knowingly supplies any of the API to a Third Party (except as for testing purposes under Section 5.4(a)(iv)) under this Agreement, including a Third Party competitor of Trevena or a generic drug product manufacturer.

(e) ***API Consumption Factor***. After Pfizer has completed its initial validation runs and during the initial stages of Pfizer's commercial manufacture of the Product, the Parties shall consult with a view to develop a strategy for maximizing the yield of the API supplied by Trevena. Based upon such consultations, the Parties shall establish a maximum API consumption factor target for the Product to be manufactured in accordance with Trevena's Purchase Orders. When Pfizer has achieved manufacturing of consistent batch quantities [*] of the Product in accordance with the maximum consumption factor target, the Parties shall set out in writing binding terms and conditions for manufacturing criteria, such as an API yield minimum, permitted variances of API usage and consequences of out-of-variance performance. Once the maximum consumption factor has been established, if, during any Commercial Year period, Pfizer's consumption of API exceeds the maximum agreed upon consumption factor Pfizer shall reimburse Trevena for any excess consumption at Trevena's cost/kg, subject to the limitation of Section 5.4(d).

5.5 Facility; Dedicated Equipment

(a) ***Facilities and Equipment***. Except as provided below, Pfizer will provide, at its own cost and expense, all facilities, equipment, machinery, and materials to manufacture the Product in accordance with the Product Specifications, and the professional and other labor necessary for the successful performance of its obligations hereunder.

(b) ***Dedicated Equipment***. The Parties have agreed that certain specialized or dedicated equipment (***"Dedicated Equipment"***) is required to manufacture Product for Trevena as set forth on Schedule 5.5. The Parties have further agreed that Pfizer shall advise Trevena of the Dedicated Equipment required and the estimated costs associated with the purchase, installation and validation of the Dedicated Equipment. [*], subject to Trevena's prior written approval of such costs, which approval will not be unreasonably withheld or conditioned. Upon such approval, Pfizer will then purchase, install and validate the equipment and bill Trevena for the associated costs in accordance with the terms agreed in the Statement of Work. [*] Title to the Dedicated Equipment shall be and remain in Trevena's name. Pfizer shall (and shall cause its Affiliates to) (i) label the Dedicated Equipment as the property of Trevena, (ii) use the Dedicated Equipment solely for the manufacture of the Product for and on behalf of Trevena, (iii) keep the Dedicated Equipment free of liens, claims and encumbrances, (iv) operate the Dedicated Equipment in accordance with the manufacturer's instructions, (v) maintain the Dedicated Equipment in good working condition and in compliance with cGMP and Applicable Laws, *provided that*, for any repairs covered by a manufacturer's warranty, Trevena shall authorize such repairs under such warranty solely to the extent Pfizer grants access to the Facility for the performance of such repairs, and (vi) ensure the Dedicated Equipment is insured at all times in the amounts adequate to replace the Dedicated Equipment. Upon the expiry or earlier termination of this Agreement, Pfizer will return or otherwise dispose of Dedicated Equipment at Trevena's direction in accordance with

Section 10.6(b).

5.6 Components; Materials

Unless otherwise agreed, Pfizer will be responsible for the procurement and qualification of the Components and other raw materials required for the manufacture of the Product. Pfizer will procure all of the Components from suppliers that have been approved and qualified by Pfizer in accordance with Pfizer's internal vendor qualification and approval processes. The Parties understand and agree that Trevena has reviewed and approved the Components and Component suppliers listed in the Product Specifications. Under no circumstances will Pfizer have any liability to Trevena, nor will Pfizer be deemed to be in breach of this Agreement, if Pfizer is unable to supply the Product to Trevena due to a failure of such suppliers to provide such Components to Pfizer, *provided, however*, that Pfizer has used all commercially reasonable efforts to obtain the relevant Components from approved Component suppliers in accordance with Trevena's forecasts. [*] The cost of the Components is included in the price of the Product.

5.7 Product Labeling

(a) ***Labeling***. Pfizer shall label the Product in accordance with the Product Specifications using content provided by Trevena. Trevena shall control the content and type of all labeling and packaging (and any changes or supplements thereto) for the Product and shall have the responsibility, at Trevena's expense, for (i) ensuring such content is compliant with the Regulatory Approval and all Applicable Law, and (ii) any changes or supplements to such content, including the expense of securing any approvals required by any applicable Regulatory Authority for any such changes or supplements. Pfizer shall be responsible for obtaining such labels, packaging and packaging Components (and any changes or supplements thereto) in accordance with content specified by Trevena.

(b) ***Labeling Changes***. Should Trevena request or be required to make any modifications to Product labeling and packaging, it shall submit a written change order to Pfizer containing the requested or required modifications, together with any documentation specifying the content of the new labeling and packaging, including all necessary photo-ready art (or its substantial equivalent). Pfizer shall promptly provide Trevena with a statement of estimated charges for the work to be performed based on its per/person, per/hour rates then in effect, and its estimated timeline for implementing the changes. Upon written approval by Trevena, which approval shall not be unreasonably withheld, Pfizer will perform all requested or required labeling and packaging work. Trevena shall pay Pfizer for the work performed, in addition to reimbursing Pfizer for the cost of any existing labeling and packaging that has become obsolete as a result of such changes; *provided, however*, that such labeling and packaging shall not exceed the quantity of labeling and packaging required for the Product forecasted by Trevena for manufacture in the relevant Firm Order Period.

5.8 Product Testing and Release

(a) ***Test Methods***. Upon completion of manufacture, Pfizer will test each batch of Products for conformance with the Product Specifications and cGMP in accordance with agreed-upon quality control test methods set forth on Schedule 7.1, the Quality & Technical Agreement or as otherwise requested by Trevena.

(b) ***Documentation***. After Pfizer has carried out and reviewed all testing in accordance with its quality control processes, procedures and other agreed test methods, Pfizer will provide Trevena with a Certificate of Analysis (and a Certificate of Compliance, if so required) confirming that the batch was manufactured in conformity with the Manufacturing Process and Applicable Law (including cGMP) and complies with the Product Specifications. Pfizer will also provide copies of batch records and all other documents and records as required by the Quality & Technical Agreement, as well as such samples of the batch as Trevena may reasonably request. Trevena will review all of the documentation and discuss its observations, if any, with Pfizer. Once all observations are resolved, and Trevena has reviewed and approved all of the documentation provided by Pfizer, Trevena will approve the batch by providing to Pfizer its authorization to release the batch for delivery (***"Release Authorization"***). Pfizer will then make the batch available to Trevena at the Facility.

(c) ***Inspection; Rejection***. Trevena shall inspect, perform its quality assurance tests, and accept or reject, the corresponding batch as conforming or non-conforming with the Product Specifications [*], the timely resolution of all error and deviation records and if, applicable, batch samples. If Trevena rejects the batch as being non-conforming, it shall promptly notify Pfizer. If, as a result of further review and testing, Pfizer determines that the batch does conform to the Product Specifications or is otherwise not defective, the Parties shall mutually confer to find the root cause of the disagreement regarding batch non-conformity. If the Parties do not agree that a non-conformity exists, the Parties shall then submit samples of such batch to an independent laboratory acceptable to both Parties as further provided in Section 5.8(f).

(d) ***Deemed Acceptance***. If Trevena does not notify Pfizer in writing of Trevena's rejection [*], Trevena shall be deemed to have accepted the Product, except that Trevena shall retain the right to revoke acceptance of Product for a Latent Defect pursuant to Section 5.8(h).

(e) ***Product Quantity***. If the quantity of Products produced in any batch manufactured and proffered for delivery to Trevena is materially less than the quantity specified in the applicable Purchase Order, then the parties will meet to discuss in good faith and agree to one or more remedies to resolve the shortage in a fair and equitable manner. For purposes of clarity, "materially less" shall mean a batch of Products with an abnormally high number of units either rejected or set aside at Pfizer's determination for sampling, stability or for other reasons outside of the ordinary course of manufacturing and based on historic experience at the Facility.

(f) ***Disputes Regarding Non-Conformity; Independent Testing***. In the event of an unresolved dispute as to whether a batch does or does not comply with Product Specifications, Pfizer and Trevena will appoint a mutually agreeable independent laboratory to perform comparative tests and/or analyses on samples of the Product claimed to not comply with the Product Specifications. The independent laboratory's results will be in writing and will be final and binding, save for manifest error on the face of its report; *provided, however*, that the independent laboratory may also determine that additional sample testing by an independent laboratory is necessary. Unless otherwise agreed to by Pfizer and Trevena in writing, the costs associated with such testing and review will be borne by the Party against whom the independent laboratory rules. Pfizer will furnish the independent laboratory such instructions regarding the storage, handling and potential hazards of any Product as are provided to or developed by Pfizer by or on behalf of Trevena. Notwithstanding the foregoing, the Parties agree that the independent testing and review processes are only relevant to determine whether a batch complies with Product Specifications and shall not apply to disputes concerning whether a batch was manufactured in accordance with the Manufacturing Process and Applicable Law (including, cGMP).

