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, 2020
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 110, 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	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.001 per share	TRVN	The Nasdaq Stock Market LLC

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 every Interactive Data File required to be submitted 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 such files). Yes ☒ No ☐

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," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.:

Large accelerated filer ☐ Accelerated filer ☐ Non-accelerated filer ☒ 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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

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, 2020, the last business day of the registrant's most recently completed second fiscal quarter, was approximately $189.4 million. Such aggregate market value was computed by reference to the closing price of the Common Stock as reported on the Nasdaq Stock Market LLC on June 30, 2020. For purposes of making this calculation only, the registrant has defined affiliates as including only directors and executive officers and stockholders holding greater than 10% of the voting stock of the registrant as of June 30, 2020.

The number of shares of the registrant's Common Stock outstanding as of March 5, 2021 was 161,273,660.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2021 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, 2020 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 also are 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, among other things, statements about:

- our ability to successfully commercialize OLINVYK and any other product candidates for which we may obtain regulatory approval;
- our sales, marketing and manufacturing capabilities and strategies;
- any ongoing or planned clinical trials and preclinical studies for our product candidates;
- the extent of future clinical trials potentially required by the FDA for 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;
- the timing and likelihood of obtaining and maintaining regulatory approvals for our product candidates;
- our plan to develop and potentially commercialize our product candidates;
- the clinical utility and potential market acceptance of our product candidates, particularly in light of existing and future competition;
- the size of the markets for our product candidates;
- the performance of third-parties upon which we depend, including contract manufacturing organizations, suppliers, contract research organizations, distributors and logistic providers;
- our ability to identify or acquire additional product candidates with significant commercial potential that are consistent with our commercial objectives;
- the extent to which health epidemics and other outbreaks of communicable diseases, including the ongoing COVID-19 pandemic, could disrupt our operations and/or materially and adversely affect our business and financial conditions;
- our intellectual property position and our ability to obtain and maintain patent protection and defend our intellectual property rights against third parties;
- ongoing litigation; and
- our ability to satisfy all applicable Nasdaq continued listing requirements.

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

We are a biopharmaceutical company focused on developing and commercializing novel medicines for patients affected by central nervous system, or CNS, disorders.

Our lead product, OLINVYK™ (oliceridine) injection, or OLINVYK, was approved by the United States Food and Drug Administration, or FDA, in August 2020. We initiated commercial launch of OLINVYK in the first quarter of 2021. OLINVYK is an opioid agonist for use in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. OLINVYK is the first new chemical entity, or NCE, in this intravenous, or IV-, drug class in decades and it offers a differentiated profile that addresses significant unmet needs in the acute pain management landscape. OLINVYK delivers IV opioid efficacy with a rapid 2-5 minute onset of action. In addition, OLINVYK requires no dosage adjustments in patients with renal impairment, a large patient population with significant medical complications. In October 2020, we announced that OLINVYK received scheduling from the U.S. Drug Enforcement Administration, or DEA, and oliceridine was classified as a Schedule II controlled substance.

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

- **TRV027:** We are developing TRV027, a novel angiotensin II type 1, or AT1, receptor selective agonist, for the treatment of acute lung injury contributing to acute respiratory distress syndrome, or ARDS, and abnormal blood clotting in patients with COVID-19. In a COVID-19 infection, the SARS-coronavirus-2 causes overactivation of the AT1 receptor resulting in downstream acute lung injury, which can lead to ARDS, and abnormal blood clotting, which can lead to pulmonary embolisms and strokes. TRV027 competitively binds to and rebalances AT1 receptor activation and also preferentially engages the beta-arrestin signaling pathway to promote reparative effects on lung tissue.

  In June 2020, we announced a collaboration with Imperial College London, or ICL, to study TRV027 in a randomized, placebo-controlled study of approximately 60 COVID-19 patients. ICL is sponsoring and funding this study, with additional support from the British Heart Foundation Centre for Research Excellence Award, and expects the primary completion date to be in the first half of 2021. TRV027 previously demonstrated efficacy, potency, and selectivity at the AT1 receptor in nonclinical studies related to acute heart failure, and it has a well-characterized pharmacokinetic profile.

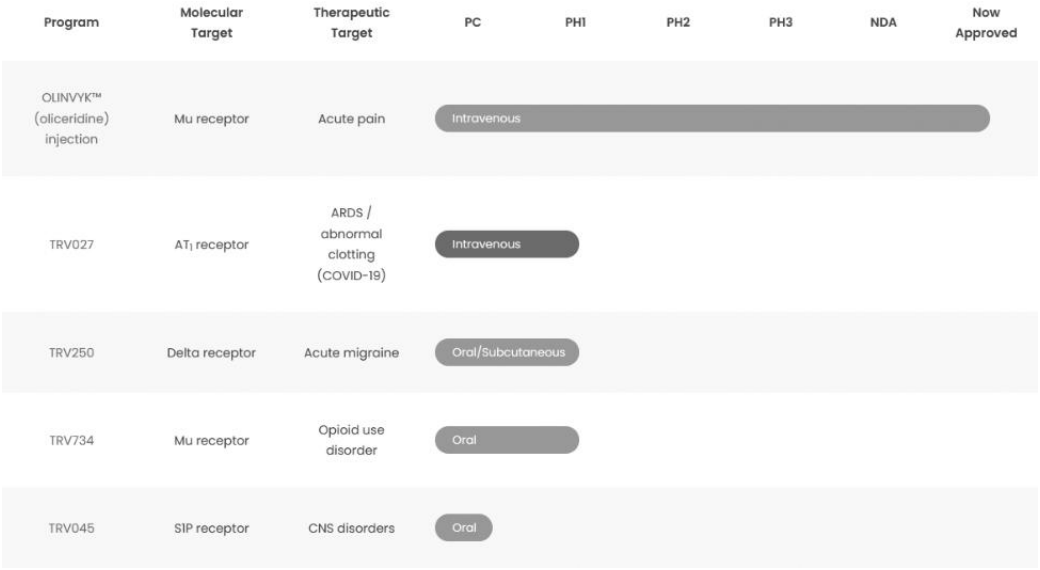
- **TRV250:** We are developing TRV250, a G-protein biased delta-opioid receptor, or DOR, agonist as a compound with a potential first-in-class novel mechanism for the treatment of acute migraine. TRV250 also may have utility in a range of other CNS indications. Because TRV250 selectively targets the DOR, we believe it will not have the addiction liability of conventional opioids or have other mu-opioid related adverse effects like respiratory depression and constipation. In June 2018, we announced the completion of our first-in-human Phase 1 study of TRV250. Data from this healthy volunteer study showed a favorable tolerability profile and pharmacokinetics supporting the advancement of TRV250 to proof-of-concept evaluation in patients. The proof-of-concept study protocol required subjects to be monitored in an in-patient setting for 24 hours, and due to the global COVID-19 pandemic we terminated the study in August 2020. In March 2021, we announced that we identified a novel oral dose formulation for TRV250. The process development work for the oral form has the potential to extend the patent for TRV250 by an additional five years to 2041. We have initiated IND-enabling activities with the oral dosage form to support future clinical development.

- **TRV734:** We also have identified and have completed the initial Phase 1 studies for TRV734, an NCE targeting the same novel mechanism of action at the MOR as OLINVYK. TRV734 was designed to be

orally available, and its mechanism of action suggests it may offer valuable benefits for two distinct areas of important unmet medical need: acute and chronic pain, and maintenance-assisted therapy for patients with opioid use disorder, or OUD. We are collaborating with the National Institute on Drug Abuse, or NIDA, to further evaluate TRV734 for the management of OUD, and NIDA initiated a proof-of-concept study for this indication in December 2019. In March 2020, we announced that due to the global COVID-19 pandemic, enrollment was paused in this trial. We intend to continue to focus our efforts for TRV734 on securing a development and commercialization partner for this asset.

- **TRV045:** We are evaluating a set of novel S1P modulators that may offer a new, non-opioid approach to managing chronic pain. In the fourth quarter of 2018, we identified a new product candidate, TRV045, a novel S1P modulator that we believe may offer a new, non-opioid approach to managing chronic pain. In the second quarter of 2019, we initiated investigational new drug, or IND, enabling work, and we will continue to evaluate the progression of this asset, either by ourselves or with a partner. In March 2020, we announced we entered into a collaboration with the U.S. National Institutes of Health, or NIH, to evaluate the potential of TRV045 as a treatment for epilepsy. In May 2020, we announced we entered into a collaboration with the NIH to evaluate the potential of TRV045 as a treatment for pain. NIH is assessing TRV045 within its Epilepsy Therapy Screening Program, or ETSP, and in its Preclinical Screening Platform for Pain, or PSPP. We expect to file an IND application with the FDA for TRV045 in the first half of 2021.

Our Product and Pipeline



OLINVYK™ (oliceridine) injection

OLINVYK is a G-protein biased MOR ligand that we are commercializing in hospitals or other controlled clinical settings for acute pain in adults that is severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. It is an NCE with a novel mechanism of action.

Pain treatment options

Approximately 45 million hospital patients in the United States were treated with an IV opioid for acute pain, according to 2017 IQVIA data. Conventional IV opioid analgesics, such as morphine, fentanyl, and hydromorphone, have been core components of pain management protocols in the immediate postoperative period. The effectiveness of conventional opioids agonists is limited by severe dose dependent side effects such as respiratory depression, nausea, vomiting, and constipation, which can be exacerbated by accumulation of active metabolites and by reduced renal clearance in patients with impaired kidney function. These shortcomings of conventional IV opioids create substantial challenges for healthcare providers in certain clinical practice situations.

Injectable non-opioid analgesics are often used together with IV opioids in multimodal protocols 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 their own potential for cardiovascular, hepatic and gastrointestinal side effects. In addition, none of these non-opioid analgesics offers sufficient efficacy to manage severe acute pain as a monotherapy in many patients.

We believe that OLINVYK addresses a significant unmet need for a highly effective IV opioid analgesic agent with a differentiated safety, tolerability, and PK/PD profile. OLINVYK delivers IV opioid efficacy with a rapid 2-5 minute onset of action and requires no dosage adjustments in patients with renal impairment, a large patient population with significant medical complications. Data from an exploratory analysis was recently published that highlights the low incidence of opioid-induced respiratory depression in patients treated with OLINYK, regardless of age or body mass index.

OLINVYK was approved by the FDA in August 2020 for both bolus and patient-controlled analgesia, or PCA, delivery and we initiated commercial launch of OLINVYK in the first quarter of 2021. The DEA has classified oliceridine as a Schedule II controlled substance. Like other opioids, the label for OLINVYK contains a “boxed” warning and important safety information. Please consult www.olinvyk.com to view the prescribing information together with important safety information and boxed warning.

OLINVYK clinical data

APOLLO 1 and APOLLO 2 Phase 3 Studies

We conducted two pivotal efficacy trials evaluating OLINVYK 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 both studies, all dose regimens achieved the primary endpoint of statistically greater analgesic efficacy than placebo, as measured by responder rate. On the secondary endpoint of summary of pain intensity difference (SPID) assessed by numerical rating scale, in the APOLLO 1 study, all dose regimens achieved statistically greater pain relief compared to placebo, while in the APOLLO 2 study, the 0.35mg and 0.5mg dose regimens achieved statistically greater pain relief compared to placebo.

The APOLLO 1 and APOLLO 2 studies were both Phase 3, multicenter, randomized, double-blind, placebo- and active-controlled studies of OLINVYK. During the study period, a loading dose of placebo, morphine (4 mg), or OLINVYK (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: placebo, 1 mg morphine, or 0.1 mg, 0.35 mg, or 0.5 mg OLINVYK. If PCA dosing was inadequate to control pain, patients could request supplemental study medication (2 mg morphine or 0.75 mg OLINVYK, no more than once an hour). If the study medication regimen did not adequately manage pain, patients could opt for an NSAID rescue analgesic. Loading, demand, and supplemental doses were volume-matched for all treatment regimens.

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. The primary efficacy outcome was measured using a categorical 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. The summary of pain intensity difference (SPID), which the FDA used as the basis of approval, was a secondary endpoint in both studies and was assessed by numerical rating scale through the randomized treatment period (48 hours in APOLLO 1 and 24 hours in APOLLO 2) and compared to placebo. 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 incidence of oxygen saturation less than 90% and incidence of supplemental oxygen use. Measures of gastrointestinal tolerability included use of rescue antiemetics, vomiting, and spontaneously reported nausea.

APOLLO 1 (bunionectomy)

- All three OLINVYK 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).

- Following the 1.5 mg initial loading dose, all OLINVYK regimens demonstrated rapid onset with statistically significant efficacy within 5 minutes ($p<0.05$).

APOLLO 2 (abdominoplasty)

- All three OLINVYK 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).

- Following the 1.5 mg initial loading dose, all OLINVYK regimens demonstrated rapid onset with statistically significant efficacy within 5 to 15 minutes ($p<0.05$).

In both studies, OLINVYK was generally well-tolerated. The most common drug related adverse events (incidence ≥10%) were nausea, vomiting, dizziness, headache, constipation, pruritus and hypoxia.

ATHENA Phase 3 Open Label Safety Study

We conducted a Phase 3, open label, multicenter study evaluating the safety and tolerability of OLINVYK 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 OLINVYK 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 OLINVYK. Pain intensity was measured as a secondary endpoint.

In the ATHENA study, 768 patients were treated with OLINVYK. 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. Adverse event rates associated with OLINVYK administered by PCA and as-needed bolus dosing were similar, supporting the potential use of OLINVYK in both administration paradigms.

OLINVYK Commercialization

We initiated commercial launch of OLINVYK in the first quarter of 2021 with a customer-facing team of approximately 40 individuals across a range of roles including Key Account Managers, Institutional Account Managers and other professionals. Our commercial focus is on hospitals as well as outpatient surgical departments and ambulatory

surgical centers and we will target a range of specialties including surgeons, anesthesiologists, hospitalists, and other healthcare providers with acute post-surgical or medical pain management responsibility.

Approximately 45 million hospital patients in the United States were treated with an IV opioid for acute pain, with the majority of doses in the inpatient setting. We estimate that 9 million of these patients are at increased risk of opioid-related adverse events such as respiratory depression or post-operative nausea and vomiting. Many of these patients are elderly and have comorbid conditions, driving surgical complexity and a potential for an increased length of stay. This growing patient population results in a significant cost burden to the hospital system, and we have completed health economic analyses framing significant cost savings due to OLINVYK relative to conventional IV opioids in these patients. We intend to publish these data in the peer-reviewed medical literature.

We believe the greatest opportunity for OLINVYK will be in the inpatient setting where patients are treated with multiple doses for an average of one to two days. Due to its quick onset and duration of analgesia, OLINVYK is also well suited for use in the growing hospital outpatient and ambulatory surgical center settings. Because many surgeons and anesthesiologists manage both inpatient and outpatient cases, we believe that early physician experiences with OLINVYK in outpatient surgery may support subsequent expansion of use to the inpatient setting.

Approximately 1,200 US hospitals are responsible for 70% of the annual volume of conventional IV opioid drugs prescribed, according to 2017 data from Symphony Health Solutions. We have identified a subset of approximately 550 high volume hospitals that have rapidly adopted new branded analgesic agents in the past as the initial account targets.

We are committed to the ethical promotion of OLINVYK. The Company's goal is not to increase opioid usage; rather, the Company and its representative are asking healthcare professionals to consider OLINVYK as a differentiated alternative versus conventional IV opioids when an IV opioid is necessary to manage the patient's acute pain.

Manufacturing

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

For OLINVYK, we have established commercial supply agreements for the manufacture of the API and finished (compounded, filled and packaged) drug product. Sterling Pharma Solutions (formerly Alcami Corporation), or Sterling, 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 Corporation, or Alcami, is contracted to supply commercial drug product from its facilities in Charleston, SC and Wilmington, NC and was included as part of our NDA submission. Pfizer CentreOne (formerly Hospira) is also contracted to supply commercial drug product in the future from its facility in Rocky Mount, NC, but was not included in our NDA submission.

In October 2020, we announced that the DEA has classified OLINVYK as a Schedule II controlled substance. All third-party facilities throughout the supply chain have the appropriate licenses from the DEA for handling Schedule II controlled substances according to each of their respective contractual roles (manufacturing, testing, distribution, etc.).

Competition

OLINVYK is approved for use in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are not adequate. We expect OLINVYK to 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, which can be exacerbated by the way these molecules are metabolized or cleared. OLINVYK will also 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; DSUVIA™ (sublingual sufentanil) marketed by AcelRx Pharmaceuticals, Inc.; and ANJESO™ (IV meloxicam), marketed by Baudax Bio, Inc.; XARACOLL™ (bupivacaine HCL) implant, marketed by Innocoll Holdings plc; and POSIMIR® (bupivacaine solution) marketed by DURECT Corporation. Together with generic versions of IV NSAIDs such as ketorolac and acetaminophen, 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 OLINVYK. AcelRx Pharmaceuticals, Inc. is developing ZALVISO™, a non-invasive PCA device containing sublingual sufentanil, which has received approval in the European Union. Heron Therapeutics Inc. has a proprietary long acting reformulation of bupivacaine in development. 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 mu opioids in clinical trials. Avenue Therapeutics, Inc. is developing an IV version of generic opioid tramadol for moderate-to-severe acute pain.

Intellectual property

We wholly own the OLINVYK patent portfolio, including four issued U.S. patents (U.S. Patent Nos. 8,835,488, 9,309,234, 9,642,842, and 9,849,119), which claim, among other things, OLINVYK, compositions comprising OLINVYK, and methods of using OLINVYK. 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, Eurasia, Europe, Hong Kong, Israel, Japan, India, South Korea, and New Zealand, which claim among other things, OLINVYK, compositions comprising OLINVYK and methods of making or using OLINVYK. The foreign portfolio also includes an application that has been allowed by the European Patent Office, which claim among other things, OLINVYK, compositions comprising OLINVYK and methods of using OLINVYK. We have patent applications pending in the United States, Europe, Japan, Israel, South Korea, Brazil, Canada, and India. 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. Following the FDA approval of OLINVYK, the FDA has added three issued U.S. patents to the Orange Book of Approved Drug Products with Therapeutic Equivalence Evaluations (U.S. Patent Nos. 8,835,488, 9,309,234, 9,642,842). In addition, the Company has filed Patent Term Extension applications with the United States Patent and Trademark Office that could extend the life of one of the patents until 2034. Finally, the FDA has designated OLINVYK as a new chemical entity, or NCE, in the Orange Book and it will therefore receive the exclusivity and protections afforded to NCE's.

TRV027

TRV027 is a novel beta-arrestin biased ligand that targets the AT1 receptor, inhibiting angiotensin II mediated G protein signaling and activating beta-arrestin signaling. We are developing TRV027 for the treatment of acute lung injury contributing to ARDS and abnormal blood clotting in patients with COVID-19. In a COVID-19 infection, the SARS-coronavirus-2 binds to and removes the ACE2 protein in the lungs and other tissues in the body, causing elevated levels of angiotensin II. This drives overactivation of the AT1 receptor resulting in downstream acute lung injury, which can lead to ARDS, and abnormal blood clotting, which can further lead to pulmonary embolisms and strokes. We believe that TRV027 has the potential to counteract the disproportionate levels of angiotensin II, by competitively binding to and rebalancing AT1 receptor activation. Additionally, we believe its unique mechanism of action preferentially engages the beta-arrestin signaling pathway to promote reparative effects on lung tissue.

Clinical Development

In June 2020, we announced a collaboration with ICL to study TRV027 in a randomized, placebo-controlled study in approximately 60 COVID-19 patients. The primary endpoint of this proof-of-concept study is a coagulation cascade biomarker, which serves as a surrogate for measuring the effect of TRV027 on adverse health outcomes associated with increased mortality in COVID-19 infections. ICL is sponsoring and funding this study, with additional

support from the British Heart Foundation Centre for Research Excellence Award and expects the primary completion date to be in the first half of 2021.

Intellectual property

We wholly own the TRV027 patent portfolio, including 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. The portfolio also includes issued U.S. Patent No. 9,518,086 that claims, among other things, crystalline forms of TRV027 and methods of using crystalline forms of TRV027 and the issued U.S. Patent No. 9,611,293 that claims, among other things, methods of synthesizing TRV027. The issued U.S. patents (U.S. Patent Nos. 9,518,086 and U.S. 9,611,293) covering crystalline forms of TRV027 and methods of synthesizing TRV027, which are expected to expire no earlier than 2035, subject to any disclaimers or extensions. Additionally, our TRV027 patent portfolio includes two pending provisional applications that are, among other things, directed to methods of treating ARDS, such as ARDS caused by COVID-19, and/or preventing and treating thrombosis using TRV027 and compounds related thereto.

