TREVENA INC
Form 10-K
March 07, 2018
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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K
(Mark
One)

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

For the fiscal year ended December 31, 2017
or

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

For the transition period from to
Commission File Number 001 36193
Trevena, Inc.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	26 1469215
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
955 Chesterbrook Blvd., Suite 200, Chesterbrook, PA	19087
(Address of Principal Executive Offices)	(Zip Code)

Registrant’s telephone number, including area code: (610) 354 8840
Securities registered pursuant to Section 12(b) of the Act:

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

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

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Indicate by check mark if the registrant is a well known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes No
Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No
Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes No
Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S K is not contained herein, and will not be contained, to the best of the registrant’s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10 K or any amendment to this Form 10 K.
Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non accelerated filer, or a smaller reporting company. See the definitions of “large accelerated filer,” “accelerated filer,” and “smaller reporting company” in Rule 12b 2 of the Exchange Act.:

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

Emerging growth company

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

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

The aggregate market value of the voting stock held by non affiliates of the registrant, as of June 30, 2017, the last business day of the registrant's most recently completed second fiscal quarter, was approximately $94.0 million. Such aggregate market value was computed by reference to the closing price of the Common Stock as reported on the NASDAQ Global Select Market on June 30, 2017. For purposes of making this calculation only, the registrant has defined affiliates as including only directors and executive officers and shareholders holding greater than 10% of the voting stock of the registrant as of June 30, 2017.

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

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DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2018 annual meeting of stockholders to be filed pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2017 are incorporated by reference into Part III of this Form 10 K.

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Cautionary Note Regarding Forward Looking Statements

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

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

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

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PART I

ITEM 1. BUSINESS

Overview

Trevena, Inc. is a biopharmaceutical company developing innovative therapies based on breakthrough science to benefit patients and healthcare providers confronting serious medical conditions. Unless the context otherwise requires, we use the terms “Trevena,” “company,” “we,” “us” and “our” to refer to Trevena, Inc.

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

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

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

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

Our Pipeline

OLINVO™ (oliceridine) Injection

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

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

Disease and treatment options

The typical treatment paradigm in the U.S. for the management of moderate to severe acute pain is to initiate injectable or IV pain medication in the preoperative or immediate postoperative period to provide rapid and effective pain relief. Conventional IV opioid analgesics, such as morphine, fentanyl, and hydromorphone, are the mainstays of pain management in the immediate postoperative period and are approximately 50% of the injectable analgesic unit market. The effectiveness of conventional opioid agonists is limited because of severe side effects such as respiratory depression, nausea, vomiting, and constipation. Injectable non opioid analgesics are often used together with IV opioids for post surgical pain management; however, these drugs, such as IV non steroidal anti inflammatory drugs, or NSAIDs, IV acetaminophen, or local anesthetics such as bupivacaine, have potential cardiovascular, hepatic and gastrointestinal side effects. None of these non opioid analgesic approaches has displaced the use of opioid analgesics as the cornerstone of IV therapy for acute moderate-to-severe pain. We believe that there remains significant unmet need for an effective analgesic agent with an improved safety and tolerability profile.

Clinical development

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

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

ATHENA Phase 3 Open Label Safety Study

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

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

APOLLO-1 and APOLLO-2 Phase 3 Studies

We have conducted two pivotal efficacy trials evaluating OLINVO in patients with moderate-to-severe acute pain: the APOLLO-1 study, which evaluated pain for 48 hours following bunionectomy, and the APOLLO-2 study, which evaluated pain for 24 hours following abdominoplasty. In February 2017, we announced positive top-line results from

the APOLLO-1 and APOLLO-2 studies. In both studies, all dose regimens achieved the primary endpoint of statistically greater analgesic efficacy than placebo, as measured by responder rate.

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

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

APOLLO-1 (bunionectomy)

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

APOLLO-2 (abdominoplasty)

- All three OLINVO dose regimens achieved the primary endpoint with statistically superior responder rates compared to placebo at 24 hours (adjusted $p<0.05$ for the 0.1 mg regimen; adjusted $p<0.001$ for the 0.35 mg and 0.5 mg regimens).
- The 0.35 mg and 0.5 mg OLINVO dose regimens demonstrated efficacy comparable to morphine at 24 hours based on responder rate ($p<0.05$ for non-inferiority of the 0.35 mg regimen vs. morphine). Both doses were also comparable to morphine for rates of rescue analgesic use.
- Following the 1.5 mg initial loading dose, all OLINVO regimens demonstrated rapid onset with statistically significant efficacy within 5 to 15 minutes ($p<0.05$).