(g) ***Replacement; Disposition of Rejected Product***. Pfizer shall use all reasonable efforts to replace, at no cost to Trevena, that portion of the batch which does not conform to the Product Specifications or was not manufactured in accordance with the Manufacturing Process and Applicable Law (including cGMP) as soon as possible, given manufacturing capacities and scheduling at the Facility [*]; *provided, however*, that [*]. Pfizer shall dispose of any rejected Products at its own cost and expense and in accordance with Applicable Law. Pfizer shall make all documentation relating to such disposition available to Trevena upon Trevena's request

(h) ***Latent Defects***. Notwithstanding the acceptance provisions of Section 5.8(c) and (d), Trevena will have the right to reject any batch of Products that are subsequently found to be non-conforming due to latent defects. For purposes of this Section 5.8(h), "latent defects" are any defects in the Product which are not discoverable using ordinary diligence and reasonable care in applying the quality control and test methods specified in the Quality & Technical Agreement, render the Product not conforming to Product Specifications and are caused by Pfizer. The Parties will consult to confirm the cause of the latent defects. If the Parties do not agree as to whether the Product is non-conforming, they will submit samples of such Product for independent testing in accordance with Section 5.8(f). If it is confirmed that the cause of the latent defect is attributable to Pfizer, then Pfizer will replace at no cost to Trevena all such latently defective Products with Products that meet the Product Specifications, subject to the provisions of Section 5.4(c) and the limitations of Section 5.4(d). All other relevant provisions of this Section 5.8 will apply to the inspection, testing and release of such replacement Products.

5.9 Waste

Pfizer will be responsible for the removal and disposal of all Waste resulting from Pfizer's manufacturing of the Product, consistent with the Product's Material Safety Data Sheet.

5.10 Miscellaneous

(a) ***Process Rework***. Pfizer will not rework or reprocess a Product unless authorized in advance by Trevena in writing and there is a validated process for such rework or reprocessing of Product. Re-inspection does not constitute rework or reprocessing. Process rework that may become necessary as a result of Trevena's changes will be billed separately at a reasonable fee to be mutually agreed between the Parties in writing.

(b) ***Sub-Lots***. Should Trevena desire Pfizer to split a manufacturing lot of Product into two (2) or more sub-lots during packaging, [*].

ARTICLE 6
FORECASTS; ORDERS; DELIVERY; INVOICING

6.1 [*] Product Supply Forecast

For capacity planning purposes, upon its submission for Regulatory Approval for the McPherson Facility, Trevena will provide Pfizer with a non-binding, written forecast of its estimated annual requirements of the Product during each of the first [*] Commercial Years of this Agreement ("***Annual Forecast***"). Thereafter, by [*] of each Commercial Year, Trevena will update the Annual Forecast for the period commencing on January 1st of the next Commercial Year. The Parties acknowledge that Trevena may adjust its Annual Forecast based on the controlled substance quota that the DEA issues for the Facility in any given year. For such purpose, Pfizer will promptly notify Trevena of any DEA quota that may be inconsistent with Trevena's Annual Forecast.

6.2 First Purchase Order

The Parties will cooperate in estimating and scheduling production for Trevena's first commercial order of Product from Pfizer, which in any case Trevena will place no later than [*] months in advance of Trevena's desired Product availability date.

6.3 Rolling Forecast

(a) ***Forecasting***. Concurrent with the placing of its first order of Product with Pfizer, and thereafter, during the first month of each calendar quarter thereafter, Trevena will provide to Pfizer a good faith, estimated rolling forecast of the quantity of Products that Trevena expects to order for the coming [*] period of time (each, a ***"Rolling Forecast"***). The first [*] of each Rolling Forecast shall be considered a binding commitment upon Trevena to purchase quantities described therein and a binding commitment upon Pfizer to produce and deliver such quantities on the delivery dates described therein (***"Firm Order Period"***). The last [*] of each Rolling Forecast shall be non-binding upon the Parties. Based upon each Rolling Forecast, Pfizer will place adequate quota requests to the DEA in a timely fashion to ensure compliance with all Applicable Laws, regulations and timing requests (including applicable reporting requirement).

(b) ***Adjustments***. Pfizer shall review Trevena's Rolling Forecasts at the time they are submitted and if any such Rolling Forecast is not consistent with the requirements of this Agreement (e.g., a change to a DEA quota), the Parties shall meet to discuss any necessary adjustments to the Rolling Forecasts. Notwithstanding the foregoing, in the event that circumstances beyond the control of both Parties cause a delay in commercialization of Product in the Territory, Trevena may cancel Products ordered within the Firm Order Period without penalty or liability to Pfizer, *provided that* [*] but (iii) if Trevena cancels any Purchase Order within [*] days of the scheduled start of manufacture, Trevena will be liable for the full price of the cancelled Purchase Order, as set forth in Section 6.9(b).

6.4 Purchase Orders

Trevena shall submit purchase orders for Product (each, a ***"Purchase Order"***) to Pfizer at the time it submits its Rolling Forecasts per Section 6.3(a), which in all cases shall be least [*] days prior to Trevena's requested delivery date as specified in the Purchase Order. Pfizer shall use its commercially reasonable efforts to meet the delivery dates set forth in each Purchase Orders, *provided, however*, that, absent any investigations, testing or other issues raised by Trevena in its inspection of the Product in accordance with Section 5.8(c), [*] after Trevena's Purchase Order submission. All Purchase Orders shall reference this Agreement and shall be governed exclusively by the terms contained herein. Trevena shall set forth in each Purchase Order (a) the quantity of Product ordered, (b) the amount of API required to fill the Purchase Order, (c) the specified delivery date and delivery instructions, and (d) the purchase price to be paid for the batch of Product.

6.5 Purchase Order Acceptance

Pfizer will confirm each Purchase Order issued by Trevena within [*] Business Days after receipt and shall confirm in writing to Trevena its acceptance of the Purchase Order, the delivery date(s), the quantity of Products ordered and the purchase price to be paid by Trevena. Provided that Trevena has placed its Purchase Orders in compliance with Section 6.4, Pfizer may not reject any Purchase Order that complies with this Agreement.

6.6 Excess Quantities

[*] Pfizer will not be obligated to supply quantities of Product over and above [*] (***"Non-Binding Excess"***) but will use commercially reasonable efforts to manufacture and deliver to Trevena all or part of the Non-Binding Excess as soon as reasonably practicable.

6.7 Format of Forecasts and Purchase Orders

Trevena will submit each Rolling Forecast electronically in spreadsheet form and will specify the quantities of Products in units and the Pfizer product number (list number/inventory number). Trevena will submit its Purchase Orders on its standard purchase order forms.

6.8 Minimum Purchase Requirement

Trevena further agrees to purchase from Pfizer in each Commercial Year not less than the minimum quantity of Products from Pfizer in accordance with the provisions of this Section 6.8 (***"Minimum Purchase Requirement"***). The Minimum Purchase Requirement shall be calculated on the basis of a percentage of the number of units/batches of Product forecasted by Trevena in the most recent twelve-month period in the Rolling Forecast that Trevena provides to Pfizer pursuant to Section 6.3(a). Provided that Pfizer is not in breach of, and materially performs all of its obligations set forth in this Agreement, [*] and waive Pfizer's manufacture and delivery obligations for the Product. In the latter event, Pfizer shall invoice Trevena for the amount payable, and Trevena shall pay Pfizer such amount [*]. Notwithstanding anything of the foregoing [*] all Product paid for by Trevena in lieu of delivery shall count towards the Minimum Purchase Requirement.

6.9 Purchase Order Changes; Cancellations

(a) ***Changes***. If Trevena requests that changes be made to any of its Purchase Orders within the Firm Order period, Pfizer will use all commercially reasonable efforts to accommodate such changes within reasonable manufacturing capabilities and efficiencies. If Pfizer can accommodate such changes, Pfizer will advise Trevena of any costs associated therewith. If Trevena indicates in writing to Pfizer that it should proceed to make the changes, Trevena will be deemed to have accepted the obligation to pay Pfizer for such costs. [*]

(b) ***Cancellations***. Except as provided in Section 6.3(b), if Trevena cancels any Purchase Order within the Firm Order Period, Pfizer shall be relieved of its manufacturing obligations relating to such order. Pfizer shall use commercially reasonable efforts to minimize its expenses and to fill any idle or unused manufacturing capacity as a result of such cancellation and Trevena shall be liable only to the extent of the time and costs actually incurred that result from Pfizer's inability to fill such idle or unused capacity; *provided, however*, [*], Trevena shall be liable for the full cost of the batch of Product to have been manufactured and supplied. Furthermore, if Trevena does not supply sufficient API (without providing appropriate notification to Pfizer and allowing for a period for both companies to evaluate the impact of such delay in API delivery) to allow Pfizer to fulfill any Purchase Order or acts improperly in any other manner to effectively prevent Pfizer's ability to perform, such action shall be deemed a cancellation and Trevena shall reimburse Pfizer for costs actually incurred as a result of such cancellation.