TRV250

TRV250 is a G-protein biased ligand targeting the DOR agonist as a compound with potential first-in-class, novel mechanism for the treatment of acute migraine. TRV250 also may have utility in a range of other CNS indications. We have completed a first-in-human Phase 1 trial of TRV250, which showed a favorable tolerability profile and pharmacokinetics. In November 2019, we initiated a proof-of-concept evaluation in patients, which required subjects to be monitored in an in-patient setting for 24 hours. Due to the global COVID-19 pandemic, we terminated the study in August 2020. In March 2021, we announced that we identified a novel oral dose formulation for TRV250. The process development work for the oral form has the potential to extend the patent for TRV250 by an additional five years to 2041. We have initiated IND-enabling activities with the oral dosage form to support future clinical development.

Clinical development

We believe our preclinical data support targeting the DOR 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. Preclinical studies in beta-arrestin knockout mice suggest that beta-arrestin plays a role in seizures. TRV250 is a potent delta receptor ligand that selectively activates G-protein coupling without engaging beta arrestin, leading to strong efficacy in animal models of migraine and other CNS disorders with reduced seizure liability. In the future, we may decide to seek a collaborator for TRV250 with CNS development and commercialization expertise outside the United States.

In June 2018, we announced the completion of our first-in-human Phase 1 study of TRV250. Data from this healthy volunteer study showed a favorable tolerability profile and pharmacokinetics. The Phase 1 study was a two part, randomized, single-blind, placebo-controlled, single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics of subcutaneous and oral TRV250 in healthy adults. Part A assessed single subcutaneous doses in 38 subjects. Four cohorts of nine or ten subjects were randomized to receive a single dose of up to 30mg TRV250 or placebo. Part B consisted of a single cohort of nine subjects administered either TRV250 as a single 6 mg oral dose (either as a capsule in the fed state or a capsule in the fasted state, n=7) or placebo (as a capsule in the fed or fasted state, n=2).

Key findings of the study included:

- Dose-related increases in plasma concentrations following subcutaneous administration of doses up to 30 mg, with rapid absorption in the first hour and duration of exposure appropriate for treating acute migraine;

- Subcutaneous doses at and above 9 mg achieved plasma concentrations that were active in preclinical models of migraine;
- Oral bioavailability similar to existing migraine medications, supporting continued development of TRV250 in oral and/or subcutaneous formulations;
- No observed drug-associated electroencephalography changes, consistent with preclinical studies in which TRV250 avoided the seizure liability associated with previous CNS-active delta receptor agonists; and
- No clinically significant changes in vital signs, laboratory values, or ECG parameters, and no severe or serious adverse events reported.

Based on the profile of TRV250, we believe it has the potential to be a first-in-class treatment option for treatment of migraine. According to Decision Resources, a healthcare consulting company, the acute migraine treatment market encompassed approximately 12 million drug-treated patients in 2017 in the United States, representing approximately $1.5 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.

Competition

Triptans, a generic family of 5-HT1B agonists, are the current standard treatment for acute treatment of migraine in the United States, and account for 70% of sales for this indication. 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 2018. Eli Lilly acquired Lasmiditan (REYVOW®), a selective 5-HT1F agonist, from Colucid Pharmaceuticals, Inc., and received FDA approval in October 2019. BioHaven launched Rimegepant (NURTEC) in 2020 and they have a second CGRP receptor antagonist candidate (vazegepant) in early development for acute treatment of migraine. In 2019, Allergan launched Ubrelvy™ (ubrogepant) an oral, small molecule anti-calcitonin gene-related peptide, or CGRP, for treatment of acute migraine.

Patients suffering from frequent or chronic migraine headaches may also use preventative agents to decrease the frequency and severity of migraines. Botox® is the historical gold standard migraine prophylactic, but certain anticonvulsants, such as topiramate, and beta-blockers, such as propranolol, have also been used. However, a new class of anti-CGRP antibody products are being marketed for preventative treatment of migraine: In 2018, Amgen and Novartis launched Aimovig® (erenumab), Eli Lilly and Company launched Emgality® (galcanezumab), and Teva Pharmaceutical Industries Limited launched Ajovy® (fremanezumab). In 2020, Alder BioPharmaceuticals Inc. launched VyeptiTM (eptinezumab-jjmr) and AbbVie announced positive phase 3 data for atogepant, an oral small molecule CGRP receptor antagonist. Allergan also has late stage migraine prevention trials underway for atogepant, an oral small molecule CGRP receptor antagonist. Biohaven is conducting clinical trials of zavegepant (also a CGRP receptor antagonist) for the prevention of migraine.

Intellectual property

We wholly own the TRV250 patent portfolio, including one issued patent (U.S. Patent No. 10,246,436) in the United States directed to compounds that modulate the delta receptor, claiming, among other things, TRV250, compositions comprising TRV250, and methods of using TRV250. The patent is expected to expire no earlier than 2036, subject to any disclaimers or extensions. We also have patent applications pending in the United States, 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. We also have one pending provisional patent application that is, among other things, directed to crystalline forms of TRV250, compositions comprising crystalline forms of TRV250, and methods of using crystalline forms of TRV250. Any patents

that may issue based on this provisional application would be expected to expire no earlier than 2041, subject to any disclaimers or extensions.

TRV734

TRV734 is a small molecule G-protein biased ligand of the MOR 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 OLINVYK, TRV734 utilizes a well-established mechanism of pain relief by targeting the MOR. Also like OLINVYK, it does so with enhanced selectivity for the G-protein signaling pathway, which in preclinical studies was linked to analgesia, as opposed to the beta-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. In addition, TRV734's mechanism of action suggests it may offer valuable benefits for another unmet medical need: the management of opioid dependence associated with OUD. We intend to continue to focus our efforts for TRV734 on securing a development and commercialization partner for this asset.

Clinical development

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 OLINVYK, 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.

In collaboration with NIDA, we intend to pursue a clinical study to determine whether TRV734 decreases symptoms of opioid withdrawal in patients with OUD. We expect to initiate a randomized, double-blind, four-period, placebo- and positive-controlled study that will enroll approximately 50 opioid-dependent patients undergoing stable methadone maintenance therapy. The primary objective of the study is to assess the ability of TRV734 to reduce acute opioid craving symptoms, as measured by the Subjective Opioid Withdrawal Scale. The study will also evaluate whether TRV734 suppresses withdrawal signs using the Clinical Opioid Withdrawal Scale. Secondary outcomes will include assessments of safety and measures of neurocognitive changes. In March 2020, we announced that due to the global COVID-19 pandemic, enrollment has been paused in this trial.

NIDA has previously generated preclinical data in a rodent model of maintenance treatment showing that chronic administration of TRV734 reduced oxycodone-seeking in rats. TRV734 may provide an alternative to existing therapies such as methadone and buprenorphine. Successful therapy with methadone is limited by side effects that include sedation and constipation, while use of buprenorphine is limited by lower maximal efficacy and challenges with initial induction of therapy. It is hypothesized that a MOR-biased agonist may provide high efficacy for preventing symptoms of opioid withdrawal while offering a more benign side-effect profile.

Intellectual property

We wholly own the TRV734 patent portfolio, including two issued U.S. patents (U.S. Patent No, 9,044,469 and 10,588,898) 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, India, South Korea, and New Zealand claiming TRV734, other compounds and/or methods of making or using the same. We also have patent applications pending in the United States, Europe, 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.

TRV045 (S1P Modulators)

We are evaluating a set of novel S1P modulators that may offer a new, non-opioid approach to managing chronic pain. The compounds we are evaluating are all NCEs, are expected to be non-addictive, and use a new mechanism of action that in preclinical models avoids the lymphocyte trafficking effects and 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.

Our first product candidate under this program is TRV045, a novel S1P modulator. In the second quarter of 2019, we initiated IND-enabling work for this product candidate, and we intend to continue to progress this asset to an IND, either independently or with a partner. We expect to file an IND application with the FDA for TRV045 in the first half of 2021.

We have entered into collaborations with the NIH to evaluate the potential of TRV045 as a treatment for chronic pain and epilepsy. NIH is assessing TRV045 within its Preclinical Screening Platform for Pain and its Epilepsy Therapy Screening Program.

Intellectual Property

We wholly own the S1P patent portfolio, including one provisional application, two Patent Cooperation Treaty, or PCT, applications, and applications filed in the United States, Australia, Brazil, Canada, China, Europe, Israel, India, Japan, South Korea, and New Zealand. The applications are directed to, amongst other things, compounds that modulate the S1P receptor and methods of using these compounds, including for methods of treating pain, epilepsy, mood disorders, anxiety disorders, and trauma-and stressor-related disorders. Patents that could issue in the future from the national phase applications would be expected to expire no earlier than 2038, subject to any disclaimers or extensions. 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 G-protein coupled receptors with biased ligands.

One or more third parties may hold intellectual property, including patent rights, that is important or necessary to the development of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially. If we were not able to obtain a license or were not able to obtain a license on commercially reasonable terms, our business could be harmed, possibly materially.

We plan to continue to expand our intellectual property estate by filing patent applications directed to dosage forms, methods of treatment 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 additional pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products much in the same manner as we did for OLINVYK. 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. See "—OLINVYK (oliceridine) injection—Manufacturing."

The use of contract manufacturing organizations, or CMOs, and reliance on collaboration partners is cost-efficient and has eliminated the need for our direct investment in manufacturing facilities and additional staff early in development. We believe available CMOs are capable of providing sufficient quantities of our product candidates to meet anticipated full-scale commercial demands.

Commercialization

We are launching the customer-facing elements of our commercial team in the first quarter of 2021. We have partnered with Syneos Health in the sourcing, training and deployment of a range of customer-facing roles including Key Account Managers, sales representatives and other professionals. Syneos Health is a well-known contract sales organization with broad experience in providing the services and support for which we have engaged them. We believe this engagement will allow us to effectively and efficiently address the community of physicians who are the key specialists in treating the patient populations for which our product is indicated. 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. 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. OLINVYK and any further 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 OLINVYK and any of our additional 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 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 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 any oral mu-opioid agonist products may be subject to a REMS, since currently marketed oral opioid products are subject to this requirement. OLINVYK is an IV opioid and is not subject to a REMS.

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. The FDA reviews NDA resubmissions in two or six months depending on the type of information included. An approval letter authorizes commercial distribution and 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. 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.

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 clinical trials in pediatric patients or other Phase 4 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-marketing 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. However, companies may share truthful and not misleading information that is otherwise consistent with a product's approved labeling. 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

OLINVYK has been classified as a Schedule II controlled substance under the Federal Controlled Substances Act of 1970, or CSA. The CSA 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. Because it is a Schedule II controlled substance, the manufacture, shipment, storage, sale and use of OLINVYK is 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, or impact the ability to fill orders of approved products such as OLINVYK.

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 transparency and 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, formulary managers, and others on the other hand. 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 and require strict compliance to offer protection. 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, as well as ownership interests held by, physicians and teaching hospitals.

The federal criminal and civil false claims laws, including the federal False Claims Act, and civil monetary penalties laws and civil monetary penalties 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. 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. 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 civil and 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.

The federal Physician Payments Sunshine Act, also known as Open Payments program, 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, as defined by such law, 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.

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, imposed 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 significant criminal, civil, and administrative penalties, damages, fines, disgorgement, 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, implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals, and data privacy requirements such as the General Data Protection Regulation (EU) 2016/679.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring such companies to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. In Europe, and throughout the world, other countries have enacted anti-bribery laws and/or regulations similar to the FCPA. Violations of any of these antibribery laws, or allegations of such violations, could have a negative impact on our business, results of operations and reputation.

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. However, decisions regarding the extent of coverage and amount of reimbursement to be provided are made on a payor-by-payor basis. 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 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 OLINVYK 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 OLINVYK 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 OLINVYK. 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, or HHS, 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 changed the way healthcare is financed by both governmental and private insurers. Among other cost containment measures, the PPACA established 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 increased 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 judicial, executive branch, and legislative activity around, attempts to repeal or repeal and replace the PPACA. For example, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the PPACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. Additionally, on December 14, 2018, a Texas U.S. District Court Judge ruled that the PPACA is unconstitutional in its entirety because the "individual mandate," the tax-based shared responsibility payment on certain individuals who fail to maintain qualifying health

coverage for all or part of a year, was repealed by Congress as part of legislation enacted in 2017, informally titled the Tax Cuts and Jobs Act of 2017, or the Tax Act. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the PPACA are invalid as well. On November 10, 2020, the U.S. Supreme Court heard arguments on the case. A ruling is expected in 2021. It is unclear how this decision, future decisions, subsequent appeals, and other efforts to repeal and replace the PPACA will impact the PPACA. 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 2029 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. At the federal level, the budget proposal for fiscal year 2020 contained further drug price control measures that could be enacted during the 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. Additionally, a "Blueprint" was released to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out-of-pocket costs of drug products paid by consumers. HHS has solicited feedback on some of these measures and has implemented others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage plans the option to use step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. While some of these and other proposed measures may require additional authorization to become effective, the federal and state governments have indicated that they will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented 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. 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, including the impact of the new presidential administration.

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. OLINVYK has been designated as a new chemical entity in the FDA's Orange Book. 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 the 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 and Human Capital Resources

Investing in, developing, and maintaining human capital is critical to our success. As of December 31, 2020, we had 25 employees, all of whom are located in the United States. We emphasize a number of measures and objectives in managing our human capital assets, including, among others, employee safety and wellness, talent acquisition and retention, employee engagement, development, and training, diversity and inclusion, and compensation and pay equity. 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.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and new employees, advisors and consultants. The principal purposes of our equity and cash incentive plans are to attract, retain and reward personnel through the granting of stock-based and cash-based compensation awards, in order to increase stockholder value and the success of our company by motivating such individuals to perform to the best of their abilities and achieve our objectives.

The success of our business is fundamentally connected to the well-being of our employees. Accordingly, we are committed to their health, safety and wellness. We provide our employees and their families with access to a variety of innovative, flexible and convenient health and wellness programs, including benefits that provide protection and security so they can have peace of mind concerning events that may require time away from work or that impact their financial well-being; that support their physical and mental health by providing tools and resources to help them improve or maintain their health status and encourage engagement in healthy behaviors; and that offer choice where possible so

they can customize their benefits to meet their needs and the needs of their families. In response to the COVID-19 pandemic, we implemented significant changes that we determined were in the best interest of our employees, as well as the community in which we operate, and which comply with government regulations, including working from home where appropriate.

Corporate Compliance Program

Our business is subject to extensive regulations. Management has designed and implemented a comprehensive corporate compliance program as part of our commitment to comply fully with applicable criminal, civil and administrative laws, rules and regulations and to maintain the high standards of conduct we expect from all of our employees. We continuously review this compliance program and work to enhance it as and when appropriate. The primary purposes of the compliance program include, among other things:

- Assessing and identifying risks affecting our Company and its products;
- training and educating employees and certain outside professionals who provide services to our Company to promote awareness of legal and regulatory requirements, a culture of compliance, and the necessity of complying with all applicable laws, rules, regulations and requirements;
- developing and implementing compliance policies and procedures and creating controls to support compliance with applicable laws, rules, regulations and requirements and our policies and procedures;
- auditing and monitoring the activities of our operations and business support functions to identify and mitigate risks and potential instances of noncompliance in a timely manner; and
- ensuring that we promptly take steps to resolve any instances of noncompliance and address areas of weakness or potential noncompliance.

We have a Code of Conduct that guides and binds each of our employees, officers and directors. We use an anonymous compliance hotline for employees and outside parties to report potential instances of noncompliance. Our Chief Legal and Compliance Officer administers the compliance program and chairs the Company's Compliance Committee. The Chief Legal and Compliance Officer reports directly to our Chief Executive Officer and meets regularly with the Chair of the Audit Committee.

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 110, Chesterbrook, PA 19087. Our telephone number is (610) 354-8840 and our internet address is www.trevena.com.

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.trevena.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 above. 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 is not incorporated into this filing.

INFORMATION ABOUT OUR EXECUTIVE OFFICERS

Name	Age	Position
Carrie L. Bourdow	58	President, Chief Executive Officer and Director
Mark A Demitrack, M.D.	63	Senior Vice President and Chief Medical Officer
Robert T. Yoder	55	Senior Vice President and Chief Commercial Officer
Barry Shin	49	Senior Vice President and Chief Financial Officer
Scott Applebaum	54	Chief Legal and Compliance Officer and Senior Vice President of Regulatory Affairs

Carrie L. Bourdow

Ms. Bourdow has served as the President and Chief Executive Officer of our Company and member of our Board of Directors since October 2018. Prior to her role as Chief Executive Officer, she joined our company as our Chief Commercial Officer in May 2015 and was appointed Executive Vice President and Chief Operating Officer in January 2018. 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 multiple therapeutic areas. Since June 2017 she has served as a member of the Board of Directors of Nabriva Therapeutics plc, a biopharmaceutical company, and she has served as a member of the Board of Directors of Sesen Bio, a biopharmaceutical company, since February 2020. Ms. Bourdow earned her B.A. from Hendrix College and her M.B.A. from Southern Illinois University.

Mark A. Demitrack, M.D.

Dr. Demitrack, a board-certified psychiatrist, joined our company as Senior Vice President and Chief Medical Officer in May 2018. From May 2017 to May 2018, he served as Vice President of Clinical Strategy at Roivant Sciences, Ltd. From July 2003 to May 2017, he served as Vice President and Chief Medical Officer of Neuronetics, Inc., where he led the clinical development of the NeuroStar TMS Therapy System. Prior to this, Dr. Demitrack was Assistant Vice President for Global Medical Affairs in Neuroscience at Wyeth Pharmaceuticals, Inc. where he was responsible for post-marketing clinical development of the Effexor XR brand. Dr. Demitrack also served as Medical Director of the New Antidepressant Team at Lilly Research Laboratories where he led the registration clinical development and the NDA submission program for the antidepressant, duloxetine (Cymbalta). Prior to his industry career, Dr. Demitrack was a faculty member of the Department of Psychiatry at the University of Michigan Medical School, where he directed the Michigan Eating Disorders Program and received federal grant funding in clinical research studying the neuroendocrine pathophysiology of eating disorders and the idiopathic conditions chronic fatigue syndrome and fibromyalgia. Dr. Demitrack received a B.A. in Physics from Columbia University, and his M.D. from the Robert Wood Johnson Medical School in New Jersey. He completed his psychiatry residency training at the University of California-San Francisco and completed a research fellowship in clinical neuroendocrinology at the National Institute of Mental Health. Dr. Demitrack is a Life Fellow of the American Psychiatric Association and a Member of the American College of Neuropsychopharmacology.

Robert T. Yoder

Mr. Yoder was appointed Senior Vice President and Chief Commercial Officer in December 2018. He joined our company as Vice President of Commercial Operations and Sales in June 2018. Prior to this, he served as Senior Vice President and Head of Global Commercial Operations, Alliance Management and IT at Orexigen Therapeutics, Inc., a biopharmaceutical company, from March 2015 through June 2018. While at Orexigen, Mr. Yoder built the commercial infrastructure with a focus on innovative, efficient, and effective business process and architecture. Additionally, he led external business development efforts that delivered 11 partnership deals spanning 67 countries. Prior to joining Orexigen, Mr. Yoder spent 28 years at Merck & Co., where he held various roles of increasing responsibility across global business operations and commercial functions. In several of these roles, he was responsible for oversight and execution of large-scale initiatives including integration following acquisitions and led a range of organizational design and corporate change initiatives. Mr. Yoder received his B.S. degree in biology from Dickinson College and earned an M.B.A. from Emory University.

Barry Shin

Mr. Shin joined our company as Senior Vice President and Chief Financial Officer in June 2019. He joined our company with extensive investment banking experience advising biopharmaceutical companies through financing and merger and acquisition, or M&A, transactions. He was Managing Director in the Healthcare Investment Banking Group at Mizuho Securities from May 2017 until he joined the Company. Prior to joining Mizuho Securities, he was a Managing Director in the Healthcare Investment Banking Group of Guggenheim Securities from May 2012 to May 2017. From February 2005 to May 2012, he served in the Healthcare Investment Banking Group of Piper Jaffray. From September 2001 to February 2005, he advised healthcare and technology companies in financing and M&A transactions as a corporate attorney. Mr. Shin received a B.Sc. and joint J.D. / M.B.A. from the University of Toronto.