- OLINVO showed a dose-related trend of improved respiratory safety burden in all three OLINVO dose regimens ($p<0.05$ for the 0.1 mg regimen vs. morphine). Consistent with this, for all dose regimens OLINVO showed dose-related trends of reduced respiratory safety events, prevalence of oxygen desaturation ($O2<90\%$) and lower prevalence of supplemental oxygen use ($p<0.05$ for the 0.1 mg regimen vs. morphine for all measures).
- OLINVO showed a dose-related trend of less antiemetic use than morphine for all three OLINVO regimens ($p<0.05$ for the 0.1 mg OLINVO regimen vs. morphine). Consistent with this, OLINVO showed dose-related trends of lower prevalence of nausea and vomiting ($p<0.05$ for the 0.1 mg regimen vs. morphine for both nausea and vomiting; $p<0.05$ for the 0.35 mg regimen vs. morphine for vomiting).

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

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

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

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

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

The aim of our Phase 2a/b clinical trial was to evaluate the efficacy and tolerability of OLINVO in the management of postoperative pain using morphine as a benchmark, using fixed dose and dose interval to characterize the performance of OLINVO. The trial was a multicenter, randomized, double blind, placebo and active controlled, multiple dose, adaptive trial in 333 women and men undergoing a primary unilateral first metatarsal bunionectomy surgery at four sites in the United States. Patients were randomized after surgery to receive OLINVO, morphine or placebo to manage their pain. Pain intensity was measured using validated numeric rating scales ranging from ten (most severe pain) to zero (no pain) at multiple time points up to 48 hours. Based on these scales, analgesic efficacy was assessed with a time weighted average change in pain score over 48 hours—a well established measure of changes in the intensity of pain over time and an FDA recommended endpoint for pain studies.

In November 2014, we announced top line data from this trial. At doses of 2 mg and 3 mg of OLINVO administered every three hours, the trial achieved its primary endpoint of statistically greater pain reduction than placebo for 48 hours, which we believe demonstrated proof of concept for OLINVO. Over the 48 hour trial period, the 3 mg dose of OLINVO administered every three hours also showed statistically superior analgesic efficacy compared to the 4 mg dose of morphine administered every four hours. Additionally, in the first three hours of dosing, when pain was most severe, the 1 mg, 2 mg, and 3 mg doses of OLINVO demonstrated superior analgesic efficacy in the trial compared to placebo, and the 2 mg, and 3 mg doses of OLINVO demonstrated superior analgesic efficacy compared to the 4 mg dose of morphine.

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

Phase 1 clinical studies of OLINVO

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

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

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

Regulatory

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

Commercialization

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

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

capital.

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

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

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

Manufacturing

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

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

Competition

If OLINVO is approved for IV management of moderate-to-severe acute pain, it will compete with generic IV opioid analgesics, such as morphine, hydromorphone and fentanyl. The analgesic effectiveness of these agents is limited by well known adverse side effects, such as respiratory depression, nausea, vomiting, constipation, and post operative ileus. OLINVO also may compete against, or be used in combination with, OFIRMEV® (IV acetaminophen), marketed by Mallinckrodt plc, EXPAREL® (liposomal bupivacaine), marketed by Pacira Pharmaceuticals, Inc., CALDOLOR® (IV ibuprofen), marketed by Cumberland Pharmaceuticals, and DYLOJECT™ (IV diclofenac) marketed by Hospira. Together with generic versions of IV NSAIDs such as ketorolac, and generic versions of local anesthetics such as bupivacaine, these non opioid analgesics are currently used in combination with opioids in the multimodal management of moderate-to-severe acute pain.

We also are aware of a number of products in mid- and late-stage clinical development that are aimed at improving the treatment of moderate-to-severe acute pain and may compete with OLINVO. AcelRx Pharmaceuticals, Inc. is developing a range of acute pain products involving sufentanil oral nanotabs in hand held dispensers including DSUVIA™ and ZALVISO™. Innocoll Holdings plc. and Heron Therapeutics Inc. have proprietary long acting reformulations of bupivacaine in development. Recro Pharma, Inc. is developing an IV version of the NSAID meloxicam. Cara Therapeutics Inc. is developing IV and oral dose forms of a peripherally restricted opioid receptor agonist, which has been administered in combination with μ opioids in clinical trials. Avenue Therapeutics, Inc. is developing an IV version of generic opioid tramadol for moderate-to-severe acute pain.

Intellectual property

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

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TRV250

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

Based on the profile of TRV250, we believe it has the potential to be a first in class treatment for migraine. According to Decision Resources, a healthcare consulting company, the acute episodic migraine market encompassed approximately 12 million drug treated patients in 2013 in the United States, representing approximately $2.2 billion of sales. We estimate that approximately 20% to 30% of these patients either do not respond to, or cannot tolerate, the market leading triptan drug class, and an additional 30% would benefit from improved efficacy compared to these drugs.

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

Patients suffering from frequent or chronic migraine headaches may also use preventative agents to decrease the frequency and severity of migraines. Botox® is currently the most wide