6.10 Shortage of Supply; Risk Mitigation; Redundancies

(a) ***Shortage of Supply***. In the event that Pfizer is unable to manufacture the Product in accordance with Trevena's Purchase Orders, Pfizer shall notify Trevena promptly. If the inability is not: (i) caused by an event of *force majeure*; (ii) attributable in whole or in part to Trevena's acts or omissions or breach of its obligations under this Agreement; or (iii) attributable in whole or in part to Pfizer's Component suppliers' acts or omissions and which are not otherwise due to Pfizer's failure timely to submit orders for Components and maintain an adequate safety stock as per Section 5.6, then Pfizer shall be solely responsible, at its sole cost and expense, for undertaking all commercially reasonable measures to minimize any possible shortage of Product to Trevena as a result of its manufacturing issues. If Pfizer cannot undertake such measures promptly, and [*], (***"Inability to Supply"***) then Trevena will be relieved of its obligations under Section 5.1, and its Minimum Purchase Requirements for the applicable Commercial Year in accordance with Section 6.8. Trevena shall have the right to procure Product from its existing Third Party contract manufacturer for so long as Pfizer's Inability to Supply continues. Thereafter, if Pfizer manufactures and delivers Product to Trevena in compliance with all Purchase Orders issued by Trevena [*], the applicable exclusivity and Minimum Purchase Requirement obligations under Section 5.1 and Section 6.8 shall be reinstated.

(b) ***Risk Mitigation; Redundancies***. If requested by Trevena, the Steering Committee will discuss measures for risk mitigation, including planning and implementing manufacturing redundancies at the Facility or one or more of Pfizer's other manufacturing facilities. Such redundancies may include the qualification of additional filling lines or other equipment to support a possible expanded validation strategy for the manufacture and additional site approval of the Product. The Parties shall mutually determine the procedures, methods, means and timing for carrying out all of the necessary qualification and validation activities to be set forth by an amendment to be made to the Project Statement of Work in accordance with the procedures of Section 3.3.

6.11 Delivery

Pfizer will deliver the Product to Trevena FCA (Incoterms 2010), the Facility. Title to and risk of loss over the Product will pass to Trevena at the time the Product is placed aboard the vehicle of Trevena' designated carrier at the loading dock of the Facility. Pfizer will not deliver any Product to Trevena until (a) Pfizer has released such Product pursuant to the Specifications and the terms of the Quality & Technical Agreement, and (b) Trevena has issued to Pfizer its Release Authorization. All freight, handling, insurance, duties and other shipping expenses will be borne by Trevena. For any shipments outside of the United States as agreed by the Parties in writing and permitted by Applicable Law, Trevena will be the exporter of record; *provided, however*, that Pfizer will assist Trevena, at no additional expense, in the preparation of any required export documentation. Trevena will be responsible for all shipping validation and transportation quality control. Should Trevena request or require Pfizer to include electronic temperature monitoring devices (***"Loggers"***) with any shipping cartons of the Product, it will comply with Pfizer's policies on the use of and responsibilities for Loggers set forth on Schedule 6.11.

6.12 Storage Fee

Trevena will use its commercially reasonable efforts to take delivery of all Products from the Facility no later than [*] days after the date of issuance of its Release Authorization. If Trevena anticipates that it will not be able to meet the delivery date, it will notify Pfizer promptly that Pfizer should store the Products at the Facility on an interim basis and indicate a date certain on which it will take delivery. [*] If Trevena has not taken delivery of the Product more than [*] days after issuing its Release Authorization, then title to and risk of loss over the Products shall be deemed to have passed to Trevena and Pfizer shall be entitled to invoice Trevena for the Products deemed to have been delivered at the prices set forth on Schedule 6.13. Pfizer shall not be liable for any loss or damage occurring to the Products kept in storage for more than [*] days after the Release Authorization or any deemed acceptance date per Section 5.8(d) for any reason, except for Pfizer's gross negligence, willful omissions or intentional acts of misconduct.

6.13 Prices

Pfizer shall invoice Trevena for the Products it delivers to Trevena at applicable [*] pricing set forth on Schedule 6.13. For the start of each Commercial Year, Pfizer will apply an assumed [*] price (***"Assumed Price"***) based on the number of units of Product set by Trevena in the most recent year of the Annual Forecast that Trevena provides to Pfizer pursuant to Section 6.1, which Assumed Price shall remain in effect for the entire Commercial Year, subject to a year-end reconciliation with the number of units actually purchased. Each of Pfizer's invoices shall reference the Assumed Price.

6.14 Invoices; Payment

Pfizer will invoice Trevena upon delivery of the Products. Trevena will make payment of all amounts in Pfizer's invoices net [*] days from the date of receipt of Pfizer's invoice. In the event of a good faith dispute between the Parties as to the amount due, Trevena will pay the undisputed amount and the Parties will attempt to resolve the disputed payment within [*] days.

6.15 Pricing Reconciliation

Within [*] days after the close of each Commercial Year, the Parties will conduct a reconciliation process to determine the actual pricing for Product manufactured and delivered to Trevena during that Commercial Year, which process shall be as follows:

(a) The Parties will jointly confirm the actual quantity of Products that Pfizer has delivered to Trevena, which shall include retained samples and stability samples but will exclude any Product rejected by or recalled by Trevena and has not yet been replaced by Pfizer under the terms of this Agreement (***"Actual Quantity"***);

(b) The Parties will then determine the corresponding actual [*] prices (***"Actual Price"***) set forth on Schedule 6.13 and will calculate a total dollar amount resulting from the Actual Quantity multiplied by the Actual Prices (***"Actual Total Amount"***);

(c) The Parties will then calculate a total dollar amount resulting from the Actual Quantity multiplied by the Assumed Price ***("Assumed Total Amount"***); and

(d) If the Actual Total Amount equals or is greater than the Assumed Total Amount, then Pfizer will issue a credit memorandum to Trevena in an amount equal to the positive difference that Trevena may use to offset any future amounts due under this Agreement. If the Actual Total Amount is less than the Assumed Total Amount, then Pfizer will issue to Trevena a debit memorandum equal to the negative difference, which Trevena will pay within [*] days after Trevena's receipt of such debit memorandum.

6.16 Price Increases

All pricing is firm through the first Commercial Year. Effective on [*] Pfizer will have the right to increase the price of the Product once annually. Price increases will be effective for deliveries of Products [*] Pfizer shall use all reasonable efforts to provide written notice to Trevena of any anticipated price increase no later than October 31st of any Commercial Year. No price increase shall be effective [*].

6.17 Taxes

Trevena shall pay all federal, state, county or municipal sales or use tax, excise, customs charges, duties or similar charge, or any other tax assessment (other than that assessed against income), licence, fee or other charge lawfully assessed or charged on the manufacture, sale or transportation of the Product that Pfizer manufactures, sells and delivers pursuant to this Agreement. In particular, Trevena will be responsible for and pay all applicable annual establishment fees specified in the Prescription Drug User Fee Amendments to the FD&C Act, with respect to the Product. For the avoidance of doubt, Trevena shall not be required to pay any such annual fees as relate to the Pfizer Facility, which shall be Pfizer's sole and exclusive obligation. Trevena shall provide Pfizer with copies of any state tax exemption form(s) if it intends to claim exemption for sales or use taxes in any state(s) where the Product is to be shipped. Under no circumstances shall Trevena be responsible for payment of any Pfizer employment related taxes or withholdings.

6.18 Continuous Improvements

Pfizer shall use reasonable commercial efforts to identify any opportunity to reduce the cost of manufacturing the Product and shall notify Trevena of such cost reduction opportunities (***"Cost Reduction Program"***). Any such measures to be undertaken must be first approved by the Steering Committee and will be implemented in accordance with the scope change provisions of Section 3.3(a),. Any cost savings realized from the Cost Reduction Program shall first be used to reimburse each Party's financial contribution to such program's development and implementation costs, thereafter, such cost savings shall be shared equally between the Parties.

ARTICLE 7
QUALITY ASSURANCE

7.1 Quality Control

Pfizer will apply its quality control procedures and in-plant quality control checks on the manufacture of Product for Trevena in the same manner as Pfizer applies such procedures and checks to products of similar nature manufactured for sale by Pfizer. Pfizer will also test and release all batches of Product in accordance with the test methods described in Schedule 7.1 to ensure that the Products meet the requirements of the Product Specifications and are manufactured in accordance with cGMP.

7.2 Quality & Technical Agreement

The Parties will use all commercially reasonable efforts to negotiate and conclude a Quality & Technical Agreement which will be attached hereto as Schedule 7.2 no later than [*] days after the Effective Date, but in any case prior to any cGMP manufacture of the Product.