Scott Applebaum

Mr. Applebaum joined our company as Chief Legal and Compliance Officer and Senior Vice President of Regulatory Affairs in February 2020. He has extensive experience providing legal counsel and regulatory guidance to biopharmaceutical companies in a variety of roles across several organizations. From September 2017 to June 2019, Mr. Applebaum served as President of Context Therapeutics LLC, a privately held biopharmaceutical company. His experience with high-growth biopharmaceutical companies includes his role as General Counsel and Corporate Secretary of Vitae Pharmaceuticals, Inc. from July 2016 to December 2016, where he played a key role in the sale of Vitae to Allergan plc. Mr. Applebaum also served as Chief Legal Officer and Corporate Secretary of Medgenics, Inc. from September 2014 to June 2016. Prior to this, he served as Senior Vice President at Shire Plc, where he held leadership roles in multiple functions, including SVP of Legal, SVP of Global Regulatory Affairs & Quality Assurance and SVP of the Global Neuroscience Business Unit. He began his biopharmaceutical career over two decades ago at Bristol-Myers Squibb where he served in various legal and compliance roles. Mr. Applebaum received a B.S.E. in Finance and Accounting from the Wharton School of the University of Pennsylvania and a J.D. from Stanford Law School.

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.

Summary of Risk Factors

- 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.
- Our prospects are highly dependent on the successful commercialization of OLINVYK. To the extent OLINVYK is not commercially successful, our business, financial condition and results of operations may be materially adversely affected, and the price of our common stock may decline.
- 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.
- 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.
- The ongoing COVID-19 pandemic could materially affect our operations, as well as the business or operations of third parties with whom we conduct business.

- The COVID-19 pandemic may negatively impact the commercialization and market acceptance of OLINVYK.
- If we are not able to obtain, or if there are delays in obtaining regulatory approval of OLINVYK for any indications in foreign jurisdictions, or regulatory approval of our other product candidates, we will not be able to market OLINVYK in other jurisdictions or market our other product candidates at all, and our ability to generate revenue will be materially impaired.
- OLINVYK has been classified as a Schedule II controlled substance, and the making, use, sale, importation, exportation and distribution of controlled substances are subject to regulation by state, federal and foreign law enforcement and other regulatory agencies which may make the successful commercialization and market acceptance more difficult.
- We are early in our development efforts and have only one product candidate, OLINVYK, for which we have recently received marketing approval from the FDA. If we are unable to successfully commercialize OLINVYK, or if we are unable to complete development of our other product candidates, or if we experience significant delays in doing so, our business will be materially harmed.
- Nonclinical 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.
- We may be unable to obtain regulatory approval for our product candidates under applicable regulatory requirements. The denial or delay of any such approval would delay commercialization of our product candidates and adversely impact our potential to generate revenue, our business and our results of operations.
- OLINVYK or any of our other product candidates for which we obtain approval 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.
- We could face legal or regulatory actions related to the sales, marketing and promotion of OLINVYK to healthcare professionals and healthcare institutions.
- If we are unable to maintain or expand our 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 OLIVNYK or any of our other product candidates if and when they are approved.
- We face substantial competition, which may result in others discovering, developing, or commercializing products before or more successfully than we do.
- We rely, and expect to continue to rely, on third parties to conduct our nonclinical 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 contract with third parties for the manufacture of commercial supply of OLIVNYK and for clinical supply of our other product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of OLIVNYK or our other product candidates or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.
- Materials necessary to manufacture our product or product candidates may not be available on commercially reasonable terms, or at all, which may delay the development and commercialization of our product or product candidates.

- 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.

- In the future, 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 are subject to securities class action and stockholder derivative litigation.

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 $29.4 million and $24.9 million for the years ended December 31, 2020 and 2019, respectively. As of December 31, 2020, we had an accumulated deficit of $442.5 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 nonclinical studies and clinical trials. In August 2020, the FDA granted approval for OLIVNYK as a treatment in the United States for the management of acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. Accordingly, we are currently focusing a substantial portion of our efforts on the commercialization of OLINVYK, which commenced in the first quarter of 2021.

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:

- commercialize OLINVYK in the United States;

- build out our sales, marketing and distribution capabilities and scale up external manufacturing capabilities to commercialize OLINVYK, 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 our other product candidates;

- seek regulatory approvals for any product candidates that successfully complete clinical trials;

- seek to identify additional product candidates;

- maintain, expand, and protect our intellectual property portfolio;

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

- defend the Company in the existing class action litigation and incur legal fees in the stockholder derivative litigation; 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 raising substantial additional funding for the Company and developing and commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing nonclinical testing and clinical trials of our product candidates, identifying additional product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates, and manufacturing, marketing, and selling OLINVYK and 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, our future profitability will depend upon the size of any markets in which our product candidates have received approval, and our ability to achieve sufficient market acceptance, reimbursement from third-party payors and adequate market share for our products in those markets.

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, whether we will have sufficient funding available to or when, or if, we will be able to achieve profitability. If, for example, we are required by the FDA or foreign regulatory authorities to perform studies in addition to those we currently anticipate conducting, 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. Absent substantial additional fundraising, the level and extent of our clinical and, if approved, commercial efforts may lead to a delay in our ability to achieve profitability.

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.

Our prospects are highly dependent on the successful commercialization of OLINVYK. To the extent OLINVYK is not commercially successful, our business, financial condition and results of operations may be materially adversely affected, and the price of our common stock may decline.

OLINVYK is our only drug that has been approved for sale and it has only been approved as a treatment in the United States for the management of acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. We are currently focusing a significant portion of our activities and resources on OLINVYK and we are highly dependent upon the successful commercialization of OLINVYK in the United States.

Successful commercialization of OLINVYK is subject to many risks. While we have established our commercial team and have hired our U.S. sales force, we will need to further expand and develop the team in order to successfully commercialize OLINVYK. Even if we are successful in developing our commercial team, there are many factors that could cause the commercialization of OLINVYK to be unsuccessful, including a number of factors that are outside our control. Because OLINVYK is an opioid agonist and is the first new chemical entity in the IV opioid drug class in decades, it is especially difficult to estimate OLINVYK's market potential for its approved indication. We do not know if our expectations of the market for this product will be accurate. Additionally, hospitals may be unwilling to add OLINVYK to their formularies or physicians may be unwilling to prescribe OLINVYK. Further, any negative publicity related to OLINVYK, or negative development for OLINVYK in our post-marketing commitments, or in regulatory processes in other jurisdictions, may adversely impact the commercial results and potential of OLINVYK.

In addition, our commercialization efforts could be adversely affected by the effects of public health threats, including the ongoing COVID-19 pandemic. In light of the lengthy duration of the pandemic, we continue to expect that sales of OLINVYK may be negatively impacted by changes in commercial practices resulting from COVID-19, such as the transition to telemedicine, possible decreases in initial diagnoses, deferral of elective procedures, and decreased access to certain market segments. The ultimate effects of COVID-19, and the duration thereof, are difficult to assess or predict at this time and no assurances can be given that the pandemic will not have a significant impact on our ability to commercialize OLINVYK, which in turn could have a material adverse effect on our business, results of operations, financial condition and prospects.

If the commercialization of OLINVYK is less successful than expected, our stock price could decline significantly and the long-term success of the product and our company could be harmed.

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.

As of December 31, 2020, we had cash and cash equivalents of $109.4 million. Based upon our current operating plan, we believe that our available cash and cash equivalents will be sufficient to fund our planned operations and capital expenditure requirements through the fourth quarter of 2022. Although we plan and budget funding for our operations, it is possible that we may have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. Over the next several years, we expect to incur significant expenses in connection with our current operations, particularly as we commercialize OLINVYK and continue the clinical trials of, and seek marketing approval for, our other drug candidates. We expect our expenses to increase as we continue to commercialize OLINVYK, including, among other things, as a result of costs associated with our sales force and increasing our marketing and distribution capabilities. Furthermore, we will continue to incur additional costs associated with operating as a public company, hiring additional personnel and expanding our facilities. Accordingly, we will need to obtain substantial additional funding for these efforts; we would seek to obtain this funding through the sale of equity, the incurrence of debt, 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 current or 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.

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

- our ability to successfully commercialize OLINVYK in the United States;
- the scope, progress, results and costs of nonclinical development, laboratory testing, and clinical trials for our product candidates, including TRV250, TRV734, TRV027, and TRV045;
- the number and development requirements of other product candidates that we pursue;
- the costs, timing, and outcome of regulatory review of any product candidates, both in the United States and in territories outside the United States;
- the costs and timing of commercializing OLINVYK and any future commercialization activities, including product manufacturing, marketing, sales, and distribution, for any of our product candidates for which we receive marketing approval;
- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;

- our ability to enter into collaborative agreements for the development and commercialization of our product candidates;
- any product liability or other lawsuits related to our products or operations;
- the expenses needed to attract and retain skilled personnel;
- 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 of the United States; and
- the impact of the COVID-19 pandemic and any future epidemics and pandemics that may arise in the future.

Identifying potential product candidates and conducting nonclinical 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 for our product candidates. In addition, our other product candidates, if approved, may not achieve commercial success or meet our expectations.

Our ability to generate commercial revenue from sales of OLINVYK is unproven, and we do not expect any other products to be commercially available for the foreseeable future, 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. The risk that additional financing is unavailable is heightened by the sustained macro-economic disruption from the COVID-19 pandemic. We cannot predict the extent or duration of the impact of the COVID-19 pandemic on the capital markets. 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.

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 are a biopharmaceutical company with a limited operating history. 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 nonclinical studies, and conducting clinical trials of our product candidates. With the exception of OLINVYK, our product candidates are in early stages of development. We have only recently begun to conduct sales, marketing, and distribution activities to commercialize OLINVYK, and we have not yet demonstrated the ability to generate significant revenue from the sale of OLINVYK. 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 and more established operating history.

We have encountered, and will continue to encounter, risks and difficulties frequently experienced by growing companies in a rapidly developing and changing industry, such as the biopharmaceutical industry, including challenges in forecasting accuracy, determining appropriate investments of our limited resources, gaining market acceptance of our products, if approved, managing a complex regulatory landscape and developing new product candidates. Our current operating model may require changes in order for us to scale our operations efficiently. You should consider our business and prospects in light of the risks and difficulties we face as a company focused on developing products in the fields of biopharmaceuticals and biotechnology.

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.

The ongoing COVID-19 pandemic could materially affect our operations, as well as the business or operations of third parties with whom we conduct business.

Our business and its operations, including but not limited to clinical development, sales and marketing efforts, supply chain operations, research and development activities, could be adversely affected by health epidemics in regions where we have business operations, and such health epidemics could cause significant disruption in the operations of third parties upon whom we rely. For example, in 2020, the President of the United States declared the COVID-19 pandemic a national emergency. The Governor of Pennsylvania declared a state of emergency and has issued orders impacting our business operations. We have implemented work-from-home policies for all employees, and have worked with Syneos to develop a process for our nationally field deployed resources that takes into account local conditions and their ability to safely and compliantly interact with customers. In cases where a live interaction is not feasible, we have trained and resourced our customer facing team to be able to engage with customers via virtual channels with approved resources. The effects of the Pennsylvania orders and our work-from-home policies may negatively impact productivity, disrupt our business, delay our clinical programs and timelines and adversely affect our commercialization and market acceptance of OLINVYK, the magnitude of which will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course. These and similar, and perhaps more severe, disruptions in our operations could negatively impact our business, operating results and financial condition.

In addition, our clinical trials may be affected by the COVID-19 pandemic. Clinical site initiation and patient enrollment may be delayed due to prioritization of hospital resources toward the COVID-19 pandemic. Also, some patients may not be able to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 and adversely impact our clinical trial operations. Limitations on global international travel may delay key trial activities, including necessary interactions with regulators, ethics committees and other important agencies and contractors. We may be faced with limitations in employee resources that would otherwise be focused on the conduct of clinical trials, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people. Any of the above could delay our planned clinical trials or prevent us from completing these clinical trials at all and harm our ability to obtain approval for our product candidates.

Moreover, we may experience additional disruptions that could severely impact our business and development activities, including, but not limited to, strain on our suppliers and other third parties, possibly resulting in supply disruptions of our product candidates for preclinical or clinical development and potential future clinical trials we expect to initiate, decrease in clinical enrollment in any clinical trials we initiate and the ability to raise capital when needed on acceptable terms, if at all. Disruptions in our operations or supply chain, whether as a result of restricted travel, quarantine requirements or otherwise, could negatively impact our ability to proceed with our clinical trials, preclinical development and other activities and delay our ability to receive product approval and generate revenue.

The extent to which COVID-19 impacts our results will depend on future developments, which are highly uncertain and cannot be predicted, including new information which may emerge concerning the severity of COVID-19, the emergence of any new mutations or variants of the virus, the duration of the outbreak, travel restrictions imposed by the United States and other countries, business closures or business disruption in the United States and other countries, and the actions taken throughout the world, including in our markets, to contain COVID-19 or treat its impact. We do not yet know the full extent of potential delays or impacts on our business, our clinical trials, our preclinical development efforts, healthcare systems or the global economy as a whole. However, these effects could have a material impact on our operations, and we will continue to monitor the COVID-19 situation closely.

The COVID-19 pandemic may negatively impact the commercialization and market acceptance of OLINVYK.

The COVID-19 pandemic may have an adverse impact on our ability to successfully commercialize and secure market acceptance of OLINVYK. The outbreak of COVID-19 poses the risk that we or our employees, contractors, suppliers, and other partners may be prevented from conducting normal business activities for an indefinite period of time, including due to continuation of government-imposed quarantines, stay-at-home orders, travel restrictions, mandated business closures and other public health safety measures.

If the spread of COVID-19 and the public safety measures taken by various governments continue, the successful commercialization and market acceptance of OLINVYK may be hindered by various factors, including the overall economy, cancellations in elective surgeries, challenges in hiring employees who are necessary to support continued commercialization, difficulties in meeting with healthcare providers, pharmacists or others involved in prescribing and formulary decisions, limited access to healthcare providers' offices, conducting necessary trainings of such new employees, attending and presenting at various conferences or other programs, delays in coverage decisions from Medicare and third-party payors, interruptions or delays in our commercial supply chain and increases in the number of uninsured or underinsured patients.

In addition, hospitals may reduce and divert staffing, divert resources to patients suffering from COVID-19 or limit hospital access for non-patients. The government-imposed travel restrictions due to COVID-19 may further impact our ability to travel to hospitals. These circumstances may negatively impact our ability to effectively market to hospital pharmacists, healthcare providers and formulary committees, which may delay or have a material adverse impact on the commercialization of OLINVYK and less traditional methods of communicating with these parties may need to be employed. In addition, the spread of COVID-19 has had, and may continue to have, an impact on the number or patients suffering from post-surgical pain, as hospitals cancel elective surgeries and patients postpone these procedures due to COVID-19 concerns, which may reduce demand for OLINVYK and negatively impact our ability to successfully commercialize OLINVYK. Hospitals and healthcare systems may be financially impacted by the costs associated with the treatment of individuals suffering from COVID-19 and the general reduction in elective surgeries. Although we are unable at this time to determine the extent of the financial impact of the COVID-19 pandemic on hospital and healthcare systems, it is possible that the negative impact of the COVID-19 pandemic may reduce hospital and healthcare system demand for OLINVYK, which could have a material adverse impact on our commercialization of OLINVYK.

The extent to which the COVID-19 pandemic will impact our efforts to successfully commercialize and secure market acceptance of OLINVYK is uncertain and will depend upon future developments. We are monitoring the situation and taking steps to minimize the disruption of the COVID-19 pandemic, but there can be no assurance that such actions will be successful, which could have a negative impact on our ability to successfully commercialize OLINVYK.

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 generated in tax years ending on or prior to December 31, 2018 will carry forward to offset future taxable income, if any, until such unused losses expire. Unused tax losses generated after December 31, 2018 under the Tax Act will not expire and may be carried forward indefinitely, but will be deductible only to the extent of 80% of current taxable income in any given year. It is uncertain if and to what extent various states will conform to the Tax Act. In addition, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (the Code), 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 or taxes may be limited. We have not completed an analysis to determine whether we have experienced an ownership change. In addition, we may experience ownership changes in the future as a result of subsequent shifts in our stock ownership. Similar provisions of state tax law may also apply to limit our use of accumulated state tax attributes. In addition, at the state level, there may be periods during which the use of net operating losses is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed. As a result, even if we attain profitability, we may be unable to use all or a material portion of our net operating losses and other tax attributes, which could adversely affect our future cash flows. As of December 31, 2020, we had federal net operating loss carryforwards of approximately $93.2 million that could be limited if we have experienced, or if in the future we experience, an ownership change.

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 European Medicines Agency 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.

We have limited resources 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 nonclinical 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.

OLINVYK has been classified as a Schedule II controlled substance under the Controlled Substances Act. The making, use, sale, importation, exportation and distribution of controlled substances are subject to regulation by state, federal and foreign law enforcement and other regulatory agencies. We anticipate that TRV734, if approved, would also be classified as a Schedule II controlled substance under the CSA.

Controlled substances 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 a high potential for abuse and 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. The FDA has designated OLINVYK (oliceridine) as a Schedule II controlled substance. Consequently, the manufacture, shipment, storage, sale, and use of OLINVYK will be subject to a high degree of regulation.

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 products 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 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, our current collaborators in South Korea and China for OLINVYK, 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.

OLINVYK and any other 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 other 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, current good manufacturing practice, or 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. However, companies may share truthful and not misleading information that is otherwise consistent with a product's FDA 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 healthcare fraud and abuse laws, as well as state consumer protection laws.

Even though the FDA has granted approval of OLINVYK, the scope and terms of the approval may limit our ability to commercialize OLINVYK and, therefore, our ability to generate substantial sales revenues. The FDA has approved OLINVYK only for use in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. The label for OLINVYK also contains a "boxed" warning about addiction, abuse, misuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, and risks from concomitant use with benzodiazepines or other central nervous system depressants. This "boxed" warning may discourage physicians from prescribing OLINVYK to patients.

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

- the need to generate additional clinical data in order to provide information to the FDA to sufficiently address any future concerns for OLINVYK or other product candidates for which we may obtain regulatory approval;
- 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, untitled letters, or Form 483s;
- 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.

If any of these actions were to occur, we may have to discontinue commercializing OLINVYK, limit our sales and marketing efforts, conduct further post-approval studies, and/or discontinue or change any other ongoing or planned clinical studies, which in turn could result in significant expense and delay or limit our ability to generate sales revenues. Moreover, the FDA's policies may change and additional government regulations may be enacted that could impose

additional post-marketing obligations on our approved products. 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 Discovery and Development of Our Product Candidates

We are early in our development efforts and have only one product candidate, OLINVYK, for which we recently received marketing approval from the FDA. If we are unable to successfully commercialize or achieve market acceptance of OLINVYK, or if we are unable to complete development of our other product candidates, or if we 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, OLINVYK, for which we have received marketing approval by 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 will depend heavily on the successful commercialization and market acceptance of OLINVYK and the development and commercialization, if approved, of our other product candidates. The success of OLINVYK and our development-stage product candidates will depend on several factors, including the following:

- successful completion of nonclinical 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;
- deploying our direct sales force and establishing market acceptance of OLINVYK;
- launching commercial sales of our other product candidates, if and when approved, whether alone or in collaboration with others;
- acceptance of our other product candidates, 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.

Nonclinical 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 additional 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 nonclinical 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 nonclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim or topline results of a clinical trial do not necessarily predict final results. Moreover, nonclinical and clinical data often are susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in nonclinical 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:

- regulatory agencies 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 regulatory agencies 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;
- regulatory agencies 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, regulatory agencies 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 nonclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant nonclinical 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.

We may be unable to obtain regulatory approval for our product candidates under applicable regulatory requirements. The denial or delay of any such approval would delay commercialization of our product candidates and adversely impact our potential to generate revenue, our business and our results of operations.

The research, testing, manufacturing, labeling, licensure, sale, marketing and distribution of biopharmaceutical products are subject to extensive regulation by the FDA and comparable regulatory authorities in the United States and other countries, and such regulations differ from country to country. We are not permitted to market our product candidates in any jurisdiction until they receive the requisite marketing approval from the applicable regulatory authorities of such jurisdictions. To gain approval to market our product candidates, we must provide the FDA and foreign regulatory authorities with preclinical and clinical data that adequately demonstrate the safety and efficacy of the product for the intended indication applied for in the applicable regulatory filing. The approval process is typically lengthy and expensive, and approval is never certain. Our receipt of regulatory approval in the United States for OLINVYK does not mean that we will be successful in obtaining regulatory approval for our other product candidates or obtaining approval for OLINVYK in other countries.