7.3 Documentation; Batch Records; Retention Samples

(a) ***Quality Assurance Documentation.*** Pfizer will prepare such records documenting the development work as foreseen in the Project Statement of Work or as are otherwise reasonably requested by Trevena. Pfizer will prepare batch manufacturing records, which include the information relating to the manufacturing, packaging and quality operations for each lot of Product at the time such operations occur. Pfizer will prepare all development work and batch records in accordance with Applicable Laws, the Quality & Technical Agreement, cGMP and any similar regulations of applicable Regulatory Authorities and Pfizer's standard operating procedures. Upon Trevena's request, Pfizer will provide Trevena with copies of such development records and batch production records, including manufacturing and analytical records.

(b) ***Document Retention***. Unless otherwise specified in the Quality & Technical Agreement, Pfizer will retain all records documenting the development work and all records relating to the manufacture of each batch of Products for [*] or for such other period as required by Applicable Law. Thereafter, Pfizer will not destroy such records without giving Trevena prior written notice and the opportunity further to store such records or to have such records shipped to Trevena, [*].

(c) ***Retention Samples***. Pfizer will be responsible for storing and maintaining retention samples of each batch of Product delivered to Trevena and associated API and other raw materials in accordance with cGMP and the Quality & Technical Agreement.

7.4 Trevena Audits Rights

(a) ***General Audit.*** [*], Trevena shall have the right to have representatives visit the Facility during normal business hours to review Pfizer's manufacturing operations relating to the Product and assess its compliance with cGMP and quality assurance standards and to discuss any related issues with Pfizer's manufacturing and management personnel. Pfizer shall provide Trevena with copies of Pfizer's manufacturing records (including the Master Batch Record) and other relevant documentation relating to the Products for the purposes of assuring Product quality and compliance with agreed-upon manufacturing procedures. Such general audits shall (i) be limited to not more than [*] auditors [*] designated by or representing Trevena, (ii) last for not more than [*] days, and (iii) may be conducted not more than [*] per calendar year.

(b) ***For Cause Audits***. Trevena shall also have the right to conduct "for-cause" audits to address significant product or safety concerns as discovered through Product failures related to Pfizer's manufacture of the Product. Product failures would include issues related to stability out of specification, sterility, labeling or container integrity. Trevena shall notify Pfizer in writing in advance of the audit and thereafter, Trevena and Pfizer shall mutually determine the timing of the audit, which shall be as soon as possible, and in any event within [*]. Each for-cause audit shall be [*], except if the parties mutually agree that a longer for-cause audit period is necessary.

(c) ***Confidential Information in Audits***. Audits by Trevena or its designees may involve the transfer of Confidential Information, and any such Confidential Information shall be subject to the terms of Article 11 hereof. The results of such audits and inspections shall be considered Confidential Information under Article 11 and shall not be disclosed to Third Parties, including the FDA and any other relevant Regulatory Authority, unless required by law and only then upon prior written notice to Pfizer.

7.5 Regulatory Authority Inspections

(a) ***Inspections***. Pfizer shall allow the FDA and any other relevant Regulatory Authority to conduct any Pre-Approval Inspection (***"PAI"***) or other inspection of the area in the Facility where the Product is to be manufactured and Pfizer agrees to cooperate with the FDA and any other relevant Regulatory Authority in connection with such inspection. Pfizer will provide Trevena with notice of any PAI as specified in the Quality & Technical Agreement. The Parties shall consult regarding the nature, extent, duration of such inspection to determine whether Trevena may have an interest to send its personnel or representatives to the Facility. Upon agreement, Pfizer shall allow, but not require, such representatives to be present at the Facility during the FDA inspection to the extent permitted by the FDA inspectors and/or Applicable Law.

(b) ***Additional PAIs***. In the event that Trevena determines to expand its sales and marketing of the Product in countries or geographic regions outside of the Territory as described in Section 3.3(b) a Regulatory Authority other than the FDA requests or requires a PAI audit of the Facility in connection therewith, Pfizer will be entitled to charge a supplementary audit fee of [*] per each such PAI.

7.6 **[*]**

7.7 Change in Product Specifications; Manufacturing Process

Except as otherwise provided in Section 5.2, each of Trevena and Pfizer agrees that it will not change the Product Specifications or any aspect of the Manufacturing Process (including change of the Components, equipment, processes or procedures used to manufacture Product) without the prior written approval of the other Party, which approval will not be unreasonably withheld, delayed, or conditioned. Upon agreement, the Parties will implement all such changes in accordance with the change control provisions of the Quality & Technical Agreement.

7.8 Failed Batch

In accordance with the Quality & Technical Agreement and Section 5.8 hereof, Pfizer will investigate, and cooperate fully with Trevena in investigating, any batch of Product that fails to comply with the Manufacturing Process or Applicable Law (including, but not limited to, cGMP) or fails to meet the Product Specifications or any Regulatory Authority requirements. Pfizer will keep Trevena informed of the status of any investigation and, upon completion of the investigation, will provide Trevena with a final written report describing the cause of the failure and summarizing the results of the investigation.

7.9 Complaints and Adverse Drug Experiences

Consistent with the terms of the Quality & Technical Agreement, each Party will promptly advise the other of any complaints, notices of Adverse Drug Experience(s) or event reports, safety issues or toxicity issues relating to the Products of which it becomes aware, and which may be the result of, or have an effect on, the Product manufacturing operations performed by Pfizer but in no event later than [*] Business Days from the date of so becoming aware. Trevena will be responsible for all reporting of such information to Regulatory Authorities. Pfizer will promptly evaluate any complaint or notice of Adverse Drug Experience(s) and reasonably assist Trevena in responding to the same.

7.10 Product Recalls

(a) ***Recalls***. In the event (i) any Regulatory Authority or other national government authority issues a request, directive or order that the Product be recalled, (ii) a court of competent jurisdiction orders such a recall, or (iii) Trevena or Pfizer reasonably determines that Product should be recalled or subject to other corrective action, the Parties will take all appropriate actions, and will cooperate in any governmental investigations surrounding the recall. Pfizer will provide to Trevena all relevant information in support of its recommendation for a recall or other corrective action; *provided, however*, that Trevena shall have the final and sole decision making authority on the action to be taken, except if Pfizer has definitive evidence that any Product on market is either misbranded or adulterated, as defined in the FD&C Act.

(b) ***Product Replacement; Expenses***. In the event that such recall results from a breach of Pfizer's express warranties under Sections 8.3(a) and 8.3(b), Pfizer will be responsible for replacing the quantity of Products that were recalled at no cost to Trevena. Pfizer will use all commercially reasonable efforts to replace such Product as soon as practicable, given scheduling at the Facility. In addition, Pfizer agrees that it will be responsible for the administrative expenses of any recall. For purposes of this Section 7.10(b), the "administrative expenses" of recall will include the reasonable expenses of notification of customers, the return, storage and destruction of the recalled Product and any costs associated with the delivery of replacement Products, [*]. In the event that the recall does not result from the breach of Pfizer's express warranties under this Agreement, [*].

ARTICLE 8
WARRANTIES; COVENANTS; INDEMNIFICATION

8.1 Mutual Representations and Warranties

Each Party represents, warrants and covenants to the other Party that:

(a) ***Good Standing***. It is duly incorporated, validly existing and in good standing under the laws of the state in which it is incorporated;

(b) ***Power and Authority***. It has the corporate power and authority to enter into this Agreement and perform its obligations hereunder and the execution, delivery and performance of this Agreement and the performance of its obligations hereunder have been duly authorized and approved by all necessary action and no other action on the part of it is necessary to authorize the execution, delivery and performance of this Agreement;

(c) ***Existence of Claims***. There are no suits, claims, or proceedings pending, or to its best knowledge and belief, after due inquiry, threatened against it or any of its Affiliates in any court or by or before any governmental body or agency which would affect its ability to perform its obligations under this Agreement; and

(d) ***No Conflicts***. The performance of its obligations under this Agreement will not result in a material violation or breach of any agreement, contract, commitment or obligation to which Trevena is a party or by which it is bound and will not conflict with or constitute a default under its corporate charter or bylaws.

8.2 Trevena's Representations, Warranties and Covenants

Trevena covenants to Pfizer that:

(a) all API that Trevena provides to Pfizer will, at the time of delivery, not be adulterated or misbranded within the meaning of the FD&C Act or within the meaning of any other Applicable Law in which the definitions of adulteration and misbranding are substantially the same as those contained in the FD&C Act, as the FD&C Act and such laws are constituted and effective at the time of delivery, and will not be an article which, under the provisions of Sections 404 and 505 of the Act, may not be introduced into interstate commerce;

(b) all API that Trevena provides to Pfizer will have been manufactured in accordance with all applicable cGMP (including ICH Q7A) and meets the API Specifications;

(c) all specifications, including API Specifications and Product Specifications that Trevena provides to Pfizer will conform to the post-NDA submission that Trevena files with the FDA or other relevant Regulatory Authorities;

(d) it will not sell any Product into any regulatory jurisdiction unless and until it receives the necessary Regulatory Approval(s); and

Trevena represents and warrants to Pfizer that, to the best of Trevena's knowledge, and after having performed a reasonably diligent search of the record, Trevena's Intellectual Property, proprietary technology, Manufacturing Processes or other proprietary rights that Trevena licenses to Pfizer under this Agreement does not infringe any patents or know-how of a Third Party.