The FDA or any foreign regulatory authorities can delay, limit or deny approval of our product candidates for many reasons, including:

- the FDA or other equivalent foreign regulatory authorities may disagree with the number, design, size, conduct or implementation of our clinical trials;
- our inability to demonstrate to the satisfaction of the FDA or the equivalent foreign regulatory authority that any of our product candidates is safe and effective for the requested indication;
- the results of our clinical trials may not meet the level of statistical significance or clinical meaningfulness required by the FDA or other equivalent foreign regulatory authorities for marketing approval;
- the FDA or other equivalent foreign regulatory authorities may not accept data generated from our clinical trial sites;
- the FDA or other equivalent foreign regulatory authorities may find the chemistry, manufacturing and controls data insufficient to support the quality of our product candidates;
- the FDA or other equivalent foreign regulatory authorities may identify deficiencies in the manufacturing processes or facilities of our CMOs;
- the FDA or equivalent foreign regulatory authorities may not approve the formulation, dosing, labeling or specifications; or
- the potential for approval policies or regulations of the FDA or the equivalent foreign regulatory authorities to significantly change in a manner rendering our clinical data insufficient for approval.

Any of these factors, many of which are beyond our control, may result in our failing to obtain regulatory approval to market any of our other product candidates or approval of OLINVYK in foreign countries, which could materially adversely affect our business, financial condition, results of operations and prospects.

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;
- our ability to recruit clinical trial investigators with appropriate competencies and experience;
- the eligibility criteria for the study in question;
- the size of the patient population required for analysis of the trial's primary endpoints;
- the perceived risks and benefits of the product candidate under study;
- availability and efficacy of approved medications for the disease under investigation;
- 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.

These factors can be exacerbated by other situations, such as the ongoing COVID-19 pandemic. 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 or following their approval by the FDA or foreign regulatory authorities, we may need to abandon or limit our development of some of our product candidates, limit the commercial profile or an approved label, or result in significant negative consequences following marketing approval, if any.

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.

OLINVYK and TRV734 are both biased ligands targeted at the MOR. Common adverse reactions for agonists of the MOR include respiratory depression, constipation, nausea, vomiting, and addiction. In rare cases, MOR agonists can cause respiratory arrest requiring immediate medical intervention. The label for OLINVYK contains a "boxed" warning about addiction, abuse, misuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, and risks from concomitant use with benzodiazepines or other central nervous system depressants. This "boxed" warning may discourage physicians from prescribing OLINVYK to patients.

TRV250, our DOR product candidate, targets the same receptor as other programs that have been associated with seizures and, accordingly, it is possible that TRV250 will be associated with similar side effects. We initiated a proof-of-concept study in subjects with a history of migraine headaches in November 2019. A primary goal of this study was to determine whether there is evidence that TRV250 may have potential as an acute treatment for migraine headaches. In addition, this study was designed to examine various aspects of the safety of TRV250, including any potential risk of seizures, risk of any cardiovascular issues, and other medically important adverse events. In August 2020, we announced that the trial was terminated due to the impact on patient enrollment caused by COVID-19.

If our clinical trials reveal a high and unacceptable severity and prevalence of side effects, these 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 we or others later identify undesirable side effects caused by OLINVYK or one or more of our other product candidates for which we may obtain marketing approval, 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 recall a product or change the way such product is administered to patients;
- regulatory authorities may require additional warnings on the label, such as a "black box" warning or a contraindication, or issue safety alerts, press releases or other communications containing warnings or other safety information about the product;
- we may be required to implement a REMS, or 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;
- additional restrictions may be imposed on the marketing or promotion of the particular product or the manufacturing processes for the product or any component thereof;
- 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, and could significantly harm our business, results of operations and prospects.

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. Although we continue to assess the future development of our pipeline, 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.

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 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.

In the future, we may conduct a substantial portion of the clinical trials for our product candidates outside of the United States and, if approved, we may 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.

In the future, we may conduct a substantial portion of our clinical trials outside of the United States and we may seek to market OLIVNYK and any other product candidates for which we obtain approval outside of the United States. We are thus subject to risks associated with doing business outside of the United States. With respect to OLIVNYK and our other 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 other 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.

Risks Related to the Commercialization of Our Product Candidates

OLINVYK or any of our other product candidates for which we obtain approval 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.

OLINVYK or any of our other product candidates for which we obtain approval may fail to gain sufficient market acceptance by physicians, patients, third-party payors, and others in the medical community. If OLINVYK or our other product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenue and we may not attain profitability. The degree of market acceptance of OLINVYK and our other product candidates for which we obtain approval will depend on a number of factors, including:

- the efficacy, safety, cost 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 payor coverage and adequate reimbursement;
- the prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- publicity concerning our products or competing products and treatments;
- FDA's and HHS's policy initiatives regarding opioids, including enforcement focused on the inappropriate promotion and marketing of opioids;
- the public perception of opioids in general and the ongoing opioid crisis;
- 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.

We cannot assure you that OLINVYK or any products for which we obtain regulatory approval in the future will achieve market acceptance among physicians, patients, patient advocacy groups, third-party payors or others in the medical community necessary for commercial success. Any failure by our product candidates that obtain regulatory

approval to achieve market acceptance or commercial success could materially adversely affect our business, financial condition, results of operations and prospects.

If we are unable to maintain or expand our 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 OLINVYK or any of our other product candidates if and when they are approved.

We have begun to implement our sales and marketing infrastructure for the commercialization of OLINVYK, our first FDA-approved product. 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 commercialization of OLINVYK is not successful or the commercial launch of another 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 successfully commercialize OLINVYK or any other drug products for which we receive marketing approval on our own, including:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel or to outsource these tasks successfully to a third party;
- the inability of sales personnel to obtain access to physicians or other relevant personnel or educate adequate numbers of physicians or others on the benefit of our product candidates;
- 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;
- unforeseen costs and expenses associated with creating a sales and marketing organization; and
- efforts by our competitors to commercialize products at or about the time when our product candidates would be coming to market.

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 OLINVYK or any of our other drug candidates for which we obtain marketing approval, 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 OLINVYK, we will need to partner with one or more third parties to sell, market and distribute this product, if approved, outside the United States. In April 2018 and May 2018, we entered into exclusive licensing agreements for the development and commercialization of OLINVYK in South Korea and China, respectively. Such partnerships in South Korea and China may not be successful, and we may be unsuccessful in our efforts to secure additional partnerships outside the United States.

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 OLINVYK and 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 OLINVYK indications and indications we are targeting with our product candidates, we also face potential competition from other drug candidates in development by other companies. OLINVYK 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; DSUVIA™ (sublingual sufentanil nanotabs) marketed by AcelRx Pharmaceuticals, Inc.; ANJESO™ (IV meloxicam), marketed by Baudax Bio, Inc.; XARACOLLTM (bupivacaine HCI) implant, marketed by Innocoll Holdings plc; and POSIMIR® (bupivacaine solution) marketed by Durect Corporation. 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 is developing ZALVISO™, a patient-controlled analgesia device which dispenses sublingual sufantanil nanotabs. AcelRX has received approval for ZALVISO in the European Union. Heron Therapeutics Inc. has a proprietary long acting reformulation of bupivacaine in development. 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 mu 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 our product candidates, 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 or lower-cost branded products. Generic products are currently on the market for the OLINVYK indications and the indications that we are pursuing for our product candidates. 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, brand recognition and expertise than we do in research and development, manufacturing, nonclinical 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.

OLINVYK or any other product candidates for which we are able to obtain regulatory approval in the future may become subject to unfavorable pricing regulations, third-party payor coverage and reimbursement policies, or healthcare reform initiatives.

Our ability to commercialize OLINVYK and 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 other 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 OLINVYK 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 OLINVYK 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 OLINVYK.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other 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 OLINVYK or 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. Private third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our or our collaborators' inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any approved drugs that we develop could adversely affect our operating results, our ability to raise capital needed to commercialize drugs and our overall financial condition.

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

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

Product liability lawsuits against us could cause us to incur substantial liabilities and limit commercialization of OLINVYK or the development or commercialization of our other product candidates.

We face an inherent risk of product liability exposure as a result of the commercial sales of OLINVYK in the United States, the testing of our other product candidates in human clinical trials, and the commercialization of such other product candidates, if approved. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. For example, we may be sued if OLINVYK or any other 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 product liability claims, we will incur substantial liabilities or be required to limit commercialization of our products. Even a successful defense would require significant financial and management resources.

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 and potential termination of clinical trial sites or entire clinical programs;
- initiation of investigations by regulatory agencies;
- 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;
- exhaustion of any available insurance and our capital resources;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

We currently maintain product liability insurance coverage at levels which may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage as we expand our commercialization efforts with respect to OLINVYK and as we initiate additional clinical trials for our other product candidates. We will need to further increase our insurance coverage if we commence commercialization of any additional product candidates for which we obtain marketing approval. Insurance coverage is increasingly expensive, and in the future may be difficult to obtain for our products and product candidates. 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. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. A successful product liability claim or series of claims brought against us could cause our stock price to fall and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business, financial condition, results of operations and prospects.

Concerns around the abuse of opioids, including law enforcement concerns over diversion of opioids and regulatory efforts to combat abuse, could decrease the potential market for OLINVYK and may adversely impact external investor perceptions of our business.

Prescription drug abuse and the diversion of opioids is a growing concern and has been referred to as an "opioid crisis" in the United States. Law enforcement and regulatory agencies may apply policies that seek to limit the availability or use of opioids. Such efforts may inhibit our ability to commercialize our products. Aggressive enforcement and unfavorable publicity regarding the use or misuse of opioids, including litigation or regulatory activity regarding sales or marketing of opioids, could have a material adverse effect on our business or reputation. Furthermore, a number of governmental entities have brought separate lawsuits against various pharmaceutical companies marketing and selling opioid pain medications, alleging misleading or otherwise improper promotion of opioid drugs to physicians and consumers. These efforts could reduce the potential size of the market for OLINVYK, decrease the revenues we are able to generate from its sale and adversely impact external investor perceptions of our business.

Many state legislatures and the federal government have enacted legislation intended to reduce opioid abuse. In addition, the FDA, CDC and HHS each have initiatives to address opioid-related overdose, death and dependence. While these initiatives are generally focused on prescribing oral opioids in an outpatient settings, some of these initiatives, and any legislation or regulations resulting from these initiatives, may apply to all opioid drugs, including those like OLINVYK that are administered through an IV in a hospital setting. Many of these changes and others could cause us to expend additional resources in developing and commercializing our products to meet additional requirements

Risks Related to Our Dependence on Third Parties

Our current collaborators are, and 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. As a result, we may in the future determine to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of these candidates or for the commercialization of OLINVYK in certain territories outside of the United States. For example, we entered into license agreements with partners in South Korea and China in 2018 whereby these parties will develop, seek regulatory approval for, and, if successful, commercialize OLINVYK. 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 third parties, 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;

- 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; and

- collaborators may be affected by political instability or instability from a regional or global pandemic disease, such as the recent coronavirus outbreak.

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 nonclinical 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 nonclinical 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. Some of these third parties may experience shutdowns or other disruptions as a result of the COVID-19 pandemic, including, but not limited to, the ability to adequately staff a project or effectively and expeditiously enroll patients in a clinical study, and therefore may be unable to provide the level of service that we received in the past.

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 nonclinical studies and clinical trials are conducted in accordance with the general investigational plan and protocols for the trial and for ensuring that our nonclinical studies are conducted in accordance with GLP, as appropriate. Moreover, the FDA requires us to comply with standards, commonly referred to as 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 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 certain clinical trials and post the results of these clinical trials when completed on a government-sponsored public 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 nonclinical 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 nonclinical 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 commercial supply of OLINVYK and for clinical and nonclinical supply of our other product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of OLINVYK or our other product candidates or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We have no internal manufacturing capabilities and do not have any manufacturing facilities. We rely, and expect to continue to rely, on third parties for the manufacture of commercial supply of OLINVYK and the manufacture of supply of our other product candidates for nonclinical and clinical testing, as well as for commercial manufacture, if any of such other product candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of OLINVYK or our other product candidates 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 other 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.

Our reliance on third-party manufacturers for commercial supply of OLINVYK and for any additional product candidates for which we obtain regulatory approval 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;
- limitations on supply availability resulting from capacity and scheduling constraints of the third parties;
- 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;
- impact on our reputation in the marketplace if manufacturers of our products, once commercialized, fail to meet the demands of our customers; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

The failure of any of our contract manufacturers to maintain high manufacturing standards could result in injury or death of clinical trial participants or patients using products. Such failure could also result in product liability claims, product recalls, product seizures or withdrawals, delays or failures in testing or delivery, cost overruns or other problems that could seriously harm our business or profitability.

The facilities used by our contract manufacturers to manufacture our product candidates (and commercial supply of those product candidates, if approved) 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. These regulations cover all aspects of the manufacturing, testing, quality control and recordkeeping relating to our product candidates and any products that we may commercialize. 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.

OLINVYK and our other product candidates that we may commercialize, if approved, may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us. Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a second source for bulk drug substance or drug product. 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 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 OLINVYK or our other MOR targeted product candidates. 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 includes the active ingredient in OLINVYK. 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 of OLINVYK.

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.

Materials necessary to manufacture our product or product candidates may not be available on commercially reasonable terms, or at all, which may delay the development and commercialization of our product or product candidates.

We currently rely on the manufacturers of our product and product candidates to purchase from third-party suppliers the materials necessary to produce the compounds for our preclinical studies and clinical trials, and we rely, or will rely, on these other manufacturers for commercial distribution of OLINVYK and any other products for which we may obtain regulatory approval. Suppliers may not sell these materials to our manufacturers at the time we need them or on commercially reasonable terms and all such prices are susceptible to fluctuations in price and availability due to transportation costs, government regulations, price controls and changes in economic climate or other foreseen circumstances. We do not have any control over the process or timing of the acquisition of these materials by our manufacturers. We may enter into agreements to purchase certain materials and provide them to our manufacturers, with all the risks and uncertainties of supply associated with those purchases. If we or our manufacturers are unable to obtain these materials for our preclinical studies and clinical trials, product testing and potential regulatory approval of our product candidates would be delayed, significantly impacting our ability to develop and commercialize our product candidates. If our manufacturers or we are unable to purchase these materials for commercial distribution of our product or, after regulatory approval has been obtained, our product candidates, the commercial launch of our product and product candidates would be delayed or there would be a shortage in supply, which would materially affect our ability to generate revenues from the sale of our product or product candidates.

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 OLINVYK and any other 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 OLINVYK and any other 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 can be enforced by individuals, on behalf of the government, through civil whistleblower or qui tam actions, and civil monetary penalty laws prohibit individuals or entities from, 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 certain healthcare providers, health plans, and healthcare clearinghouses, known as covered entities, 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 Physician Payments Sunshine Act, also known as 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. Beginning in 2022, applicable manufacturers also will be required to report such information regarding payments and transfers of value provided, as well as ownership and investment interests held, during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists and certified nurse-midwives; 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, marketing expenditures, or drug pricing; state and local laws that require the registration of pharmaceutical sales representatives; and state and foreign laws, such as the General Data Protection Regulation (EU) 2016/679, 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, disgorgement, 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 significant 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 federal False Claims Act and the federal 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 now agree to offer 70% 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.

There remain judicial and Congressional challenges to certain aspects of the PPACA, as well as efforts by the federal government to repeal or replace certain aspects of the PPACA. There have been 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. 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, several bills affecting the implementation of certain taxes under the PPACA have been signed into law. The Tax Act included a provision which repealed, 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." In addition, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the PPACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and

medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the PPACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." On December 14, 2018, a Texas U.S. District Court Judge ruled that the PPACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Act. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the PPACA are invalid as well. On November 10, 2020, the U.S. Supreme Court heard arguments on the case. A ruling is expected in 2021. It is unclear how this decision, future decisions, subsequent appeals, and other efforts to repeal and replace the PPACA will impact the PPACA and our business.

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 2029 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.

In October 2018, the Substance Use Disorder Prevention That Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act was enacted. Among other things, this legislation provides funding for research and development of non-addictive painkillers that could potentially compete with our products. It also clarifies FDA's authority to require that certain opioids be dispensed in packaging that limits their abuse potential, makes changes to Medicare and Medicaid in an effort to limit over-prescription of opioid painkillers, and increases penalties against manufacturers and distributors related to the over-prescription of opioids, including the failure to report suspicious orders and keep accurate records. The ultimate effect of this legislation is currently not known, but could potentially have a material adverse effect on our business.

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. Congress has indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented 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 or consultants 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 or consultants 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.

In the future, 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.

In the future, we expect 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, 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 civil, criminal and administrative penalties, including, without limitation, damages, fines, disgorgement, 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.

Risks Related to Ownership of Our Common Stock

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 $0.39 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:

- the success of our commercialization of OLIVNYK for use in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate;

- the status and cost of our post-marketing commitments for OLIVNYK;

- the status and cost of development and commercialization of OLIVNYK in jurisdictions other than the United States;
- 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;
- changes in the structure of healthcare payment systems;
- 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;
- public concern as to, and legislative action with respect to, genetic testing or other research areas of biopharmaceutical companies, the pricing and availability of prescription drugs, or the safety of drugs and drug delivery techniques;
- disruptions caused by man-made or natural disasters or public health pandemics or epidemics or other business interruptions, including, for example, the COVID-19 pandemic;
- economic and political factors, including but not limited to economic and financial crises, wars, terrorism, and political unrest; and
- sales of our common stock, including sales by our directors and officers or specific stockholders.

If we are not able to comply with the applicable continued listing requirements or standards of The Nasdaq Stock Market, Nasdaq could delist our common stock.

Our common stock is currently listed on The Nasdaq Stock Market. In order to maintain that listing, we must satisfy minimum financial and other continued listing requirements and standards, including those regarding director independence and independent committee requirements, minimum stockholders' equity, minimum share price, and certain corporate governance requirements. There can be no assurances that we will be able to comply with the applicable listing standards.

In the event that our common stock is delisted from The Nasdaq Stock Market and is not eligible for quotation or listing on another market or exchange, trading of our common stock could be conducted only in the over the counter market or on an electronic bulletin board established for unlisted securities such as the Pink Sheets or the OTC Bulletin Board. In such event, it could become more difficult to dispose of, or obtain accurate price quotations for, our common stock, and there would likely also be a reduction in our coverage by securities analysts and the news media, which could cause the price of our common stock to decline further. Also, it may be difficult for us to raise additional capital if we are not listed on a major exchange.

Such a de-listing would also likely have a negative effect on the price of our common stock and would impair your ability to sell or purchase our common stock when you wish to do so. In the event of a de listing, we may take actions to restore our compliance with The Nasdaq Stock Market's listing requirements, but we can provide no assurance that any such action taken by us would allow our common stock to become listed again, stabilize the market price or improve the liquidity of our common stock, prevent our common stock from dropping below The Nasdaq Stock Market minimum bid price requirement or prevent future non-compliance with The Nasdaq Stock Market's listing requirements.

We are subject to securities class action and stockholder derivative litigation.

As described in "Item 3. Legal Proceedings" of this Annual Report on Form 10-K, in October and November 2018, we and certain of our current and former officers and directors were sued in three purported class actions filed in the U.S. District Court for the Eastern District of Pennsylvania, or the EDPA, alleging violations of the federal securities laws. In January 2019, the three lawsuits were consolidated into one action, and on May 29, 2019, the District Court appointed a group of five individual investors as lead plaintiffs. A consolidated amended complaint was filed on August 2, 2019, alleging, among other things, that we and two of our former officers made false and misleading statements regarding our business, operations, and prospects, including certain statements made relating to our End-of-Phase 2 meeting with the FDA, and certain statements concerning top-line results from our Phase 3 studies. The plaintiffs seek, among other remedies, unspecified damages, attorneys' fees and other costs, and unspecified equitable or injunctive relief. On August 28, 2020, the EDPA granted in part and denied in part defendants' motion to dismiss. On October 2, 2020, we and the individual defendants filed an answer to the amended complaint, denying all liability. On February 11, 2021, the parties agreed in principle to a settlement, which is subject to final documentation and approval by the Court. We and the individual defendants do not acknowledge any wrongdoing as part of the settlement, and a monetary payment will be made to the plaintiffs and their counsel, all of which will be funded by the Company's insurance carriers. We continue to believe that the claims are without merit, and if necessary we intend to vigorously defend ourselves and our former officers against the allegations.

In December 2018, a shareholder derivative action was filed on behalf of the Company and against certain current and former officers and directors in the EDPA, and in February 2019, two additional, similar shareholder derivative actions were filed in the U.S. District Court for the District of Delaware. A fourth similar shareholder derivative action was filed in the EDPA in September 2019, and a fifth similar derivative action was filed in the EDPA in November 2019. A similar sixth derivative action was filed in the EDPA in September 2020. These cases, which involve facts similar to the consolidated securities lawsuits, assert claims against the individual defendants for, among other things, breach of fiduciary duty, waste of corporate assets, violations of the federal securities laws, and unjust enrichment, and they make a number of demands, including for monetary damages and other equitable and injunctive relief. Some of the derivative actions have been stayed in favor of the consolidated securities lawsuits. These factors may materially and adversely affect the market price of our common stock.