8.3 Pfizer's Representations, Warranties and Covenants

Pfizer covenants to Trevena that:

(a) all Product that Pfizer delivers to Trevena hereunder will, at the time of delivery, not be adulterated or misbranded within the meaning of the FD&C Act or within the meaning of all Applicable Laws in which the definitions of adulteration and misbranding are substantially the same as those contained in the FD&C Act, as the FD&C Act and such laws are constituted and effective at the time of delivery and will not be an article which may not under the provisions of Sections 404 and 505 of the FD&C Act be introduced into interstate commerce;

(b) all Product Pfizer delivers to Trevena hereunder will, at the time of delivery, be free from defects in material and workmanship and will be (i) in conformity with the Product Specifications, and (ii) manufactured in compliance with all Applicable Laws, including those relating to the environment, food or drugs and occupational health and safety, including those enforced or promulgated by the FDA (including compliance with cGMP);

(c) Pfizer will perform all of its services under this Agreement using personnel who have been properly qualified and trained in accordance with its internal SOP's and qualification programs and Applicable Laws;

Pfizer represents and warrants to Trevena that, to the best of Pfizer's knowledge, Pfizer's Intellectual Property, proprietary technology, manufacturing processes or other proprietary rights that Pfizer licenses to Trevena under this Agreement, does not infringe any patents or know-how of a Third Party and in its performance of its obligations under this Agreement, Pfizer will not knowingly incorporate into the Manufacturing Process any patents or know-how of a Third Party for which it does not have a licence that permits it to do so and/or to be able to grant to Trevena the licences and other rights otherwise required to be granted to Trevena hereunder.

The foregoing warranties will not extend to any nonconformity or defect which relates to or is caused by API supplied by Trevena to Pfizer. Subject to Pfizer's indemnity obligations in Section 8.5, the replacement provisions of Sections 5.4(c), 5.4(d), 5.8(g), 5.8(h) and 7.10(b) will be Trevena's sole and exclusive remedies for nonconforming or defective Products.

PFIZER MAKES NO OTHER WARRANTIES, EXPRESS OR IMPLIED, WITH RESPECT TO THE PRODUCTS. PFIZER HEREBY DISCLAIMS ALL OTHER WARRANTIES, EXPRESS OR IMPLIED, INCLUDING THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE.

8.4 Indemnification by Trevena

Trevena hereby agrees to save, defend, indemnify and hold harmless Pfizer and its Affiliates and their respective officers, directors, employees and representatives (each, a "***Pfizer Indemnitee***") from and against any and all losses, damages, liabilities, expenses and costs, including reasonable legal expense and attorneys' fees ("***Losses***"), to which any Pfizer Indemnitee may become subject as a result of any claim, demand, action or other proceeding by any Third Party (a "***Claim***") against a Pfizer Indemnitee arising or resulting directly or indirectly from (a) Trevena's breach of any representation or warranty set forth in Section 8.1 or Sections 8.2(a) through 8.2(d), (b) infringement of any Intellectual Property right of any Third Party relating to the API Specifications, Product Specifications, API, Drug, Product or the Manufacturing Process, other than Pfizer's processes used in the manufacture of the Product pursuant to this Agreement, (c) the use of or lack

of safety or efficacy of the Product, or (d) any negligent or wrongful act or omission on the part of Trevena, its employees, agents or representatives and which relate to Trevena's performance hereunder except, in each case, to the extent such Losses result from the negligence or willful misconduct of any Pfizer Indemnitee or the breach by Pfizer of any express warranty or representation made by Pfizer in this Agreement.

8.5 Indemnification by Pfizer

Pfizer will indemnify and hold harmless Trevena and its Affiliates and their respective officers, directors, employees and representatives (each, a ***"Trevena Indemnitee***") from and against any and all Losses to which any Trevena Indemnitee may become subject as a result of any Claim against a Trevena Indemnitee arising or resulting, directly or indirectly, from (a) Pfizer's breach of any representation or warranty set forth in Section 8.1 or Sections 8.3(a) through Section 8.3(c), (b) infringement of any Intellectual Property right of any Third Party relating to Pfizer's manufacturing processes used in the manufacture of Product pursuant to this Agreement (excluding the API Specifications, Product Specifications, API, Drug, Product or the Manufacturing Process), or (c) any negligent or wrongful act or omission on the part of Pfizer or any Pfizer Indemnitee and which relate to Pfizer's performance hereunder except, in each case, to the extent such Losses result from the negligence or willful misconduct of any Trevena Indemnitee or the breach by Trevena of any express warranty or representation made by Trevena in this Agreement.

8.6 Conditions of Indemnification

A Party (an ***"Indemnified Party"***) which intends to claim indemnification under this Article 8 shall notify the other Party (an ***"Indemnifying Party"***) within a reasonable time in writing [*] of any Claim, in respect of which the Indemnified Party believes it is entitled to claim indemnification; *provided, however*, that the failure to give timely notice to the Indemnifying Party shall not release the Indemnifying Party from any liability to the Indemnified Party to the extent the Indemnifying Party is not prejudiced thereby. The Indemnifying Party shall have the right, by notice to the Indemnified Party, to assume the defense of any such action or claim within [*] of any Claim with counsel of the Indemnifying Party's choice and at the sole cost of the Indemnifying Party. If the Indemnifying Party does not so assume the defense of such Claim, the Indemnified Party may assume such defense with counsel of its choice and at the sole cost of the Indemnifying Party. If the Indemnifying Party so assumes such defense, the Indemnified Party may participate therein through counsel of its choice, but at the sole cost of the Indemnified Party. The Party not assuming the defense of any such claim shall render all reasonable assistance to the Party assuming such defense, and all reasonable out-of-pocket costs of such assistance shall be for the account of the Indemnifying Party. No such Claim shall be settled other than by the Party defending the same, and then only with the consent of the other Party which shall not be unreasonably withheld; *provided, however*, that the Indemnified Party shall have no obligation to consent to any settlement of any such Claim which imposes on the Indemnified Party any liability or obligation which cannot be assumed and performed in full by the Indemnifying Party, and the Indemnified Party shall have no right to withhold its consent to any settlement of any such Claim if the settlement involves only the payment of money by the Indemnifying Party or its insurer.

8.7 No Consequential Damages

EXCEPT FOR A PARTY'S INDEMNIFICATIOIN OBLIGATIONS OR BREACH OF ARTICLE 11, NEITHER PARTY WILL BE LIABLE TO THE OTHER FOR INDIRECT, INCIDENTAL, SPECIAL, PUNITIVE, EXEMPLARY OR CONSEQUENTIAL DAMAGES, LOST PROFITS, BUSINESS OR USE RESULTING FROM ANY BREACH OF THIS AGREEMENT, EVEN IF SUCH PARTY HAS BEEN ADVISED OF THE POSSIBILITY THEREOF, AND REGARDLESS OF THE LEGAL OR EQUITABLE THEORY (CONTRACT, TORT, OR OTHERWISE).

ARTICLE 9
INTELLECTUAL PROPERTY RIGHTS

9.1 Background Intellectual Property

(a) ***Pfizer IP***. The Parties acknowledge that all rights to and interest in Intellectual Property developed or obtained by or on behalf of Pfizer (i) prior to the Effective Date and or (ii) independent of this Agreement, and (iii) without the use of or reliance upon the Confidential Information of Trevena or any Trevena Background IP (as defined below) (collectively the "***Pfizer Background IP***") will remain the exclusive property of Pfizer. Pfizer hereby represents and warrants that Pfizer owns, or holds sufficient rights to use for the purposes of manufacturing Product, all Pfizer Background IP used by Pfizer in the manufacture of Product(s) pursuant to this Agreement.

(b) ***Trevena IP***. The Parties acknowledge that all rights to and interest in Intellectual Property, including, collectively (i) the Drug and the API, (ii) the Product, (iii) API Specifications, (iv) the Intellectual Property of Trevena developed or obtained by or on behalf of Trevena (A) prior to the Effective Date, or (B) independent of this Agreement and without the use of the Confidential Information of Pfizer, and (v) the Manufacturing Process, and any intermediates or derivatives thereof as contained in b(i)-(v) hereof are referred to herein as "***Trevena Background IP***" will remain the exclusive property of Trevena. Trevena hereby grants to Pfizer a non-exclusive, royalty-free, non-transferable license (with no rights to sublicense), under the Trevena Background IP, solely for purposes of performing its obligations under this Agreement, during the Term hereof. Pfizer agrees that its rights to Trevena Background IP are for the limited purpose of performing Pfizer's obligations under this Agreement and for no other purpose, express or implied, and shall not be shared with any Third Party, competitor or

generic drug manufacturer.