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.

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

We are a "smaller reporting company" as defined in Rule 12b-2 promulgated under the Securities Exchange Act of 1934, as amended, or the Exchange 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 smaller reporting companies, including reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. 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.

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 200,000,000 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 seek to expand the number of authorized common shares, and 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.

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.

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. Investors seeking cash dividends should not purchase our common stock.

General Risk Factors

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, or that include covenants requiring us to meet certain obligations, such as minimum cash requirements or net revenue targets.

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 our current or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

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, 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.

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. 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.

Changes in tax laws or regulations that are applied adversely to us or our customers may have a material adverse effect on our business, cash flow, financial condition or results of operations.

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could adversely affect our business operations and financial performance. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the Tax Act enacted many significant changes to the U.S. tax laws. Future guidance from the Internal Revenue Service and other tax authorities with respect to the Tax Act may affect us, and certain aspects of the Tax Act could be repealed or modified in future legislation. In addition, it is uncertain if and to what extent various states will conform to the Tax Act or any newly enacted federal tax legislation. Changes in corporate tax rates, the realization of net deferred tax assets relating to our operations, the taxation of foreign earnings, and the deductibility of expenses under the Tax Act or future reform legislation could have a material impact on the value of our deferred tax assets, could result in significant one-time charges, and could increase our future U.S. tax expense.

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 Exchange Act, the Sarbanes-Oxley Act of 2002, as amended, or 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, 2020, 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 Annual Report on Form 10-K filing for that year, as required by Section 404(a) of the Sarbanes-Oxley Act.

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. 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.

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 operations and those of our contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, outbreak of regional or global pandemic diseases, such as the recent coronavirus outbreak, 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 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.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our principal office is located at 955 Chesterbrook Boulevard, Chesterbrook, Pennsylvania, where we currently lease approximately 8,231 square feet of developed office space on the first floor and 40,565 square feet of developed office space on the second floor. The lease term for this space extends through May 2028. On October 11, 2018, we entered into an agreement with The Vanguard Group, Inc., or Vanguard, whereby Vanguard agreed to sublease the 40,565 square feet of space on the second floor for an initial term of 37 months. On October 2, 2020, Vanguard notified the Company that they exercised the first option to extend the sublease term for three years through November 30, 2024. Vanguard has a second option to extend the sublease term for an additional three years through November 30, 2027. The sublease provides for rent abatement for the first month of the term; thereafter, the rent payable to us by Vanguard under the sublease is (i) $0.50 less during months 2 through 13 of the sublease and (ii) in month 14 and thereafter of the sublease, $1.00 less than the base rent payable by us under our master lease with Chesterbrook Partners, L.P. Vanguard also is responsible for paying to us all tenant energy costs, annual operating costs, and annual tax costs attributable to the subleased space during the term of the sublease.

ITEM 3. LEGAL PROCEEDINGS

In October and November 2018, the Company and certain current and former officers and directors were sued in three purported class actions filed in the U.S. District Court for the Eastern District of Pennsylvania, or the EDPA, alleging violations of the federal securities laws. In January 2019, the three lawsuits were consolidated into one action, and on May 29, 2019, the EDPA appointed a group of five individual investors as lead plaintiffs. A consolidated amended complaint was filed on August 2, 2019, alleging, among other things, that the Company and two former officers made false and misleading statements regarding the Company's business, operations, and prospects, including certain statements made relating to the Company's End-of-Phase 2 meeting with the FDA related to OLINVYK, and certain statements concerning top-line results from the Company's Phase 3 studies related to OLINVYK. The plaintiffs seek, among other remedies, unspecified damages, attorneys' fees and other costs, and unspecified equitable or injunctive relief. On August 28, 2020, the EDPA granted in part and denied in part defendants' motion to dismiss. On October 2, 2020, the Company and the individual defendants filed their answer to the amended complaint, denying all liability. On February 11, 2021, the parties agreed in principle to a settlement, which is subject to final documentation and approval by the Court. The Company and the individual defendants do not acknowledge any wrongdoing as part of the settlement, and an $8.5 million payment will be made to the plaintiffs and their counsel, all of which will be funded by the Company's insurance carriers. Upon entry into the agreement in principle, the Company's liability related to this settlement became estimable and probable. Accordingly, the Company recorded in the fourth quarter of 2020 an estimated liability of $8.5 million and a corresponding insurance recovery of the same amount. The Company continues to believe that the claims are without merit, and if necessary the Company intends to vigorously defend itself and its former officers against the allegations.

In December 2018, a shareholder derivative action was filed on behalf of the Company and against certain current and former officers and directors in the EDPA, and in February 2019, two additional, similar shareholder derivative actions were filed in the U.S. District Court for the District of Delaware. A fourth similar shareholder derivative action was filed in the EDPA in September 2019, and a fifth, similar derivative action was filed in the EDPA in November 2019. A similar sixth derivative action was filed in the EDPA in September 2020. These cases, which involve facts similar to the consolidated securities lawsuits, assert claims against the individual defendants for, among other things, breach of fiduciary duty, waste of corporate assets, violations of the federal securities laws, and unjust enrichment, and they make a number of demands, including for monetary damages and other equitable and injunctive relief. Some of the derivative actions have been stayed in favor of the consolidated securities lawsuits. The Company recorded in the fourth quarter of 2020 an estimated liability of $0.5 million and a corresponding insurance recovery of the same amount.

Except as described above, 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.

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 Capital Market under the symbol "TRVN." On March 5, 2021, there were 6 holders of record of our common stock.

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.

Recent Sales of Unregistered Securities

We did not sell any equity securities during the fiscal year ended December 31, 2020 in transactions that were not registered under the Securities Act.

ITEM 6. SELECTED FINANCIAL DATA

Not required.

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. Please also see the section entitled "Cautionary Note Regarding Forward-Looking Statements."

Overview

We are a biopharmaceutical company focused on developing and commercializing novel medicines for patients affected by central nervous system, or CNS, disorders. Our lead product, OLINVYK™ (oliceridine) injection, or OLINVYK, was approved by the United States Food and Drug Administration, or the FDA, in August 2020. In October 2020, we announced that OLINVYK had received scheduling from the U.S. Drug Enforcement Administration, or DEA, and was classified as a Schedule II controlled substance. We initiated commercial launch of OLINVYK in the first quarter of 2021. OLINVYK is an opioid agonist for use in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. We are also developing a pipeline of product candidates based on our proprietary product platform, including TRV027 for the treatment of acute lung injury contributing to acute respiratory distress syndrome and abnormal blood clotting in patients with COVID-19; TRV250 for acute migraines; TRV734 for moderate-to-severe acute and chronic pain and opioid use disorders; and TRV045 for chronic pain and epilepsy.

Since our incorporation in late 2007, our operations have included organizing and staffing our company, business planning, raising capital, discovering and developing our product candidates, and establishing our intellectual property portfolio. We have financed our operations primarily through private placements and public offerings of our equity securities and debt borrowings. As of December 31, 2020, we had an accumulated deficit of $442.5 million. Our net loss was $29.4 million and $24.9 million for the years ended December 31, 2020 and 2019, 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 successfully commercialize OLINVYK or obtain marketing approval for and commercialize TRV027, TRV250, TRV734, or TRV045.

We expect to incur significant expenses and operating losses for the foreseeable future as we begin to commercialize OLINVYK and continue the development and clinical trials of our other product candidates. 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.

Recent Developments

COVID-19

The impact of the COVID-19 pandemic on the global economy and on our business continues to be a fluid situation. We responded quickly across our organization to guard the health and safety of our team and participants in our clinical trials, support our partners and vendors and mitigate risk. Thus far, our employees have rapidly adapted to working remotely and we are monitoring the COVID-19 pandemic on a daily basis to ensure we have all necessary plans in place for mitigating disruptions in our operations. Like other companies, our clinical trials have experienced some degree of disruption due to access limitations to institutions currently impacted, and we may need to make further adjustments to clinical trials in the future to comply with evolving FDA guidance or otherwise. The extent to which the COVID-19 pandemic will impact our efforts to commercialize OLINVYK and to achieve market acceptance is uncertain and will depend upon future developments.

We continue to proactively assess, monitor and respond to domestic and international developments related to the COVID-19 pandemic, and we will implement risk-mitigation plans as needed to minimize the impact on our clinical trials and business operations, including our commercialization efforts of OLINVYK. In addition, we have taken steps to protect the health and welfare of our employees by temporarily closing our offices and suspending business-related travel.

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 (formerly Square 1 Bank), or the lenders, pursuant to which the lenders agreed to lend us up to $35.0 million in a three-tranche series of term loans, or the Term Loans. 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. Payments of principal in equal monthly installments and accrued interest began on January 1, 2018 and continued until the loan matured on March 1, 2020. On March 2, 2020, we made our final payment under the loan and security agreement with the lenders. Upon the last payment date of the amounts borrowed under the agreement, we were required to pay a final payment fee of $1.9 million, equal to 6.6% of the aggregate amounts borrowed.

In connection with entering into the agreement, we issued to the lenders and the placement agent certain warrants to purchase an aggregate of 7,678 shares of our common stock. As of December 31, 2020, warrants exercisable for 5,728 shares of common stock remain outstanding. These warrants were exercisable upon issuance 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 our draw of the second term loan tranche, we issued to the lenders and the 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 our draw of the third term loan tranche, 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 qualified for equity classification and were allocated based upon the relative fair value of the base instrument and the warrants, according to the guidance of ASC 470-20-25-2.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States. The preparation of our 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.

Our significant accounting policies are more fully described in the notes to our audited financial statements for the year ended December 31, 2020 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.

Revenue Recognition

In accordance with FASB's ASC 606, Revenue from Contracts with Customers, or ASC 606, we recognize revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that the Company determines are within the scope of ASC 606, we perform the following five steps:

(i) identify the contract(s) with a customer;

(ii) identify the performance obligations in the contract;

(iii) determine the transaction price;

(iv) allocate the transaction price to the performance obligations in the contract; and

(v) recognize revenue when (or as) the entity satisfies a performance obligation.

We apply the five-step model to contracts when we determine that it is probable we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations and assess whether each promised good or service is distinct. We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Product Revenue

Product revenue is recognized at the point in time when our performance obligations with our customers have been satisfied. At contract inception, we determine if the contract is within the scope of ASC Topic 606 and then evaluate the contract using the following five steps: (1) identify the contract with the customer; (2) identify the performance obligations; (3) determine the transaction price; (4) allocate the transaction price to the performance obligations; and (5) recognize revenue at the point in time when the Company satisfies a performance obligation.

Revenue is recorded at the transaction price, which is the amount of consideration we expect to receive in exchange for transferring products to a customer. We determine the transaction price based on fixed consideration in our contractual agreements, which includes estimates of variable consideration, and the transaction price is allocated entirely to the performance obligation to provide pharmaceutical products. In determining the transaction price, a significant financing component does not exist since the timing from when we deliver product to when the customers pay for the product is less than one year and the customers do not pay for product in advance of the transfer of the product.

We record product revenue net of any variable consideration, which includes estimated chargebacks, prompt pay discounts, returns and distribution service fees. We utilize the expected value method to estimate chargebacks and returns and we utilize the most likely method to estimate prompt pay discounts and distribution service fees. The variable consideration is recorded as a reduction of revenue at the time revenues are recognized. We will only recognize revenue to the extent that it is probable that a significant revenue reversal will not occur in a future period. These estimates may differ from actual consideration amount received and we will re-assess these estimates each reporting period to reflect known changes in factors.

Distributor Chargebacks

When a product is sold to a third party that is subject to a contractual price agreement, the difference between the price paid to us by the wholesaler and the price under the specific contract is charged back to us by the wholesaler. Utilizing this information, we estimate a chargeback percentage for each product and record an allowance for chargebacks as a reduction to revenue when we record our sale of the products. We reduce the chargeback allowance when a chargeback request from a wholesaler is processed. Reserves chargebacks are included in accounts receivable, net on the consolidated balance sheet.

Prompt Payment (Cash) Discounts

We provide customers with prompt payment discounts which may result in adjustments to the price that is invoiced for the product transferred, in the case that payments are made within a defined period. Our prompt payment discount reserves are based on actual net sales and contractual discount rates. Reserves for prompt payment discounts are included in accounts receivable, net on the consolidated balance sheet.

Distribution Service Fees

We pay distribution service fees to our customers based on a fixed percentage of the product price. These fees are not in exchange for a distinct good or service and therefore are recognized as a reduction of the transaction price. We

reserve for these fees based on actual net sales, contractual fee rates negotiated with the customer and the mix of the products in the distribution channel that remain subject to fees. Reserves for distribution service fees are included in accounts receivable, net on the consolidated balance sheet.

Product Returns

Generally, our customers have the right to return any unopened product during the eighteen (18) month period beginning six (6) months prior to the labeled expiration date and ending twelve (12) months after the labeled expiration date in addition to slow moving or discontinued products. Six (6) months following the launch of OLINVYK, our customers may have the right to return inventory remaining from their initial purchase, if any, subject to certain terms and conditions. Since we currently do not have a history of OLINVYK returns, we estimate returns based on industry data for comparable products in the market. As we distribute our product and establish historical sales over a longer period of time (i.e., two to three years), we will be able to place more reliance on historical purchasing, demand and return patterns of our customers when evaluating our reserves for product returns. OLINVYK has a forty-eight (48) month shelf life.

We recognize the amount of expected returns as a refund liability, representing the obligation to return the customer's consideration. Since the returns primarily consist of expired and short dated products that will not be resold, we do not record a return asset for the right to recover the goods returned by the customer at the time of the initial sale (when recognition of revenue is deferred due to the anticipated return). Accrued product return estimates are recorded in accrued expenses and other current liabilities on the consolidated balance sheet.

License Revenues

Our licensing agreements typically include payment to us of one or more of the following: nonrefundable, up-front license fees; regulatory and commercial milestone payments; payments for manufacturing supply services; materials shipped to support development; and royalties on net sales of licensed products.

We also assess whether there is an option in a contract to acquire additional goods or services. An option gives rise to a performance obligation only if the option provides a material right to the customer that it would not receive without entering into that contract. Factors that we consider in evaluating whether an option represents a material right include, but are not limited to: (i) the overall objective of the arrangement, (ii) the benefit the collaborator might obtain from the arrangement without exercising the option, (iii) the cost to exercise the option (e.g. priced at a significant and incremental discount) and (iv) the likelihood that the option will be exercised. With respect to options determined to be performance obligations, we recognize revenue when those future goods or services are transferred or when the options expire.

Our licensing revenue arrangements may include the following:

Up-front License Fees: If a license is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenues from nonrefundable, up-front fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. We evaluate the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Milestone Payments: At the inception of an agreement that includes regulatory or commercial milestone payments, we evaluate whether each milestone is considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or the control of the licensee, such as regulatory approvals, are not considered probable of being

achieved until those approvals are received. At each reporting period, we assess the probability of achievement of each milestone under our current agreements.

Research and Development Activities: Under our current collaboration and license arrangements, if we are entitled to reimbursement for costs for services that we provided, we expect such reimbursement would be an offset to research and development expenses.

Royalties: If we are entitled to receive sales-based royalties from our collaborator, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, provided the reported sales are reliably measurable, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Manufacturing Supply and Research Services: Arrangements that include a promise for future supply of drug substance or drug product for either clinical development or commercial supply at the licensee's discretion are generally considered as options. We assess if these options provide a material right to the licensee and if so, they are accounted for as separate performance obligations.

We receive payments from our licensees based on schedules established in each contract. Upfront payments are recorded as deferred revenue upon receipt and may require deferral of revenue recognition to a future period until we perform our obligations under these arrangements. Amounts are recorded as accounts receivable when our right to consideration is unconditional. We do not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less.

Research and Development

Research and development costs 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 us reporting amounts that are too high or too low for any particular period. For the years ended December 31, 2020 and 2019, there were no material adjustments to our prior period estimates of accrued expenses for clinical trials.

Stock-Based Compensation

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 unit 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 unit awards, may be granted to new employees.

At December 31, 2020, we had two stock-based compensation plans, which are more fully described in Note 7 to the financial statements included in Part II of this Annual Report on Form 10-K. 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 expense for all stock-based awards based on the estimated grant-date fair values. For restricted stock unit awards to employees, the fair value is based on the closing price of our 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 on a straight-line basis 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. We elected an accounting policy to record forfeitures as they occur.

See Note 7 to the financial statements included in Part II of this Annual Report on Form 10-K for a discussion of the assumptions we used 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 our stock-based compensation plan for all years presented.

Recent Accounting Pronouncements

See Note 2 to the financial statements included in Part II of this Annual Report on Form 10-K for information on recent accounting pronouncements.

Results of Operations

Comparison of Years Ended December 31, 2020 and 2019

(in thousands, except per share data)

	Year Ended December 31,		
	2020	2019	Change
Revenue:			
Product revenue	$ 69	$ —	$ 69
License revenue	3,000	31	2,969
Total revenue	3,069	31	3,038
Operating expenses:			
Cost of goods sold	182	—	182
General and administrative	19,248	13,212	6,036
Research and development	13,124	13,291	(167)
Impairment of property and equipment	—	108	(108)
Total operating expenses	32,554	26,611	5,943
Loss from operations	(29,485)	(26,580)	(2,905)
Other income (expense):			
Other income, net	205	2,222	(2,017)
Interest income	240	418	(178)
Interest expense	(29)	(931)	902
Total other income	416	1,709	(1,293)
Loss before income tax expense	(29,069)	(24,871)	(4,198)
Foreign income tax expense	(300)	—	(300)
Net loss attributable to common stockholders	$ (29,369)	$ (24,871)	$ (4,498)

Revenue

To date, we have derived revenue mainly from activities pursuant to our licensing agreements related to the development and commercialization of OLINVYK in China and South Korea. We have not generated material revenue from commercial product sales. For the year ended December 31, 2020, we recorded $0.1 million in product revenue from the shipment of drug product to wholesalers. We had product available in the trade channel during the fourth quarter of 2020 in advance of the planned commercial launch in the first quarter of 2021.

There was $3.1 million of revenue recorded for the year ended December 31, 2020, primarily related to the milestone payment that became payable by Nhwa upon FDA approval of OLINVYK. Revenue recorded for the year ended December 31, 2019 relates to materials shipped to Nhwa to support the development of OLINVYK in China.

Cost of goods sold

Cost of goods sold for product revenue includes third party logistics costs, shipping costs, and indirect overhead costs which are recorded as period costs in the period incurred.

We expensed the cost of producing validation batches of OLINVYK that we are using in the commercial launch as research and development expense prior to the regulatory approval and DEA scheduling of OLINVYK. We expect cost of sales to increase as we deplete these inventories.

The following table provides information regarding cost of goods sold during the periods indicated, including percent changes (dollar amounts in thousands):

	Year Ended December 31,		
	2020	2019	% Increase (Decrease)
Cost of goods sold	$ 182	$ —	100%

Cost of goods sold increased by $0.2 million, or 100% for the year ended December 31, 2020 compared to the same period in 2019, primarily related to distribution and indirect costs following the regulatory approval and DEA scheduling of OLINVYK.

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 expenses associated with stock-based compensation and travel. Other general and administrative expenses include professional fees for legal, market research, consulting, and accounting services.

General and administrative expenses increased by $6.0 million, or 46%, for the year ended December 31, 2020 compared to the same period in 2019, primarily related to increases in pre-commercialization activities.

Research and development expense

Research and development expenses consist primarily of costs incurred for research and the development of our product candidates, including costs associated with the regulatory approval process. In addition, research and development expenses include salaries and related costs for our research and development personnel and stock-based compensation expense and travel expenses for such individuals. Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size, complexity and duration of later-stage clinical trials.

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 $0.2 million, or 1% in 2020 as compared to 2019. The following table summarizes our research and development expenses (in thousands):

	Year Ended December 31,	
	2020	2019
Personnel-related costs	$ 5,410	$ 5,617
OLINVYK	2,560	6,003
TRV027	519	1
TRV250	1,892	783
Other research and development	2,743	887
	$ 13,124	$ 13,291

The decrease in research and development expenses during the year ended December 31, 2020 was primarily driven by lower spending in 2020 for OLINVYK following the resubmission of the OLINVYK NDA in 2019, partially offset by higher expenditures in 2020 on the manufacture of validation batches for OLINVYK and the activities to support the development of TRV027, TRV045 and TRV250.

Total other income

Total other income decreased by $1.3 million, or 76%, during the year ended December 31, 2020 compared to the same period in 2019, primarily due to the sale of R&D tax credits in 2019, partially offset by lower interest expense due to the repayment of a loan during the year ended December 31, 2020 and by lower bond accretion.

Liquidity and Capital Resources

We have historically funded substantially all of our operations through the sale and issuance of our equity securities, debt securities and borrowings under debt facilities. We have also received an aggregate of $8.8 million pursuant to licensing agreements for the development and commercialization of OLINVYK in China and South Korea.

At December 31, 2020, we had an accumulated deficit of $442.5 million, working capital of $102.5 million, cash and cash equivalents of $109.4 million, restricted cash of $1.3 million, and no marketable securities. In November 2020, we filed a $250.0 million shelf registration statement, which includes the HCW ATM Program, of which there was approximately $50.0 million of available capacity as of December 31, 2020.

Our primary use of cash is to fund operating expenses, which consist of research and development expenditures and general and administrative expenditures. We anticipate these expenses to increase in 2021, given that we recently began to commercialize OLINVYK. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in accounts payable and accrued expenses. Net cash used in operating activities was $21.4 million and $23.7 million for the years ended December 31, 2020 and 2019, respectively. We incurred net losses of $29.4 million and $24.9 million for those same periods.

Cash Flows

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

	Year Ended December 31,	
	2020	2019
Net cash (used in) provided by:		
Operating activities	$ (21,394)	$ (23,667)
Investing activities	3,473	25,583
Financing activities	95,020	(2,497)
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 77,099	$ (581)

Net cash used in operating activities

Net cash used in operating activities was $21.4 million for the year ended December 31, 2020 as compared to $23.7 million for the year ended December 31, 2019. Net cash used in operating activities for the year ended December 31, 2020 consisted primarily of a net loss of $29.4 million partially offset by non-cash expenses for stock compensation of $3.3 million and a $3.4 million increase in accounts payable, accrued expenses and other liabilities.

Net cash used in operating activities for the year ended December 31, 2019 consisted primarily of a net loss of $24.9 million and an increase in prepaid expenses of $1.1 million primarily related to the TRV250 study. Cash outflows were partially offset by non-cash expenses for stock compensation of $3.2 million and other non-cash adjustments.

Net cash provided by investing activities

Net cash provided by investing activities was $3.5 million for the year ended December 31, 2020, as compared to $25.6 million for the year ended December 31, 2019. Investing activities consisted primarily of payments related to the maturities of marketable securities.

Net cash (used in) provided by financing activities

Net cash provided by financing activities was $95.0 million for the year ended December 31, 2020, as compared to net cash used in financing activities of $2.5 million for the year ended December 31, 2019. Net cash provided by financing activities for the year ended December 31, 2020 was primarily due to net proceeds of approximately $53.7 million from our August 2020 underwritten public offering of 25.0 million shares of our common stock, at a public offering price of $2.30 per share, and net proceeds of $47.3 million from the sale of common stock through our HCW ATM Program, partially offset by principal repayments on our Term Loans of $3.2 million and an additional final fee payment of $1.9 million.

Net cash used in financing activities for the year ended December 31, 2019 was primarily due to principal repayments on our Term Loans of $12.7 million, offset by net proceeds of $9.2 million from the February 2019 registered direct offering and net proceeds of $1.1 million from the sale of common stock through our HCW ATM Program. 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 begin to commercialize OLINVYK, advance clinical development of TRV027, continue clinical development of TRV250, and continue IND-enabling work for TRV045. Over the next twelve months, we anticipate that our total operating expenses will increase compared to the previous twelve months.

We believe that our cash and cash equivalents as of December 31, 2020, together with interest thereon, will be sufficient to fund our operating expenses and capital expenditure requirements through the fourth quarter of 2022. Our anticipated operating expenses involve significant risks and uncertainties and are dependent on our current assessment of the extent and costs of activities required to commercialize OLINVYK and advance our other product candidates. In the future, we anticipate that we will need to raise substantial additional financing 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 significant dilution to our stockholders. We may offer and sell shares of our common stock under the existing registration statement 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:

- our ability to successfully commercialize OLINVYK and our other product candidates;
- our ability to generate sales and other revenues from OLINVYK or any of our other product candidates, once approved, including setting an acceptable price for and obtaining adequate coverage and hospital formulary acceptance of such products;
- the size and growth potential of the markets for OLINVYK and our ability to serve those markets;
- 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 number and development requirements of any other product candidates that we may pursue;
- our ability to enter into collaborative agreements for the development and/or commercialization of our product candidates, including for OLINVYK;

- the costs, timing, and outcome of any regulatory review of OLINVYK and any future product candidates, both in the United States and in territories outside the United States;
- the costs, timing, and extent of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;
- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- any product liability or other lawsuits, including the recently filed class action complaints, related to our products or us;
- the expenses needed to attract and retain skilled personnel; and
- the costs involved in preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending our intellectual property-related claims, both in the United States and in territories outside the United States.

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

Contractual Obligations and Commitments

The following is a summary of our long-term contractual cash obligations as of December 31, 2020 (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)	$ 10,788	$ 1,376	$ 2,826	$ 2,924	$ 3,662
Total	$ 10,788	$ 1,376	$ 2,826	$ 2,924	$ 3,662

(1) Operating lease obligations reflect our obligation to make payments in connection with the leases for our office space in Chesterbrook, Pennsylvania. Future rent streams of $1.1 million to be collected in less than one year and $3.3 million to be collected between one and three years are not offset against operating lease obligations.

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.

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

Off-Balance Sheet Arrangements

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

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Not required.

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 or detect all errors 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. The design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions; over time, controls may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and may not be detected.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2020. 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" (2013). Based on the assessments of our internal control over financial reporting, our management, including our Chief Executive Officer and Chief Financial Officer, believe that, as of December 31, 2020, our internal control over financial reporting was 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, 2020 and 2019, the related statements of operations and comprehensive loss, stockholders' equity, and cash flows, for each of the two years in the period ended December 31, 2020, 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, 2020 and 2019, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2020, 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 such 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 included 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.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which they relate.

Accounting for Loss Contingencies

Description of the Matter

As described in Note 8 to the financial statements, the Company is involved in various claims and legal proceedings. The Company accrues a liability for an estimated loss if the potential loss from any claim or legal proceeding is considered probable, and the amount can be reasonably estimated, and recognizes an asset for proceeds from related insurance claims that are considered probable of recovery. The Company also performs an assessment of the materiality of loss contingencies where a loss is either reasonably possible or it is reasonably possible that an exposure to loss exists in excess of the amount accrued. If it is reasonably possible that such a loss or an additional loss may have been incurred and the effect on the financial statements is material, the Company discloses the nature of the loss contingency and an estimate of the possible loss or range of loss or a statement that such an estimate cannot be made within the notes to the financial statements.

Auditing management's determination of whether a loss is probable and reasonably estimable, reasonably possible or remote, and the related disclosures, as well as whether insurance claims are probable of recovery, is highly subjective and requires significant judgment. In particular, these determinations are sensitive to the uncertainties related to the ultimate outcome of the legal contingency, the status and uncertainty of the litigation

and/or the appeals process, the jurisdiction where the lawsuit has been filed, the extent of recovery of losses from insurers, and the status of any settlement discussions associated with the legal contingency.

How We Addressed the Matter in Our Audit

To test the Company's legal contingencies, we assessed the completeness of the legal contingencies subject to evaluation by the Company, and assessed the Company's determination of the probability of outcomes for legal contingencies through inspection of responses to inquiry letters sent to both internal and external legal counsel, discussions with legal counsel to confirm our understanding of the allegations, and we obtained written representations from executives of the Company.

For those legal contingencies for which the Company has determined that a loss is probable and reasonably estimable and is therefore required to be recognized, we evaluated the measurement of the recorded loss. For those legal contingencies for which the Company has determined that a loss is either probable or reasonably possible, but the Company is unable to estimate the range of loss, and is therefore required to be disclosed, we assessed the sufficiency of the disclosures of legal contingencies. We assessed the Company's estimate of the amount of the loss, for both contingencies that are probable and reasonably possible, through inspection of correspondence received from internal and external legal counsel and direct discussions with legal counsel. We evaluated the extent of recovery of losses from insurers through the review of correspondence received by the Company from the insurers. We also obtained written representations from executives of the Company.

/s/ Ernst & Young LLP

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

Philadelphia, Pennsylvania
March 9, 2021

TREVENA, INC.

Balance Sheets
(in thousands, except share and per share data)

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 109,403	$ 32,305
Accounts receivable, net	71	—
Marketable securities	—	3,500
Insurance recovery	9,000	—
Prepaid expenses and other current assets	570	1,683
Total current assets	119,044	37,488
Restricted cash	1,310	1,309
Property and equipment, net	2,253	2,705
Right-of-use lease asset	5,119	5,472
Other assets	13	20
Total assets	$ 127,739	$ 46,994
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable, net	$ 1,693	$ 1,047
Accrued expenses and other current liabilities	5,168	2,403
Estimated settlement liability	9,000	—
Current portion of loans payable, net	—	5,037
Lease liability	703	620
Total current liabilities	16,564	9,107
Leases, net of current portion	7,101	7,804
Warrant liability	6	5
Total liabilities	23,671	16,916
Commitments and contingencies (Note 8)		
Stockholders' equity:		
Common stock—$0.001 par value; 200,000,000 shares authorized at December 31, 2020 and December 31, 2019; 159,999,917 and 94,213,760 shares issued and outstanding at December 31, 2020 and December 31, 2019, respectively	160	94
Preferred stock—$0.001 par value; 5,000,000 shares authorized, none issued or outstanding at December 31, 2020 and December 31, 2019	—	—
Additional paid-in capital	546,422	443,129
Accumulated deficit	(442,514)	(413,145)
Total stockholders' equity	104,068	30,078
Total liabilities and stockholders' equity	$ 127,739	$ 46,994

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,	
	2020	2019
Revenue:		
Product revenue	$ 69	$ —
License revenue	3,000	31
Total revenue	3,069	31
Operating expenses:		
Cost of goods sold	182	—
General and administrative	19,248	13,212
Research and development	13,124	13,291
Impairment of property and equipment	—	108
Total operating expenses	32,554	26,611
Loss from operations	(29,485)	(26,580)
Other income (expense):		
Other income, net	205	2,222
Interest income	240	418
Interest expense	(29)	(931)
Total other income	416	1,709
Loss before income tax expense	(29,069)	(24,871)
Foreign income tax expense	(300)	—
Net loss attributable to common stockholders	$ (29,369)	$ (24,871)
Other comprehensive gain, net:		
Unrealized gain on marketable securities	—	9
Other comprehensive gain, net	—	9
Comprehensive loss	$ (29,369)	$ (24,862)
Per share information:		
Net loss per share of common stock, basic and diluted	$ (0.23)	$ (0.27)
Weighted average common shares outstanding, basic and diluted	127,623,859	91,677,963

See accompanying notes to financial statements.

TREVENA, INC.
Statements of Stockholders' Equity
For the Period from January 1, 2019 to December 31, 2020
(in thousands, except share data)

	Stockholders' Equity					
	Common Stock				Accumulated Other	
	Number of Shares	$0.001 Par Value	Additional Paid-in Capital	Accumulated Deficit	Comprehensive Income (Loss)	Total Stockholders' Equity
Balance, January 1, 2019	82,323,413	$ 82	$ 429,727	$ (388,274)	$ (9)	$ 41,526
Stock-based compensation expense	—	—	3,232	—	—	3,232
Exercise of stock options	41,968	—	28	—	—	28
Shares repurchased by the Company	(122)	—	—	—	—	—
Issuance of warrants to underwriters in connection with equity offering	—	—	347	—	—	347
Issuance of common stock upon vesting of RSUs, net of shares withheld for employee taxes	406,093	—	(158)	—	—	(158)
Issuance of common stock, net of issuance costs	11,442,408	12	9,953	—	—	9,965
Unrealized gain on marketable securities	—	—	—	—	9	9
Net loss	—	—	—	(24,871)	—	(24,871)
Balance, December 31, 2019	94,213,760	$ 94	$ 443,129	$ (413,145)	$ —	$ 30,078
Stock-based compensation expense	—	—	3,284	—	—	3,284
Exercise of stock options	197,640	1	135	—	—	136
Issuance of common stock upon vesting of RSUs, net of shares withheld for employee taxes	1,042,238	1	(1,072)	—	—	(1,071)
Issuance of common stock, net of issuance costs	64,344,354	64	100,946	—	—	101,010
Net exercise of common stock warrant	201,925	—	—	—	—	—
Net loss	—	—	—	(29,369)	—	(29,369)
Balance, December 31, 2020	159,999,917	$ 160	$ 546,422	$ (442,514)	$ —	$ 104,068

See accompanying notes to financial statements.

TREVENA, INC.

Statements of Cash Flows
(in thousands)

	Year Ended December 31,	
	2020	**2019**
Operating activities:		
Net loss	$ (29,369)	$ (24,871)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	477	562
Stock-based compensation	3,284	3,232
Noncash interest expense on loans	8	331
Impairment of property and equipment	—	108
Loss on disposal of assets	2	12
Revaluation of warrant liability	1	4
Accretion of bond discount on marketable securities	—	(484)
Change in right-of-use asset	353	301
Changes in operating assets and liabilities:		
Accounts receivable, prepaid expenses and other assets	1,049	(1,122)
Operating lease liabilities	(610)	(482)
Accounts payable, accrued expenses and other liabilities	3,411	(1,258)
Net cash used in operating activities	(21,394)	(23,667)
Investing activities:		
Purchases of property and equipment	(27)	—
Maturities of marketable securities	3,500	79,389
Purchases of marketable securities	—	(53,806)
Net cash provided by investing activities	3,473	25,583
Financing activities:		
Proceeds from exercise of common stock options	136	28
Proceeds from issuance of common stock, net	101,010	10,312
Payment of employee withholding taxes on vested restricted stock units	(1,071)	(158)
Capital lease payments	(10)	(12)
Repayments of loans payable, net	(5,045)	(12,667)
Net cash provided by (used in) financing activities	95,020	(2,497)
Net increase (decrease) in cash, cash equivalents and restricted cash	77,099	(581)
Cash, cash equivalents and restricted cash—beginning of period	33,614	34,195
Cash, cash equivalents and restricted cash—end of period	$ 110,713	$ 33,614
Supplemental disclosure of cash flow information:		
Cash paid for interest	$ 19	$ 600
Fair value of common stock warrants issued to underwriters	$ —	$ 347

See accompanying notes to financial statements.

TREVENA, INC.

Notes to Financial Statements

December 31, 2020

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 focused on the development and commercialization of novel medicines for patients affected by central nervous system, or CNS, disorders. 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 nonclinical studies and clinical trials. The Company has never been profitable. In late 2017, the Company submitted a new drug application, or NDA, for OLINVYK™ (OLINVYK) injection, or OLINVYK, to the United States Food and Drug Administration, or the FDA. In August 2020, the FDA approved the NDA for OLINVYK and the Company initiated commercial launch of OLINVYK in the first quarter of 2021.

Since the Company's inception, the Company has incurred losses and negative cash flows from operations. At December 31, 2020, the Company had an accumulated deficit of $442.5 million. The Company's net loss was $29.4 million and $24.9 million for the years ended December 31, 2020 and 2019, respectively. The Company follows the provisions of Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 205-40, *Presentation of Financial Statements—Going Concern*, or ASC 205-40, which requires management to assess the Company's ability to continue as a going concern for one year after the date the financial statements are issued. The Company expects that its existing balance of cash and cash equivalents as of December 31, 2020 is sufficient to fund operations for more than one year after the date of this filling, through the fourth quarter of 2022. There can be no assurance that the Company will be successful in raising additional capital or that such capital, if available, will be on terms that are acceptable to the Company, or that the Company will be successful in deferring certain operating expenses, or that the COVID-19 pandemic will not have an impact on the Company's ability to raise capital or fund its operations as planned. If the Company is unable to raise sufficient additional capital or defer sufficient operating expenses, the Company may be compelled to reduce the scope of its operations and planned capital expenditures.

Certain prior period amounts have been reclassified to conform to the current period presentation, the effect of which was not material to the Company's interim financial statements.

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 ASC and Accounting Standards Updates, or ASUs, of the 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 assumptions 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 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 Company is also subject to certain contingent liabilities with respect to existing or potential claims, lawsuits and other proceedings. The Company accrues liabilities when it considers probable that future costs will be incurred and such costs can be reasonably estimated, and recognizes an asset for proceeds from related insurance claims that are considered probable of recovery. 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, 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 and U.S. Treasury securities.

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, 2020, the Company had no available-for-sale investments. As of December 31, 2019, the Company had $3.5 million in available-for-sale investments, all classified as current assets. The Company had no marketable securities as of December 31, 2020. 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 has recorded this deposit 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, 2019 is the nominal value of the loan payable, net of unamortized debt discount and deferred charges. The Company had no loans payable at December 31, 2020. 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 are 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. $0.1 million of impairment losses were recorded during the year ended December 31, 2019.No impairment losses were recorded during the year ended December 31, 2020.

Leases

At the commencement of a lease, the Company recognizes a liability to make lease payments and an asset representing the right to use the underlying asset during the lease term. The lease liability is measured at the present value of lease payments over the lease term, including variable fees that are known or subject to a minimum floor. The lease liability includes lease component fees, while non-lease component fees are expensed as incurred for all asset classes. When a contract excludes an implicit rate, the Company utilizes an incremental borrowing rate based on information available at the lease commencement date including lease term and geographic region. The initial valuation of the right-of-use, or ROU, asset includes the initial measurement of the lease liability, lease payments made in advance of the lease commencement date, and initial direct costs incurred by the Company and excludes lease incentives.

Leases with an initial term of 12 months or less are classified as short-term leases and are not recorded on the balance sheet. The lease expense for short-term leases is recognized on a straight-line basis over the lease term. The Company tests for impairment of the ROU assets whenever circumstances indicate that the carrying amount of the asset may not be recoverable.

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. The value of these warrants was immaterial as of December 31, 2020 and 2019.

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 and Note 7 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

In accordance with FASB's ASC 606, Revenue from Contracts with Customers, or ASC 606, the Company recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that the Company determines are within the scope of ASC 606, it performs the following five steps:

(i) identify the contract(s) with a customer;

(ii) identify the performance obligations in the contract;

(iii) determine the transaction price;

(iv) allocate the transaction price to the performance obligations in the contract; and

(v) recognize revenue when (or as) the entity satisfies a performance obligation.

The Company applies the five-step model to contracts when it determines that it is probable it will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied. See Note 9 and Note 10, respectively, for a full discussion of the Company's product revenue and license revenue.

Research and Development

Research and development costs 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, 2020 and 2019, there were no material adjustments to the Company's prior period estimates of accrued expenses for clinical trials.

Stock-Based Compensation

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 unit awards, may be granted to employees, non-employee directors, and non-employee consultants. At December 31, 2020, the Company had two stock-based compensation plans, which are more fully described in Note 7. 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.

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 expense for all stock-based awards based on the estimated grant-date fair values. For restricted stock unit 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 on a straight-line basis 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. The Company elected an accounting policy to record forfeitures as they occur. For stock awards that vest based on performance conditions (e.g., achievement of certain milestones), expense is recognized when it is probable that the conditions will be met. 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 informally titled the Tax Cuts and Jobs Act of 2017, 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 14.

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 August 2018, the FASB issued ASU 2018-13,*Fair Value Measurement (Topic 820): Disclosure Framework – Changes to the Disclosure Requirements for Fair Value Measurement*. The new guidance modifies the disclosure requirements related to fair value measurements in Topic 820, *Fair Value Measurement*, including removing certain previous disclosure requirements, adding certain new disclosure requirements, and modifying certain other disclosure requirements. The ASU is effective for fiscal years beginning after December 15, 2019, including interim periods within those fiscal years. The effective date for this standard was January 1, 2020. The Company adopted this standard on January 1, 2020. There was no impact to the Company's financial statements or related disclosures upon the adoption.

Recent Accounting Standards Not Yet Adopted

In December 2019, the FASB issued ASU 2019-12,*Simplifying the Accounting for Income Taxes*, which removed certain exceptions to the general principles of the accounting for income taxes and also improves consistent application of and simplification of other areas when accounting for income taxes. The guidance will be effective for the Company beginning in the first quarter of fiscal year 2021. Early adoption is permitted. The Company has determined that the adoption of this standard will have no material impact on its financial statements and related disclosures.