9.2 Development IP

All Intellectual Property developed by Pfizer in performance of its obligations under this Agreement including (a) improvements to Trevena's Manufacturing Processes; and/or (b) improvements to the API or Product or the processing of the API used in the manufacturing of the Product shall be owned by Trevena (***"Trevena Development IP"***). Pfizer shall assign, and does hereby assign, to Trevena all right title and interest in and to such Trevena Development IP. Pfizer will promptly notify Trevena of any such Trevena Development IP, and will provide as much information about such Trevena Development IP as may be reasonably requested by Trevena. For the sake of clarity, improvements to Pfizer Background IP by Pfizer in performance of the development activities and any other developments or discoveries that Pfizer may make in the performance of its obligations hereunder that relate to general technology for fill-finish operations of injectable drugs, for example, aseptic filling, terminal sterilization, lyophilization and the like and that do not use any Trevena Background IP or Trevena Development IP or Trevena Confidential Information shall be owned by Pfizer (***"Pfizer Development IP"***). In the event that Pfizer incorporates any Pfizer Background IP, Pfizer Development IP or Pfizer Confidential Information into the processing, filling, and/or finishing of the Product in the performance of its obligations hereunder, Pfizer will grant, and does hereby grant to Trevena a non-exclusive, perpetual, worldwide, fully paid-up, transferrable (with rights to sub-license) and royalty-free license solely to develop, have developed, make, have made, use, import, export, commercialize, register, modify, enhance, improve, offer for sale and sell the Product.

9.3 No Implied Licenses

No right or license is granted under this Agreement by either Party to the other, either expressly or by implication, except those specifically set forth herein.

ARTICLE 10
TERM AND TERMINATION

10.1 Term

This Agreement will commence on the Effective Date and, unless earlier terminated as provided in this Article 10, [*] (***"Initial Term"***). This Agreement will [*] (***"Renewal Term"***), unless either Party gives notice of non-renewal at least [*] months prior to the expiry date of the Initial Term or any Renewal Term.

10.2 Termination of Project

Either Party shall have the right to terminate the Project in accordance with the provisions herein. The Party wishing to terminate the Project shall request in writing a pre-termination consultation with the other Party to review potential concerns and to make reasonable efforts to continue with this Agreement. [*] days following said consultation, either Party may terminate the Project upon a further [*] days' prior written notice to the other Party if the terminating Party determines in good faith that the development of the Product is not clinically, commercially or technically feasible using commercially reasonable efforts. If the Project or this Agreement is terminated in accordance with this Section 10.2, Pfizer will advise Trevena of the costs it has incurred under the Project up to the date of such termination Trevena will pay to Pfizer that portion of the Development Fees that represents (a) the work that Pfizer has completed and for which payment has not yet been received, and (b) on a *pro rata* basis, all work that Pfizer has undertaken but not yet completed as of the date of notice of termination. In addition, Trevena will reimburse Pfizer for all of its out-of-pocket costs related to any non-cancelable commitments for raw materials, Components and other services that Pfizer has undertaken as part the Project in accordance with the Statement of Work. Trevena shall pay Pfizer any amount [*].

10.3 General Termination Rights

Either Party may terminate this Agreement:

(a) ***Failure to Obtain Regulatory Approval***. Upon [*] days written notice if the FDA or other relevant Regulatory Authority does not grant Regulatory Approval for the Product by December 31, 2019; or

(b) ***Bankruptcy***. Immediately by providing written notice to the other Party: (i) if proceedings in voluntary or involuntary bankruptcy are initiated by, on behalf of or against the other Party (and, in the case of any such involuntary proceeding, not dismissed within [*] days); or (ii) if the other Party is adjudicated bankrupt, files a petition under applicable insolvency laws, is dissolved or has a receiver appointed for substantially all of its property; or

(c) ***Material Breach***. By giving to the other Party [*] days' prior written notice upon the breach of any warranty or any other material provision of this Agreement by the other Party if the breach is not cured within [*] days after written notice thereof to the Party in default;

(d) ***Force Majeure***. Upon simple notice to the other Party should the other Party continue to be unable to perform

its obligations under this Agreement for a period in excess of [*] days by reason of *force majeure*, in accordance with Section 12.1(a).

10.4 Pfizer Specific Termination Rights

Pfizer shall have the right to terminate this Agreement:

(a) ***Failure to Purchase Minimums***. [*] and waives Pfizer's manufacturing and delivery obligations pursuant to Section 6.8.

10.5 Termination Without Cause

Either Party may terminate this Agreement at any time and for any reason or for no reason upon providing [*] notice to the other Party; *provided, however*, that neither Party shall issue such notice until after the third Commercial Year.

10.6 Consequences of Termination

Upon expiry or termination of this Agreement for whatever reason the Parties will wind-up this Agreement and settle all outstanding issues in accordance with the principles described below.

(a) ***Cessation of Manufacturing***. Pfizer will cease all manufacturing-in-progress and other ongoing activities in an orderly manner, unless Pfizer reasonably determines that manufacturing-in-progress or other ongoing activities must be completed in order to comply with applicable laws and regulations.

(b) ***Disposition of Inventory, API, Dedicated Equipment***. At a time to be mutually agreed between the Parties, Pfizer will return to Trevena, at Trevena's option and election (i) any quantities of work-in-progress at price(s) to be mutually agreed, (ii) any inventory of API remaining in Pfizer's possession, and (iii) all items of Dedicated Equipment. All expenses associated with the preparation, packing and delivery of the work-in-progress, API, and Dedicated Equipment shall be borne by Trevena, unless termination shall have been as a result of a material breach by Pfizer, in which case Pfizer will be responsible for such expenses. If Trevena does not elect to take back the work-in-progress, API, or Dedicated Equipment, Trevena may direct Pfizer to destroy such work-in-progress, API or Dedicated Equipment. If Trevena does not elect either option, Pfizer may dispose of such items as it deems appropriate. In no instance may Pfizer share any such items with a competitor or generic drug manufacturer.

(c) ***Reimbursement for Components and Materials***. In addition, Trevena will reimburse Pfizer for Pfizer's cost of all Components and other raw materials purchased and on hand or on order, if such Components and materials were ordered by Pfizer based on Trevena's Product forecasts, and Pfizer cannot reasonably use such Components and materials for other purposes. Pfizer will invoice Trevena for all amounts due hereunder and Trevena will pay such invoice on the terms set forth in Section 6.14.

(d) ***Return of Confidential Information***. Upon expiry or earlier termination of this Agreement for any reason, each Party shall promptly return [*] to the other all of the other Party's Confidential Information, in any form or medium disclosed by the disclosing Party. In lieu of returning all Confidential Information, each Party shall have the option to destroy any Confidential Information in place and/or purge it from its respective electronic information systems; *provided, however*, that neither Party shall be required to destroy any computer files stored securely by a Party that are created during automatic system back-up, all of which shall remain bound by the confidentiality provisions of in Article 11 of this Agreement and any prior confidentiality agreement between the Parties notwithstanding the expiration or termination of such agreements. Notwithstanding the foregoing, each Party shall be allowed to retain one (1) copy of the other's Confidential Information to ensure continuing compliance with Article 11. *provided, however*, that all Confidential Information shall be returned no more than [*] years following expiration or termination of this Agreement or such longer period as may be required by Applicable Law.

10.7 Accrued Obligations

Termination of this Agreement will not relieve either Party of any liability which has accrued prior to the effective date of such termination, nor will prejudice either Party's right to obtain performance of any obligation provided for in this Agreement, which by its express terms or context survive termination.

10.8 Nonexclusive Rights and Remedies

Termination is not an election of remedies. Except as otherwise provided herein, all rights and remedies of the Parties provided under this Agreement are not exclusive and are in addition to any other rights and remedies provided by law or under this Agreement.

10.9 Survival

The terms, provisions, representations, and warranties contained in this Agreement that by their sense and context are intended to survive the performance hereof by either or both Parties will so survive the completion of performance and termination of this Agreement,

including, confidentiality obligations and the making of any and all payments due hereunder.

ARTICLE 11
CONFIDENTIAL INFORMATION

11.1 Confidential Information

As used in this Agreement, ***"Confidential Information"*** means, collectively, all of Party's written or oral information, whether or not it has been identified as confidential or that by the nature of the information or the circumstances surrounding disclosure ought reasonably to be treated as confidential and/or proprietary, including, but not limited to, any oral, written, graphic or machine-readable information relating to a Party's and its Affiliates' businesses, protocols, projects or products, whether patentable or not, including but not limited to, know-how, scientific information, chemical structures, compounds, devices, data, documents, methods, trade secrets, patent applications, work product, intellectual property, technology, financial or business information and transactions already entered into or contemplated that have been disclosed or will be disclosed in the future by such Party or its designee ("disclosed" shall include any information learned or witnessed by the other Party), or information exchanged for the purpose of exploring a potential business transaction between the Parties and/or their Affiliates or any information which already is subject to an existing confidentiality agreement. For the avoidance of doubt, the definition of Confidential Information shall include Confidential Information of each Party's Affiliates. The Party disclosing Confidential Information shall be referred to as the ***"Discloser"*** and the Party receiving Confidential Information shall be referred to as the ***"Recipient"***. The Parties agree that any Confidential Information disclosed between them under the pre-existing Mutual Nondisclosure Agreement, dated as of March 3, 2015 (as amended and extended), shall be subsumed under the terms of this Article 11. Confidential Information does not include information that (a) is in possession of the receiving Party at the time of disclosure, as reasonably demonstrated by written records and without obligation of confidentiality and not subject to a prior confidentiality agreement, (b) is or later becomes part of the public domain through no fault of the receiving Party, (c) is received by the receiving Party from a Third Party without obligation of confidentiality, or (d) is developed independently by the Recipient without use of, reference to, or reliance upon the Discloser's Confidential Information by individuals who did not have access to Confidential Information. The Discloser shall, to the extent practical, use reasonable efforts to label or identify as confidential, at the time of disclosure all such Confidential Information that is disclosed in writing or other tangible form. Confidential Information of Pfizer includes all of Pfizer's manufacturing processes, technology and know-how**,** whether or not labeled confidential. Confidential Information of Trevena includes among other things, Trevena's processes, technology, know-how, API and materials **,** whether or not labeled confidential.