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, 2020 and 2019 (in thousands):

	December 31, 2020						
	Adjusted Cost	Unrealized Gains	Unrealized Losses	Fair Value	Cash and Cash Equivalents	Restricted Cash	Marketable Securities
Cash	$ 6,100	$ —	$ —	$ 6,100	$ 4,790	$ 1,310	$ —
Level 1 (1):							
Money market funds	104,613	—	—	104,613	104,613	—	—
U.S. treasury securities	—	—	—	—	—	—	—
Subtotal	104,613	—	—	104,613	104,613	—	—
Level 2 (2):							
U.S. government agency securities	—	—	—	—	—	—	—
Total	$ 110,713	$ —	$ —	$ 110,713	$ 109,403	$ 1,310	$ —

	December 31, 2019						
	Adjusted Cost	Unrealized Gains	Unrealized Losses	Fair Value	Cash and Cash Equivalents	Restricted Cash	Marketable Securities
Cash	$ 9,302	$ —	$ —	$ 9,302	$ 7,993	$ 1,309	$ —
Level 1 (1):							
Money market funds	18,306	—	—	18,306	18,306	—	—
U.S. treasury securities	5,996	—	—	5,996	2,496	—	3,500
Subtotal	24,302	—	—	24,302	20,802	—	3,500
Level 2 (2):							
U.S. government agency securities	3,510	—	—	3,510	3,510	—	—
Total	$ 37,114	$ —	$ —	$ 37,114	$ 32,305	$ 1,309	$ 3,500

(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, 2020, the Company did not hold any investment securities exceeding a one-year maturity.

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 has recorded this deposit and accumulated interest thereon as restricted cash on its balance sheet.

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 on marketable securities during the years ended December 31, 2020 and 2019. To date, the Company has not recorded any impairment charges on marketable securities related to other-than-temporary declines in market value.

Accretion of bond discount on marketable securities is included in other income as a separate component of other income (expense) on the statement of operations and comprehensive loss. Interest income on marketable securities is recorded as interest income on the statement of operations and comprehensive loss.

The Company recognizes transfers between levels of the fair value hierarchy as of the end of the reporting period. The Company does not hold material Level 3 securities, and therefore, there were no transfers in or out of Level 3 in the hierarchy during the years ended December 31, 2020 or 2019.

4. Property and Equipment, net

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

	Estimated Useful Life in Years	December 31, 2020	December 31, 2019
Computers and software	3 - 5	$ 476	$ 480
Office equipment and furniture	5	721	706
Manufacturing equipment	5	10	10
Leasehold improvements	10	3,082	3,082
Leased assets	5	45	45
Total property and equipment		4,334	4,323
Less accumulated depreciation and amortization		(2,081)	(1,618)
Property and equipment, net		$ 2,253	$ 2,705

Depreciation and amortization expense was $0.5 million and $0.6 million for the years ended December 31, 2020 and 2019, respectively.

5. Accrued Expenses and Other Current Liabilities

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

	December 31,	
	2020	2019
Compensation and benefits	$ 2,919	$ 1,786
Commercial expenses	605	—
Legal expenses	784	86
Pharmaceutical development expenses	413	445
Accrued interest	—	18
Other accrued expenses and other current liabilities	447	68
Total accrued expenses and other current liabilities	$ 5,168	$ 2,403

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 1 Bank) (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). In September 2014, December 2015 and March 2017, the Company incurred borrowings under the agreement in the aggregate initial principal amount of $28.5 million. Term Loans A and B accrued interest at6.5% per annum and Term Loan C accrued interest at 6.98% per annum. The Company was required to make payments of interest only on borrowings under the loan agreement on a monthly basis through and including January 1, 2018; payments of principal in equal monthly installments and accrued interest began on January 1, 2018 and continued until the loan matured on March 1, 2020. On March 2, 2020, the Company made its final payment under the loan and security agreement with the lenders. Upon the last payment date of the amounts borrowed under the agreement, the Company was required to pay a final payment fee of $1.9 million, equal to 6.6% of the aggregate amounts borrowed.

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's common stock. Warrants exercisable for an aggregate of5,728 shares remain outstanding as of December 31, 2020. These warrants were exercisable upon issuance 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 the Company's 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 the Company's 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.

As of December 31, 2020, there areno borrowings outstanding attributable to Term Loans A, B, or C. Interest expense of $0.02 million and $0.6 million was recorded during the years ended December 31, 2020 and 2019, respectively. The Company incurred lender and third-party costs of $1.0 million related to the issuance of its term loans. Per ASU 2015 03, 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 were amortized to interest expense over the life of the loans using the effective interest method. Immaterial amounts of debt discount and debt issuance cost were amortized to interest expense during the year ended December 31, 2020. A total of $0.1 million of debt discount and debt issuance costs were amortized to interest expense during the year ended December 31, 2019.

The following table summarizes how the issuance of Term Loans A, B, and C are reflected on the balance sheet at December 31, 2020 and 2019 (in thousands):

	December 31,	
	2020	2019
Gross proceeds	$ —	$ 3,167
Debt discount and debt issuance costs (1)	—	1,870
Carrying value	—	5,037
Current portion of loans payable, net	—	5,037
Loans payable, net	$ —	$ —

(1) Includes the final fee payment due upon last payment date of the amounts borrowed.

7. Stockholders' Equity

Equity Offerings

Under its certificate of incorporation, the Company was authorized to issue up to200,000,000 shares of common stock as of December 31, 2020 and December 31, 2019. The Company also was authorized to issue up to 5,000,000 shares of preferred stock as of December 31, 2020 and December 31, 2019. 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.

Registered Underwritten Public Offering

In August 2020, the Company closed a registered underwritten public offering of25,000,000 shares of its common stock, including the full exercise of a 30 day option to purchase additional shares which we granted to the underwriters, at a public offering price of $2.30 per share. This transaction resulted in net proceeds to the Company of approximately $53.7 million, after deducting underwriting discounts and commissions and offering expenses.

ATM Programs

On April 17, 2019, the Company entered into a Common Stock Sales Agreement with H.C. Wainwright & Co., LLC, or Wainwright, pursuant to which the Company may offer and sell through Wainwright, from time to time at the Company's sole discretion, shares of its common stock, having an aggregate offering price of up to $50.0 million, or the HCW ATM Program. Sales of the shares of common stock are deemed to be "at-the-market offerings," as defined in Rule 415 under the Securities Act. On December 31, 2020, the Company and Wainwright entered into Amendment No. 1 to Common Stock Sales Agreement, or the Amendment, to amend the Common Stock Sales Agreement to, among other things, update the reference to the registration statement pursuant to which the shares of Common Stock may be sold and to include an additional $50.0 million of shares of Common Stock in the HCW ATM Program. For the year ended December 31, 2020, the Company issued and sold approximately 39.3 million shares of common stock under the HCW ATM Program. The net offering proceeds to the Company in 2020 for sales under the HCW ATM Program were approximately $47.3 million after deducting related expenses, including commissions. As of December 31, 2020, and following the Amendment, there was approximately $50.0 million remaining available for future issuances under the HCW ATM Program.

Registered Direct Offering and Concurrent Warrant Issuance

On January 29, 2019, the Company entered into securities purchase agreements withtwo institutional investors wherein the Company agreed to sell to the investors an aggregate of 10,000,000 shares of its common stock, at an offering price of $1.00 per share, in a registered direct offering. The net proceeds to the Company from the offering were $9.2 million, after deducting fees and the expenses of the placement agent. Pursuant to a letter agreement dated January 28, 2019, the Company engaged Wainwright to act as its exclusive placement agent in connection with the issuance and sale of the shares. The Company paid Wainwright 7.0% of the aggregate gross proceeds in the offering and $50,000 for

certain expenses, and it issued warrants to purchase500,000 shares of common stock to certain designees of Wainwright. These warrants have a term of five years, are immediately exercisable and have an exercise price of $1.25 per share. During the year ended December 31, 2020, 327,500 of these warrants were exercised in a cashless exercise for 201,925 common shares. The warrants are classified as equity and were recorded at fair value as of the date of issuance on the Company's Consolidated Balance Sheets and no further adjustments to their valuation are made. The letter agreement also includes indemnification obligations of the Company and other provisions customary for transactions of this nature.

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. For performance-based stock awards, the Company recognizes expense when achievement of the performance condition is probable, over the requisite service period.

The estimated grant-date fair value of the Company's share-based awards is amortized on a straight-line basis over the awards' service periods. Share-based compensation expense recognized was as follows (in thousands):

	Year Ended December 31,	
	2020	2019
Research and development	$ 781	$ 825
General and administrative	2,497	2,407
Cost of goods sold	6	—
Total stock-based compensation	$ 3,284	$ 3,232

Stock Options

A summary of stock option activity and related information from January 1, 2019 through December 31, 2020 follows:

	Options Outstanding		
	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)
Balance, January 1, 2019	8,265,207	$ 3.99	6.99
Granted	1,033,000	1.10	
Exercised	(41,968)	0.68	
Forfeited/Cancelled	(1,687,935)	(4.94)	
Balance, December 31, 2019	7,568,304	$ 3.40	7.01
Granted	2,477,486	1.90	
Exercised	(197,640)	0.68	
Forfeited/Cancelled	(283,631)	(3.33)	
Balance, December 31, 2020	9,564,519	$ 3.07	7.17
Vested or expected to vest at December 31, 2020	9,564,519	$ 3.07	7.17
Exercisable at December 31, 2020	5,536,713	$ 3.88	5.94

The intrinsic value of the options exercisable as of December 31, 2020 was $1.6 million, based on the Company's closing stock price of $2.14 per share and a weighted average exercise price of $3.88 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 years ended December 31, 2020 and 2019 was estimated at $1.48 and $0.86 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,	
	2020	2019
Expected term of options (in years)	6.1	6.1
Risk-free interest rate	0.6 %	1.9 %
Expected volatility	97.3 %	98.9 %
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.

- Expected stock price volatility: The Company estimates the expected volatility based on the actual historical volatility of the Company's stock price using daily closing prices over a period equal to the expected term of the associated award. Prior to January 1, 2018, the Company estimated the expected volatility based on actual historical volatility of the stock price of similar companies with publicly-traded equity securities.

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

- Estimated forfeiture rate: The Company elected to record forfeitures upon occurrence, rather than utilizing an estimate.

As of December 31, 2020, there was $4.4 million of total unrecognized compensation expense related to unvested stock options that will be recognized over the weighted average remaining period of 3.26 years.

Restricted Stock Units

During the year ended December 31, 2020, the Company granted2,536,850 restricted stock units, or RSUs, to employees. The units vest annually over a four year period. The weighted average fair market value per RSU on the grant date was $2.11, which is equal to the closing price of the Company's common stock on the date of the grant

RSU-related expense is recognized on a straight-line basis over the vesting period. Upon vesting, these awards may be settled on a net-exercise basis to cover any required withholding tax with the remaining amount converted into an equivalent number of shares of common stock.

There were 477,255 shares of common stock underlying vested RSUs that were withheld during the year ended December 31, 2020, based on the value of the RSU awards as determined by the Company's closing stock price on the applicable vesting date. The shares withheld for taxes are again available for issuance under the plan.

The following is a summary of changes in the status of non-vested RSUs from January 1, 2019 through December 31, 2020:

	Number of Awards	Weighted Average Grant Date Fair Value
Non-vested at January 1, 2019	1,255,000	$ 0.65
Granted	2,500,585	0.74
Vested	(572,500)	0.65
Forfeited/Cancelled	(237,500)	0.65
Non-vested at December 31, 2019	2,945,585	$ 0.73
Granted	2,536,850	2.11
Vested	(1,519,493)	0.71
Forfeited	(191,600)	0.69
Non-vested at December 31, 2020	3,771,342	$ 1.66

For the years ended December 31, 2020 and 2019, the Company recorded $1.1 million and $0.5 million, respectively, in stock-based compensation expense related to RSUs, which is reflected in the statements of operations and comprehensive loss.

As of December 31, 2020, there was $6.1 million of total unrecognized compensation expense related to unvested RSUs that will be recognized over the weighted average remaining period of 3.57 years.

Shares Available for Future Grant

At December 31, 2020, the Company has the following shares available to be granted:

	2013 Plan	Inducement Plan
Available at December 31, 2019	4,394,301	205,000
Authorized	3,768,550	—
Granted	(5,014,336)	—
Shares withheld for taxes not issued	477,255	—
Forfeited/Cancelled	427,731	47,500
Available at December 31, 2020	4,053,501	252,500

Shares Reserved for Future Issuance

At December 31, 2020, the Company has reserved the following shares of common stock for issuance:

Stock options outstanding under 2013 Plan	9,317,019
Restricted stock units outstanding under 2013 Plan	3,771,342
Shares reserved for future issuance under 2013 Plan	4,053,501
Stock options outstanding under Inducement Plan	247,500
Shares reserved for future issuance under Inducement Plan	252,500
Shares reserved for future issuance under 2013 Employee Stock Purchase Plan	225,806
Warrants outstanding	295,591
Total shares of common stock reserved for future issuance	18,163,259

8. Commitments and Contingencies

Leases

The Company leases office space in Chesterbrook, Pennsylvania and equipment. The Company's principal office is located at 955 Chesterbrook Boulevard, Chesterbrook, Pennsylvania, where the Company currently leases approximately 8,231 square feet of developed office space on the first floor and 40,565 square feet of developed office space on the second floor. The lease term for this space extends through May 2028. On October 11, 2018, the Company entered into an agreement with The Vanguard Group, Inc., or Vanguard, whereby Vanguard agreed to sublease the 40,565 square feet of space on the second floor for an initial term of37 months. On October 2, 2020, Vanguard notified the Company that they exercised the first option to extend the sublease term for three years through November 30, 2024. Vanguard has a second option to extend the sublease term for an additional three years through November 30, 2027. The sublease provides for rent abatement for the first month of the term; thereafter, the rent payable to the Company by Vanguard under the sublease is (i) $0.50 less during months 2 through 13 of the sublease and (ii) in month 14 and thereafter of the sublease, $1.00 less than the base rent payable by the Company under its master lease with Chesterbrook Partners, L.P. Vanguard also is responsible for paying to the Company all tenant energy costs, annual operating costs, and annual tax costs attributable to the subleased space during the term of the sublease. Rent expense and associated sublease income are recorded in the Company's statements of operations and comprehensive loss as other income (expense).

Supplemental balance sheet information related to leases was as follows (in thousands):

	December 31, 2020	December 31, 2019
Operating leases:		
Operating lease right-of-use assets	$ 5,119	$ 5,472
Other current liabilities	696	611
Operating lease liabilities	7,097	7,793
Total operating lease liabilities	$ 7,793	$ 8,404
Finance leases:		
Property and equipment, at cost	$ 45	$ 45
Accumulated depreciation	(34)	(25)
Property and equipment, net	11	20
Other current liabilities	7	9
Other long-term liabilities	4	11
Total finance lease liabilities	$ 11	$ 20

The components of lease expense were as follows (in thousands):

	Year Ended December 31,	
	2020	2019
Operating lease costs:		
Operating lease rental expense	$ 1,256	$ 1,187
Other income	(1,195)	(1,263)
Total operating lease costs	$ 61	$ (76)
Finance lease costs:		
Amortization of right-of-use assets	$ 9	$ 11
Interest on lease liabilities	1	2
Total finance lease costs	$ 10	$ 13

Supplemental cash flow information related to leases was as follows (in thousands):

	Year Ended December 31,	
	2020	2019
Cash paid for amounts included in the measurement of lease liabilities		
Operating cash flows from operating leases	$ (179)	$ (167)
Operating cash flows from finance leases	—	—
Financing cash flows from finance leases	(10)	(12)

Our operating lease liabilities will mature, as follows (in thousands):

	Operating Leases	Financing Leases
2021	$ 1,376	$ 8
2022	1,401	4
2023	1,425	—
2024	1,450	—
2025 and beyond	5,136	—
Total minimum lease payments	$ 10,788	$ 12
Interest Expense	(2,995)	(1)
Lease liability	$ 7,793	$ 11

Per the terms of our sublease, we expect the following inflows (in thousands):

	Sublease
2021	$ 1,098
2022	1,118
2023	1,139
2024	996
2025 and beyond	—
Total minimum lease payments	$ 4,351

Weighted average lease term and discount rates are as follows:

	Year Ended December 31,	
	2020	2019
Weighted average remaining lease term (years)		
Operating leases	7	8
Finance leases	1	2
Weighted average discount rate		
Operating leases	9.2%	9.2%
Finance leases	6.5%	6.5%

The Company had no deferred rent at December 31, 2020 or 2019 related to its facility leases.

Legal Proceedings

In October and November 2018, the Company and certain current and former officers and directors were sued inthree purported class actions filed in the U.S. District Court for the Eastern District of Pennsylvania, or the EDPA, alleging violations of the federal securities laws. In January 2019, the three lawsuits were consolidated into one action, and on May 29, 2019, the District Court appointed a group of five individual investors as lead plaintiffs. A consolidated amended complaint was filed on August 2, 2019, alleging, among other things, that the Company and two former officers made false and misleading statements regarding the Company's business, operations, and prospects, including certain statements made relating to the Company's End-of-Phase 2 meeting with the FDA, and certain statements concerning top-line results from the Company's Phase 3 studies. The plaintiffs seek, among other remedies, unspecified damages, attorneys' fees and other costs, and unspecified equitable or injunctive relief. On August 28, 2020, the EDPA granted in part and denied in part the defendants' motion to dismiss. On October 2, 2020, the Company and the individual defendants filed their answer to the amended complaint, denying all liability. On February 11, 2021, the parties agreed in principle to a settlement, which is subject to final documentation and approval by the Court. The Company and the individual defendants do not acknowledge any wrongdoing as part of the settlement, and a monetary payment of $8.5 million will be made to the plaintiffs and their counsel, all of which will be funded by the Company's insurance carriers. The Company has recorded the $8.5 million estimated settlement liability and the $8.5 million

estimated insurance recovery in its 2020 financial statements. The Company continues to believe that the claims are without merit, and if necessary, the Company intends to vigorously defend itself and its former officers against the allegations.

In December 2018, a shareholder derivative action was filed on behalf of the Company and against certain current and former officers and directors in the EDPA, and in February 2019, two additional, similar shareholder derivative actions were filed in the U.S. District Court for the District of Delaware. A fourth similar shareholder derivative action was filed in the EDPA in September 2019, and a fifth, similar derivative action was filed in the EDPA in November 2019. A similar sixth derivative action was filed in the EDPA in September 2020. These cases, which involve facts similar to the consolidated securities lawsuits, assert claims against the individual defendants for, among other things, breach of fiduciary duty, waste of corporate assets, violations of the federal securities laws, and unjust enrichment, and they make a number of demands, including for monetary damages and other equitable and injunctive relief. Some of the derivative actions have been stayed in favor of the consolidated securities lawsuits. The Company recorded in the fourth quarter of 2020 an estimated liability of $0.5 million and a corresponding insurance recovery of the same amount.

9. Product Revenue

Performance Obligation

The Company's performance obligation is the supply of finished pharmaceutical products to its customers. The Company's customers consist of major wholesale distributors. The Company's customer contracts generally consist of both a master agreement, which is signed by the Company and its customer, and a customer submitted purchase order, which is governed by the terms and conditions of the master agreement.

Revenue is recognized when the Company transfers control of its products to the customer, which occurs at a point-in-time, upon delivery.

The Company offers standard payment terms to its customers and has elected the practical expedient to not adjust the promised amount of consideration for the effects of a significant financing, since the period between when the Company transfers the product to the customer and when the customer pays for that product is one year or less. Taxes collected from customers relating to product revenue and remitted to governmental authorities are excluded from revenues. The consideration amounts due from customers as a result of product revenue are subject to variable consideration, as described further below.

The Company offers standard product warranties which provide assurance that the product will function as expected and in accordance with specifications. Customers cannot purchase warranties separately and these warranties do not give rise to a separate performance obligation. The Company permits the return of product under certain circumstances, mainly upon at or near product expiration, instances of shipping errors or where product is damaged in transit. The Company accrues for the customer's right to return as part of its variable consideration. See below for further details.

Variable Consideration

The Company includes an estimate of variable consideration in its transaction price at the time of sale, when control of the product transfers to the customer. Variable consideration includes distributor chargebacks, prompt payment (cash) discounts, distribution service fees and product returns.

The Company assesses whether or not an estimate of its variable consideration is constrained and has determined that the constraint does not apply, since it is probable that a significant reversal in the amount of cumulative revenue will not occur in the future when the uncertainty associated with the variable consideration is subsequently resolved. The Company's estimates for variable consideration are adjusted as required at each reporting period for specific known developments that may result in a change in the amount of total consideration it expects to receive.

Distributor Chargebacks

When a product that is subject to a contractual price agreement is sold to a third party, the difference between the price paid to the Company by the wholesaler and the price under the specific contract is charged back to the Company by the wholesaler. Utilizing this information, the Company estimates a chargeback percentage for each product and records an allowance for chargebacks as a reduction to revenue when the Company records sales of the products. We reduce the chargeback allowance when a chargeback request from a wholesaler is processed. Reserves for distributor chargebacks are included in accounts receivable, net on the consolidated balance sheet.

Prompt Payment (Cash) Discounts

The Company provides customers with prompt payment discounts which may result in adjustments to the price that is invoiced for the product transferred, in the case that payments are made within a defined period. The Company's prompt payment discount reserves are based on actual net sales and contractual discount rates. Reserves for prompt payment discounts are included in accounts receivable, net on the consolidated balance sheet.

Distribution Service Fees

The Company pays distribution service fees to its customers based on a fixed percentage of the product price. These fees are not in exchange for a distinct good or service and therefore are recognized as a reduction of the transaction price. The Company reserves for these fees based on actual net sales, contractual fee rates negotiated with the customer and the mix of the products in the distribution channel that remain subject to fees. Reserves for distribution service fees are included in accounts receivable, net on the consolidated balance sheet.

Product Returns

Generally, the Company's customers have the right to return any unopened product during the eighteen (18) month period beginning six (6) months prior to the labeled expiration date and endingtwelve (12) months after the labeled expiration date. Six (6) months following the launch of OLINVYK, the Company's customers may have the right to return inventory remaining from their initial purchase, if any, subject to certain terms and conditions. Since the Company currently does not have a history of OLINVYK returns, the Company estimates returns based on industry data for comparable products in the market. As the Company distributes its product and establishes historical sales over a longer period of time (i.e., two to three years), the Company will be able to place more reliance on historical purchasing, demand and return patterns of its customers when evaluating its reserves for product returns. OLINVYK has a forty-eight (48) month shelf life.

The Company recognizes the amount of expected returns as a refund liability, representing the obligation to return the customer's consideration. Since the returns primarily consist of expired and short dated products that will not be resold, the Company does not record a return asset for the right to recover the goods returned by the customer at the time of the initial sale (when recognition of revenue is deferred due to the anticipated return). Accrued product return estimates are recorded in accrued expenses and other current liabilities on the consolidated balance sheet.

Concentration of Revenue

Two of the Company's largest customers account for 100% of total product revenue for the year ended December 31, 2020.

The following table presents a rollforward of the major categories of sales-related deductions included in trade receivable allowances for the year ended December 31, 2020 (in thousands):

	Sales Discounts	Chargebacks	Fee for Service
Balance, January 1, 2020	$ —	$ —	$ —
Provision related to current period sales	2	5	10
Adjustment related to prior period sales	—	—	—
Credit or payments made during the period	—	—	—
Balance, December 31, 2020	$ 2	$ 5	$ 10

10. License Revenue

License and Commercialization Agreement with Pharmbio Korea Inc.

In April 2018, the Company entered into an exclusive license agreement with Pharmbio Korea Inc., or Pharmbio, for the development and commercialization of OLINVYK for the management of moderate to severe acute pain in South Korea. Under the terms of the agreement, the Company received an upfront, non-refundable cash payment of $3.0 million (less applicable withholding taxes of $0.5 million) in June 2018, and will receive a cash commercial milestone of up to $0.5 million if OLINVYK is approved in South Korea and tiered royalties on product sales in South Korea ranging from high single digits to 20%, less applicable withholding taxes. As part of the agreement, the Company also granted Pharmbio an option to manufacture OLINVYK, on a non-exclusive basis, for the development and commercialization of the product in South Korea, subject to a separate arrangement to be entered into if Pharmbio exercises the option. The license agreement is terminable by Pharmbio for any reason upon 180 days written notice.

In accordance with the terms of the agreement, Pharmbio is solely responsible for all development and regulatory activities in South Korea. The parties have formed a Joint Development Committee with equal representation from the Company and Pharmbio to provide overall coordination and oversight of the development of OLINVYK in South Korea. The parties also agreed to form a Joint Manufacturing and Commercialization Committee at least six months prior to the anticipated date of regulatory approval of OLINVYK in South Korea to provide overall coordination and oversight of the manufacture and commercialization of OLINVYK in South Korea.

License Agreement with Jiangsu Nhwa Pharmaceutical Co. Ltd.

In April 2018, the Company also entered into an exclusive license agreement with Jiangsu Nhwa Pharmaceutical Co. Ltd., or Nhwa, for the development and commercialization of OLINVYK for the management of moderate to severe acute pain in China. Under the terms of this agreement, the Company received an upfront, non-refundable cash payment of $2.5 million (less applicable withholding taxes of $0.3 million) in July 2018. In August 2020, the Company received a milestone payment of $3.0 million (less applicable withholding taxes of $0.3 million), that became payable by Nhwa upon FDA approval of OLINVYK. The Company is also eligible to receive a cash milestone payment of $3.0 million, subject to Chinese withholding taxes, upon regulatory approval of OLINVYK in China, up to an additional $6.0 million of commercialization milestone payments based on product sales levels in China, and a ten percent royalty on all net product sales in China, less applicable withholding taxes. As part of the agreement, the Company also granted Nhwa an option to manufacture OLINVYK, on an exclusive basis in China, for the development and commercialization of the product in China. In the second quarter of 2018, Nhwa elected to exercise this manufacturing option and the Company and Nhwa expect to enter into a separate agreement for such services. The license agreement is terminable by Nhwa for any reason upon 180 days written notice.

In accordance with the terms of the agreement, Nhwa is solely responsible for all development and regulatory activities in China. The parties have formed a Joint Development Committee with equal representation from the Company and Nhwa to provide overall coordination and oversight of the development of OLINVYK in China. The parties also agreed to form a Joint Manufacturing and Commercialization Committee at least six months prior to the anticipated date of regulatory approval of OLINVYK in China to provide overall coordination and oversight of the manufacture and commercialization of OLINVYK in China.

For the year ended December 31, 2020 and 2019, license revenue in the accompanying statements of operations and comprehensive loss is comprised of the following:

	Year Ended December 31,	
	2020	2019
Pharmbio Korea Inc.	$ —	$ —
Jiangsu Nhwa Pharmaceutical Co. Ltd.	3,000	31
Total license revenues	$ 3,000	$ 31

11. Restructuring Charges

On November 8, 2018, upon the approval of the Company's Board of Directors, the Company announced a restructuring of approximately one-third of the Company's workforce, or 14 employees, as well as other cost saving initiatives intended to lower the Company's annualized net operating cash burn. The Company completed the restructuring on December 31, 2018. The Company determined that the total costs related to the restructuring were approximately $1.4 million, all of which resulted in future cash outlays, primarily related to severance costs and benefit-related expenses. The Company recorded these charges in the fourth quarter of 2018.

The following table summarizes the restructuring balances at December 31, 2020 and 2019 (in thousands):

	Year Ended December 31,	
	2020	2019
Balance, January 1	$ —	$ 1,419
Current year restructuring costs	—	—
Payment of employee severance costs	—	(1,419)
Balance, December 31	$ —	$ —

12. 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,	
	2020	2019
Basic and diluted net loss per common share calculation:		
Net loss	$ (29,369)	$ (24,871)
Net loss attributable to common stockholders	$ (29,369)	$ (24,871)
Weighted average common shares outstanding	127,623,859	91,677,963
Net loss per share of common stock - basic and diluted	$ (0.23)	$ (0.27)

The following outstanding securities at December 31, 2020 and 2019 have been excluded from the computation of diluted weighted shares outstanding, as they would have been anti-dilutive:

	December 31,	
	2020	2019
Options outstanding	9,564,519	7,568,304
RSUs outstanding	3,771,342	2,945,585
Warrants	295,591	623,091
Total	13,631,452	11,136,980

13. 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, 2019	$ (9)
Net unrealized gain on marketable securities	9
Balance, December 31, 2019	$ —
Net unrealized gain on marketable securities	—
Balance, December 31, 2020	$ —

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

14. Income Taxes

The income tax provision for the years ended December 31, 2020 and 2019 are as follows (in thousands):

	December 31,	
	2020	2019
Current:		
Foreign	$ 300	$ —
Federal	—	—
State	—	—
Total	300	—
Deferred		
Foreign	—	—
Federal	—	—
State	—	—
Total	—	—
Total income tax provision (benefit)	$ 300	$ —

Deferred tax assets and liabilities reflect the net effects of net operating losses, or NOLs, 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. Realization of the deferred tax assets is contingent on future taxable income and based upon the level of historical losses, management has concluded that the deferred tax assets do not meet the more-likely-than-not threshold for realizability. Accordingly, a full valuation allowance continues to be recorded against the Company's deferred tax assets as of December 31, 2020 and 2019. The Company’s valuation allowance increased by $5.9 million and $9.0 million for the years ended December 31, 2020 and 2019, respectively.

Significant components of the Company's net deferred tax assets as of December 31, 2020 and 2019 are as follows (in thousands):

	December 31,	
	2020	2019
Deferred tax assets:		
NOLs	$ 25,949	$ 22,033
Research and development credits	14,920	14,138
Research and development expenses capitalized for tax purposes	93,812	92,350
Equity-based compensation	4,130	4,586
Deferred rent	772	847
Depreciation	246	162
Other temporary differences	730	538
Total deferred tax assets	140,559	134,654
Deferred tax liabilities:		
Prepaid expenses	(119)	(86)
Total deferred tax liabilities	(119)	(86)
Net deferred tax assets	140,440	134,568
Less valuation allowance	(140,440)	(134,568)
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,	
	2020	2019
Percent of pre-tax income:		
U.S. federal statutory income tax rate	21.0 %	21.0 %
Permanent Differences	1.0 %	— %
State taxes, net of federal benefit	4.8 %	8.3 %
Research and development credit	2.6 %	3.4 %
Withholding Tax	(1.0)%	— %
Stock compensation	(6.9)%	— %
Other	(2.3)%	3.3 %
Change in valuation allowance	(20.2)%	(36.0)%
Effective income tax rate	(1.0)%	— %

As of December 31, 2020, the Company had U.S. federal and state NOLs of $90.2 million and $88.8 million, respectively, that begin to expire starting in 2027. As of December 31, 2020, the Company had federal research and development tax credit carryforwards of $14.9 million that begin to expire in 2027. Net operating loss and tax credit carryforwards may become subject to annual limitations in the event of certain cumulative changes in the ownership interest of significant stockholders over a three-year period in excess of 50%, as defined by Sections 382 and 383 of the Internal Revenue Code as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities.

The Company files income tax returns in the U.S. and the Commonwealth of Pennsylvania. Tax years for 2017 and thereafter 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 any tax attributes from a tax period that may otherwise be closed due to statute expiration, the Internal Revenue Service, state tax authorities, or other governing parties may still adjust the tax attributes upon their examination of the future period in which the attribute was utilized. There are no uncertain tax positions recorded for any federal or state positions. The Company's policy is to record interest and penalties related to tax matters in income tax expense.

15. 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 each of the years ended December 31, 2020 and 2019, the Company provided matching contributions of $0.2 million.

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 Exchange Act as of December 31, 2020.

Based on that evaluation, our management, including our CEO and CFO, concluded that as of December 31, 2020 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

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.

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information concerning our executive offers required by this Item 10 is provided under the caption "Information about our Executive Officers" in Part I, Item 1 of this Annual Report on Form 10-K. All other information required by this Item 10 is incorporated herein by reference to the information responsive thereto contained in our definitive proxy statement related to the 2021 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 responsive thereto contained in our definitive proxy statement related to the 2021 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

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, 2020:

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
Equity compensation plans approved by stockholders	13,088,361	$ 3.11	4,053,501
Equity compensation plans not approved by stockholders	247,500	1.78	252,500
Total	13,335,861	$ 3.08	4,306,001

(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 4,053,501 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, 2020, 252,500 shares remain eligible for issuance under the Inducement Plan.

Other

The other information required by Item 12 is incorporated by reference to the information responsive thereto contained in our definitive proxy statement related to the 2021 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 responsive thereto contained in our definitive proxy statement related to the 2021 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 ACCOUNTING FEES AND SERVICES

The information required by Item 14 is incorporated by reference to the information responsive thereto contained in our definitive proxy statement related to the 2021 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, 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	Certificate of Amendment of Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to Registrant's Current Report on Form 8-K, filed with the SEC on May 21, 2018).
3.3	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 3.3.
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 the Registrant's Current Report on Form 8-K, filed with the SEC on December 23, 2015).
4.4	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).
4.5	Form of Warrant issued by Trevena, Inc. to H.C. Wainwright & Co., LLC or its designees (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K, filed with the SEC on February 1, 2019).
4.6	Description of the Registrant's Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1934 (incorporated by reference to Exhibit 4.6 to the Registrant's Annual Report on Form 10-K filed with the SEC on March 12, 2020).
10.1	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), filed with the SEC on October 9, 2013).
10.2	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 the Registrant's Annual Report on Form 10-K filed with the SEC on March 8, 2017).
10.3	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 the Registrant's Quarterly Report on Form 10-Q filed with the SEC on August 3, 2017).
10.4	Sublease Agreement dated as of October 11, 2018 by and between The Vanguard Group, Inc. and Trevena, Inc. (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed with the SEC on November 8, 2018).
10.5+	2008 Equity Incentive Plan, as amended to date (incorporated by reference to Exhibit 10.9 to the Registrant's Registration Statement on Form S 1, as amended (File No. 333 191643), filed with the SEC on October 9, 2013).
10.6+	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), filed with the SEC on October 9, 2013).
10.7+	2013 Equity Incentive Plan (incorporated by reference to Exhibit 99.1 to the Registrant's Registration Statement on Form S 8 (File No. 333 195957), filed with the SEC on May 14, 2014).

10.8+	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), filed with the SEC on October 9, 2013).
10.9+	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).
10.10+	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), filed with the SEC on October 9, 2013).
10.11+	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).
10.12+	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).
10.13+	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).
10.14+	Trevena, Inc. Incentive Compensation Plan, effective as of January 1, 2015 (incorporated by reference toExhibit 10.1 to Registrant's Current Report on Form 8-K, filed with the SEC on January 5, 2015).
10.15+	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).
10.16+	Trevena, Inc. Non-Employee Director Compensation Policy, effective as of February 28, 2018 (incorporated by reference to Exhibit 10.1 to the Registrant's Form 8-K filed with the SEC on March 2, 2018).
10.17+	2013 Employee Stock Purchase Plan (incorporated by reference toExhibit 10.15 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-191643), filed with the SEC on October 9, 2013).
10.18+	Form of Indemnity Agreement with executives and directors (incorporated by reference toExhibit 10.16 to the Registrant's Registration Statement on Form S-1, as amended (File No. 333-191643), filed with the SEC on October 9, 2013).
10.19+	Executive Employment Agreement dated as of February 10, 2020 by and between Trevena, Inc. and Scott Applebaum (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form10-Q, filed with the SEC on May 7, 2020).
10.20+	Amended and Restated Executive Employment Agreement dated as of May 1, 2020, by and between Trevena, Inc. and Carrie L. Bourdow (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed with the SEC on May 7, 2020).
10.21+	Amended and Restated Executive Employment Agreement dated as of May 1, 2020 by and between Trevena, Inc. and Mark A. Demitrack (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q, filed with the SEC on May 7, 2020).
10.22+	Amended and Restated Executive Employment Agreement dated as of May 1, 2020 by and between Trevena, Inc. and Robert T. Yoder (incorporated by reference to Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed with the SEC on May 7, 2020).
10.23+	Amended and Restated Executive Employment Agreement dated as of May 1, 2020 by and between Trevena, Inc. and Barry Shin (incorporated by reference to Exhibit 10.5 to Registrant's Quarterly Report on Form 10-Q filed with the SEC on May 7, 2020).
10.24	Loan and Security Agreement, dated September 19, 2014, by and among Trevena, Inc., as borrower, Oxford Finance LLC, as collateral agent and lender, and Square 1 Bank, as lender (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, filed with the SEC on September 22, 2014).
10.25	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).

10.26	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).
10.27	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).
10.28	Fourth Amendment and Consent to Loan and Security Agreement dated as of October 11, 2018 by and between Oxford Finance LLC, Pacific Western Bank, and Trevena, Inc. (incorporated by reference to Exhibit 10.2 to Registrant's Quarterly Report on Form 10-Q, filed with the SEC on November 8, 2018).
10.29*	Master Commercial Supply Agreement dated October 20, 2017 by and between Alcami Corporation and Trevena, Inc. (incorporated by reference to Exhibit 10.45 to Registrant's Annual Report on Form 10-K/A filed with the SEC on June 14, 2018).
10.30*	Development and Supply Agreement by and between Pfizer, Inc. and Trevena, Inc. dated as of December 15, 2016 (incorporated by reference to Exhibit 10.46 to Registrant's Annual Report on Form 10-K/A filed with the SEC on June 14, 2018).
10.31	Amendment No. 2 to Development and Supply Agreement by and between Pfizer, Inc. and Trevena, Inc., dated December 2, 2019 (incorporated by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K, filed with the SEC on December 9, 2019).
10.32	Common Stock Sales Agreement, dated April 17, 2019, by and between Trevena, Inc. and H.C. Wainwright & Co., LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K, filed with the SEC on April 17, 2019).
10.33	Amendment No, 1 to Common Stock Sales Agreement, dated December 31, 2020, by and between Trevena, Inc. and H.C. Wainwright & Co., LLC (incorporated by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K, filed with the SEC on December 31, 2020).
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, 2020 and 2019, formatted in Inline XBRL (eXtensible Business Reporting Language): (i) Balance Sheets as of December 31, 2020 and 2019, (ii) Statements of Operations and Comprehensive Loss for the years ended December 31, 2020 and 2019, (iii) Statement of Redeemable Convertible Preferred Stock and Stockholders' Equity as of December 31, 2020 and 2019, (iv) Statements of Cash Flows for the years ended December 31, 2020 and 2019 and (v) Notes to Financial Statements, tagged as blocks of text.
104#	Cover Page Interactive Data File – The cover page interactive data file does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document.

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 9, 2021

TREVENA, INC.
By: /s/ Carrie L. Bourdow

Carrie L. Bourdow
President and Chief Executive Officer
(Principal 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/ Carrie L. Bourdow Carrie L. Bourdow	President, Chief Executive Officer and Director (Principal Executive Officer)	March 9, 2021
/s/ Barry Shin Barry Shin	Chief Financial Officer (Principal Financial and Accounting Officer)	March 9, 2021
/s/ Leon O. Moulder, Jr. Leon O. Moulder, Jr	Chairman, Board of Directors	March 9, 2021
/s/ Maxine Gowen Maxine Gowen, Ph.D.	Director	March 9, 2021
/s/ Scott Braunstein Scott Braunstein, M.D.	Director	March 9, 2021
/s/ Michael R. Dougherty Michael R. Dougherty	Director	March 9, 2021
/s/ Julie H. McHugh Julie H. McHugh	Director	March 9, 2021
/s/ Jake R. Nunn Jake R. Nunn	Director	March 9, 2021
/s/ Anne M. Phillips Anne M. Phillips, M.D.	Director	March 9, 2021
/s/ Barbara Yanni Barbara Yanni	Director	March 9, 2021

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

1) Registration Statement (Form S-8 No. 333-193735) pertaining to the 2008 Equity Incentive Plan, the 2013 Equity Incentive plan and the 2013 Employee Stock Purchase Plan of Trevena, Inc.
2) Registration Statements (Form S-8 Nos. 333-195957, 333-201672, 333-208948, 333-215421, 333-222471, 333-229161, 333-235942, and 333-252350) pertaining to the 2013 Equity Incentive Plan of Trevena, Inc.
3) Registration Statement (Form S-8 No. 333-215420) pertaining to the Trevena, Inc. Inducement Plan.
4) Registration Statement (Form S-3 No. 333-225685) of Trevena Inc.
5) Registration Statement (Form S-3 No. 333-251006) of Trevena Inc.

of our report dated March 9, 2021, with respect to the financial statements of Trevena, Inc included in this Annual Report (Form 10-K) of Trevena, Inc. for the year ended December 31, 2020.

/s/ Ernst & Young LLP

Philadelphia, Pennsylvania
March 9, 2021

Exhibit 31.1

Certification of Principal Executive Officer of Trevena, Inc.
Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Carrie L. Bourdow, 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 Rules13a-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 9, 2021

/s/ CARRIE L. BOURDOW
Carrie L. Bourdow
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, Barry Shin, 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 Rules13a-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 9, 2021

/s/ BARRY SHIN
Barry Shin
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, 2020, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Carrie L. Bourdow, 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 9, 2021

/s/ CARRIE L. BOURDOW
Carrie L. Bourdow
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, 2020, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Barry Shin, Chief Financial Officer, 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 9, 2021

/s/ BARRY SHIN
Barry Shin
Chief Financial Officer
(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.