11.2 Duty of Nondisclosure and Non-Use; Exceptions

Each Party agrees (a) to keep confidential the Confidential Information of the other Party, (b) not to disclose the other Party's Confidential Information to any Third Party, including, any generic drug manufacturers or companies without the prior written consent of such other Party, and (c) to use such Confidential Information only as necessary to fulfill its obligations or in the reasonable exercise of rights and obligations granted to it hereunder. Notwithstanding the foregoing, a Party may disclose (i) Confidential Information of the other Party to its Affiliates, and to its and their directors, employees, consultants, and authorized agents in each case who have a specific need to know such Confidential Information and who are bound by a either and effective written agreement or professional obligation of confidentiality and restrictions on use at least no less restrictive as contained herein, (ii) its respective Development IP, to the extent required to exploit its rights under Article 9 of this Agreement, and (iii) Confidential Information of the other Party to the extent such disclosure is required to comply with Applicable Law or to defend or prosecute litigation; *provided, however*, that the Recipient provides prior written notice of such disclosure to the Discloser and takes reasonable and lawful actions to avoid or minimize the degree of such disclosure. Furthermore, Trevena may disclose Confidential Information of Pfizer relating to the Project and/or the manufacture of Product to Regulatory Authorities and entities with whom Trevena has (or may have) a marketing and/or development collaboration and who have a specific need to know such Confidential Information and who is or are abound Party to an effective agreement protecting the Confidential Information on terms no less restrictive than those contained herein.

11.3 Public Announcements

Neither Party will make any public announcement concerning the transactions contemplated herein, or make any public statement or filing which includes the name of the other Party or any of its Affiliates, or otherwise use the name of the other Party or any of its Affiliates in any public statement or document, except as may be required by law, the rules of a stock exchange or judicial order, without the written consent of the other Party, which consent will not be unreasonably withheld. Subject to any legal or judicial disclosure obligation, any such public announcement or filing proposed by a Party that names the other Party will first be provided in draft to the other Party.

11.4 Injunctive Relief

The Parties acknowledge that either Party's breach of this Article 11 may cause the other Party irreparable injury for which it would not have an adequate remedy at law. In the event of a breach, the non-breaching Party may be entitled to injunctive relief in addition to any other remedies it may have at law or in equity.

ARTICLE 12
MISCELLANEOUS

12.1 Force Majeure and Failure of Suppliers.

(a) ***Force Majeure***. Neither Party will be considered to be in breach of this Agreement if a delay in the performance of any of its duties or obligations hereunder (except the payment of money) has been caused by or is the result of an act of God, acts of a public enemy, acts of terrorism, insurrections, riots, embargoes, labor disputes, including strikes, lockouts, job actions, boycotts, fires, explosions, floods, shortages of material or energy, or other unforeseeable causes beyond the control and without the fault or negligence of the Party so affected (each an event of ***"force majeure"***). The performance of the affected Party will be extended for a period equal to the period of such delay; *provided, however*, that affected Party will give prompt notice to the other Party of such cause, and will promptly take whatever reasonable steps are necessary to relieve the effect of such *force majeure* and resume compliance with this Agreement as soon as possible. Should the event of *force majeure* continue for a period longer than [*] days, then the Party not so affected may terminate this Agreement in accordance with Section 10.3(d).

(b) ***Transfer of Production***. If Pfizer becomes subject to an event of *force majeure* which interferes with production of Product at the Facility, the Parties will mutually agree on implementation of an agreed-upon action plan to transfer production of Product to another Pfizer manufacturing facility. The Parties will, after the execution of this Agreement and at the request of either Party, meet to discuss and define such an action plan.

12.2 Notices

All notices, requests, claims, demands and other communications between the Parties will be in writing. All notices will be given (a) by delivery in person, (b) by a nationally recognized next day courier service, (c) by first class, registered or certified mail, postage prepaid, (d) by facsimile, or (e) by PDF scanned copy sent by electronic mail to the following addresses of the respective Parties:

If to Trevena:

Trevena, Inc.
1018 W. 8th Avenue, Suite A
King of Prussia, PA 19406

Attention: Michael Lark
Facsimile: (610) 354-8850
Email: mlark@trevenainc.com

With a copy to: Trevena Legal Department

Trevena, Inc.
1018 W. 8th Avenue, Suite A
King of Prussia, PA 19406

Attention: General Counsel
Facsimile: (610) 354-8850
Email: jlimongelli@trevena.com

If to Pfizer:

Pfizer CentreOne
Pfizer, Inc.
275 North Field Drive
Lake Forest, Illinois 60045

Attention: V.P. Contract Manufacturing
Facsimile: (224) 212-3210
Email: kevin.orfan@pfizer.com

With copy to:

Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Attention: General Counsel
Facsimile: (212) 309 0874
Email: generalcounsel@pfizer.com

Notices will be effective (w) upon receipt, if personally delivered, (x) is sent by courier, [*] Business Day after the delivery time promised by the nationally recognized next day courier service, (y) if delivered by facsimile or electronic mail, on the [*] Business Day after the date of receipt by the transmitting person of written confirmation of successful transmission (which confirmation may be produced by the transmitting person's facsimile or electronic mail equipment), or (z) [*] Business Days after being deposited in the United States mail, with proper postage and documentation, for first-class registered or certified mail, prepaid. A Party may change its address listed above by written notice to the other Party.

12.3 Governing Law

This Agreement will be construed, interpreted and governed by the laws of the State of Delaware, excluding its choice of law provisions. The United Nations Convention on the International Sale of Goods is hereby expressly excluded.

12.4 Alternative Dispute Resolution

The Parties recognize that bona fide disputes may arise which relate to the Parties' rights and obligations under this Agreement. The Parties agree that except as provided in Section 11.4, any such dispute will be resolved by alternative dispute resolution in accordance with the procedures set forth in Schedule 12.4.

12.5 Assignment

Neither Party will assign this Agreement nor any part thereof without the prior written consent of the other Party; *provided, however*, that either Party may, without such consent, assign the rights and obligations of this Agreement (a) to one of its Affiliates, subsidiaries or parent corporation, and (b) in connection with the transfer, sale or divestiture of substantially all of its business to which this Agreement pertains or in the event of its spin-off, merger or consolidation with another company. Any permitted assignee will assume all obligations of its assignor under this Agreement. No assignment will relieve either Party of responsibility for the performance of any accrued obligation which such Party then has hereunder.

12.6 Severability

This Agreement is subject to the restrictions, limitations, terms and conditions of all applicable governmental regulations, approvals and clearances. If any term or provision of this Agreement will for any reason be held invalid, illegal or unenforceable in any respect, such invalidity, illegality or unenforceability will not affect any other term or provision hereof, and this Agreement will be interpreted and construed as if such term or provision, to the extent the same will have been held to be invalid, illegal or unenforceable, had never been contained herein.

12.7 Modification of Agreement; Waiver

No waiver or modification of any of the terms of this Agreement will be valid unless in writing and signed by authorized representatives of both Parties. Failure by either Party to enforce any such rights under this Agreement will not be construed as a waiver of such rights, nor will a waiver by either Party in one or more instances be construed as constituting a continuing waiver or as a waiver in other instances

12.8 Relationship of the Parties

The relationship of the Parties under this Agreement is that of independent contractors. Nothing contained in this Agreement or the performance of any obligations under this Agreement will create an association, partnership, joint venture, or relationship of principal and agent, master and servant, or employer and employee between the Parties hereto. Neither Party has any express or implied right or authority under this Agreement to assume or create any obligations or make any representations or warranties on behalf of or in the name of the other Party or its Affiliates.

12.9 Insurance

Each party will procure and maintain, at its own expense, for the duration of the Agreement, and for five (5) years thereafter if written on a claim made or occurrence reported form, the types of insurance specified below with carriers rated A- VII or better with A. M. Best or like rating agencies:

(a) Workers' Compensation in accordance with applicable statutory requirements and [*] Employers Liability and each party shall provide a waiver of subrogation in favor of the other party and its affiliate;

(b) Commercial General Liability including premises operations, products & completed operations, blanket contractual liability, personal injury and advertising injury including fire legal liability for bodily injury and property damage in an amount [*] per occurrence and [*] in the aggregate;

(c) Commercial Automobile Liability for owned, hired and non-owned motor vehicles with a combined single limit in an amount [*];

(d) Marine Insurance covering all shipments from warehouse to warehouse as described on the bill of lading at full replacement cost, except as otherwise provided herein.

Each party will include the other party and its Affiliates, directors, officers, employees and agents as additional insureds with respect to Commercial General Liability (via CG20101185 or its equivalent), Commercial Automobile Liability and Excess Liability but only as required by written contract. Prior to commencement of the development services, and annually thereafter, each party will furnish to the other party certificates of insurance evidencing the insurance coverages stated above At least [*] days written notice to the other party shall be provided prior to any cancellation, non-renewal or material change in said coverage. In the case of cancellation, non-renewal or material change in said coverage, each party will promptly provide to the other party a new certificate of insurance evidencing that the coverage meets the requirements in this Section 12.9. Each party, to the extent of its negligence, agrees that its insurance will act as primary and noncontributory from any other valid and collectible insurance maintained by the other party. Pfizer may, at its option, satisfy, in whole or in part, its obligation under this Section 12.9 through its self-insurance program. Each party may satisfy its insurance requirements by any combination of primary and excess coverage. Each party shall provide a waiver of subrogation in favor of the other party and its affiliates on all required coverages, above. All deductibles/retentions are the sole responsibility of the named insured.

12.10 Schedules

All Schedules referred to herein are hereby incorporated by reference.

12.11 Binding Effect

This Agreement will be binding upon and inure to the benefit of each of the Parties and such Party's successors and permitted assigns.

12.12 Debarment Warranty

Pfizer and Trevena represent and warrant that neither Party uses nor will use in the future use in any capacity the services of any person debarred under Section (a) or (b) of 21 U.S.C. Section 335a.

12.13 Compliance with Laws

Each Party will comply with all Applicable Laws, statutes, rules and regulations governing its performance of the terms of this Agreement.

12.14 Entire Agreement

This Agreement and the Quality & Technical Agreement, together with the Schedules referenced and incorporated herein, constitute the entire agreement between the Parties concerning the subject matter hereof and supersede all written or oral prior agreements or understandings with respect thereto. If there is any conflict, discrepancy, or inconsistency between the terms of the Quality & Technical Agreement, this Agreement or other form used by the Parties, the Quality & Technical Agreement will control as regards all issues related to quality assurance; in all other cases, the Agreement will control.

12.15 Condition Precedent

This Agreement will enter into force as of the Effective Date, but will remain conditional upon the Parties negotiating and delivering a Quality & Technical Agreement, signed by all required authorized quality officers and representatives of both Parties.

12.16 Construction

In construing this Agreement, unless expressly specified otherwise (a) references to Articles, Sections and Schedules are to articles, sections of, and Schedules to, this Agreement, (b) except where the context otherwise requires, use of either gender includes the other gender, and use of the singular includes the plural and vice versa, (c) headings and titles are for convenience only and do not affect the interpretation of this Agreement, (d) any list or examples following the word "including" will be interpreted without limitation to the generality of the preceding words, (e) except where the context otherwise requires, the word "or" is used in the inclusive sense, (f) all references to "dollars" or "$" herein will mean United States Dollars, and (g) each Party represents that it has been represented by legal counsel in connection with this Agreement and acknowledges that it has participated in the drafting hereof. In interpreting and applying the terms and provisions of this Agreement, the Parties agree that no presumption will apply against the Party which drafted such terms and provisions. Any terms or conditions contained in an invoice that are inconsistent or in conflict with this Agreement will be deemed not to be a part of such invoice.

12.17 Counterparts

This Agreement may be executed in any number of counterparts, each of which will be deemed an original, and all of which together will constitute one and the same instrument. Signatures provided by facsimile transmission or in Adobe™ Portable Document Format (PDF) sent by electronic mail will be deemed to be original signatures. Any Party delivering an executed counterpart of this Agreement by facsimile or electronic mail will also deliver an original executed counterpart, but the failure to do so will not affect the validity, enforceability or binding effect of this Agreement.

IN WITNESS WHEREOF, the Parties intending to be bound by the terms and conditions hereof have caused this Agreement to be signed by their duly authorized representatives as of the date first above written.

PFIZER CENTREONE **PFIZER, INC.**	**TREVENA, INC.**
By: _____ (Signature)	By: _____ (Signature)
Name: Kevin Orfan	Name: Michael W. Lark, Ph.D.

Title: Vice President
Pfizer CentreOne
Contract Manufacturing Services

Title: Senior Vice President, Research and Chief Scientific Officer

SCHEDULE 1.2

API Specifications

[*]

SCHEDULE 1.25

Product Specifications

[*]

SCHEDULE 2.1

Project Statement of Work

[*]
(10 pages omitted)

SCHEDULE 3.1

Estimated Payment Schedule

[*]

SCHEDULE 3.2

Stability Studies

[*]
(2 pages omitted)

SCHEDULE 5.5

Dedicated Equipment

[*]

SCHEDULE 6.11

Pfizer Logger Policies

[*]

SCHEDULE 6.13

Product Price Estimates

[*]

SCHEDULE 7.1

Product Test Methods

[*]

SCHEDULE 7.2

Quality & Technical Agreement

[*]

SCHEDULE 12.4

Alternative Dispute Resolution

[*]

ANNEX 1

Letter of Engagement

(LOE attached following this Annex 1 cover page)

Exhibit 12.1

TREVENA, INC.

COMPUTATION OF RATIO OF EARNINGS TO FIXED CHARGES

	2013	2014	2015	2016	2017
			(in thousands)		
Determination of earnings					
Income/(loss) before income taxes	$ (23,251)	$ (49,701)	$ (50,528)	$ (102,994)	$ (71,865)
Add:					
Fixed Charges	303	234	531	1,927	3,232
Total Earnings/(loss)	(22,948)	(49,467)	(49,997)	(101,067)	(68,633)
Fixed charges:					
Interest expense and amortization of debt discount and deferred financing costs	150	71	334	1,738	2,781
Estimated interest component of rent expense	153	163	197	189	541
Total fixed charges	303	234	531	1,927	3,322
Ratio of earnings to fixed charges(1)					
Deficiency of earnings to cover fixed charges	$ 23,251	$ 49,701	$ 50,528	$ 102,994	$ 71,865

(1) For all periods presented, no ratios are provided as earnings were insufficient to cover fixed charges.

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-208538) and Forms S-8 (Nos. 333-193735, 333-195957, 333-201672, 333-208948, 333-215420, 333-215421, and 333-222471) of our report dated March 7, 2018, with respect to the financial statements of Trevena, Inc. included in this Annual Report on Form 10-K for the year ended December 31, 2017.

/s/ Ernst & Young LLP

Philadelphia, Pennsylvania
March 7, 2018

Exhibit 31.1

Certification of Principal Executive Officer of Trevena, Inc.
Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Maxine Gowen, certify that:

1. I have reviewed this Annual Report on Form 10-K of Trevena, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, 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;

   c. Evaluated the effectiveness of the registrant's disclosure controls and procedures, and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 7, 2018

/s/ Maxine Gowen

Maxine Gowen
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

Certification of Principal Financial Officer of Trevena, Inc.
Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Roberto Cuca, certify that:

1. I have reviewed this Annual Report on Form 10-K of Trevena, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, 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;

   c. Evaluated the effectiveness of the registrant's disclosure controls and procedures, and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 7, 2018

/s/ Roberto Cuca

Roberto Cuca
Senior Vice President and Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

Certification Of
Principal Executive Officer
Pursuant To 18 U.S.C. Section 1350,
As Adopted Pursuant To
Section 906 Of The Sarbanes-Oxley Act Of 2002

In connection with the Annual Report of Trevena, Inc. (the "Company") on Form 10-K for the year ended December 31, 2017, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Maxine Gowen, President and Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2) The information contained in the Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Report and results of operations of the Company for the period covered by the Report.

Date: March 7, 2018

/s/ Maxine Gowen

President and Chief Executive Officer
(Principal Executive Officer)

This certification accompanies the Report and shall not be deemed "filed" by the Company with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Report), irrespective of any general incorporation language contained in such filing.

Exhibit 32.2

Certification Of
Principal Financial Officer
Pursuant To 18 U.S.C. Section 1350,
As Adopted Pursuant To
Section 906 Of The Sarbanes-Oxley Act Of 2002

In connection with the Annual Report of Trevena, Inc. (the "Company") on Form 10-K for the year ended December 31, 2017, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Roberto Cuca, Senior Vice President and Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2) The information contained in the Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Report and results of operations of the Company for the period covered by the Report.

Date: March 7, 2018

/s/ Roberto Cuca

Chief Financial Officer and Treasurer
(Principal Financial Officer)

This certification accompanies the Report and shall not be deemed "filed" by the Company with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Report), irrespective of any general incorporation language contained in such filing.