August 10, 2020

Trevena Announces FDA Approval of OLINVYK™ (oliceridine) injection

OLINVYK is a new chemical entity approved in adults for the management of acute pain severe enough to require an IV opioid analgesic

OLINVYK product availability expected in fourth quarter of 2020

Company funded through year-end 2021, including OLINVYK commercialization

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Company to host conference call at 8:30 a.m., today, August 10, 2020

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CHESTERBROOK, Pa., Aug. 10, 2020 (GLOBE NEWSWIRE) -- **Trevena, Inc. (Nasdaq: TRVN)**, a biopharmaceutical company focused on the development and commercialization of novel medicines for patients with central nervous system (CNS) disorders, today announced that the U.S. Food and Drug Administration (FDA) has approved OLINVYK in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. OLINVYK will be commercially available when the U.S. Drug Enforcement Administration (DEA) issues its controlled substance schedule in approximately 90 days.

“The approval of OLINVYK marks an exciting step forward in Trevena’s mission of translating cutting-edge scientific discovery into therapeutic benefit for patients in need. I would like to thank all of the patients, investigators, and our employees who helped us achieve this important milestone,” said Carrie L. Bourdow, President and Chief Executive Officer. “We will work quickly to bring this novel IV analgesic to patients and healthcare providers in need of alternative treatment options.”

Each year, approximately 45 million hospital patients in the United States receive an IV opioid to treat their acute pain. Many of these patients are complex and difficult to treat, such as the elderly, obese, or renally-impaired. Current hospital trends suggest that the number of these complex patients is growing, representing an increasing burden on the healthcare system.

OLINVYK is an opioid agonist that is the first new chemical entity in this IV drug class in decades and offers a differentiated profile that addresses a significant unmet need 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.

The FDA approval of OLINVYK was based on results from the Phase 3 development

program, which evaluated OLINVYK in over 1,500 patients with moderate to severe acute pain. In two pivotal efficacy studies in hard- and soft-tissue surgical models, OLINVYK demonstrated rapid analgesic efficacy statistically significant vs. placebo. In a large, open-label, “real world” safety study, OLINVYK was safe and well-tolerated in a medically complex patient population, including the elderly, obese, and patients with comorbid conditions such as diabetes and sleep apnea.

“Complex patients present unique challenges in the management of their postoperative acute pain, due to the presence of medical comorbidities that can complicate dosing,” said Gregory Hammer, M.D., Professor of Anesthesiology, Perioperative and Pain Medicine, and of Pediatrics at Stanford University. “OLINVYK represents a new alternative for clinicians, due to its rapid onset of action, effective pain relief, and unique profile.”

The Company expects to make OLINVYK available in the fourth quarter of 2020 following scheduling by the DEA, which may take up to 90 days. The Company is committed to an ethical and responsible marketing campaign for OLINVYK and will have safeguards in place to monitor for and mitigate the risk of non-medical uses of OLINVYK.

The Company also today announced $54.8 million in cash and cash equivalents as of June 30, 2020, which the Company expects will be sufficient to fund operating expenses, including the commercialization of OLINVYK, through year-end 2021.

Conference Call and Webcast Information

The Company will host a conference call and webcast with the investment community on August 10, 2020, at 8:30 a.m. Eastern Time featuring remarks by Carrie Bourdow, President and Chief Executive Officer, Mark Demitrack, M.D., Chief Medical Officer, Robert Yoder, Chief Business Officer, and Barry Shin, Chief Financial Officer.

Title:	Conference Call to Provide Update Following Recent FDA Approval of OLINVYK
Date:	Monday, August 10, 2020
Time:	8:30 a.m. ET
Conference Call Details:	Toll-Free: 855-465-0180 International: 484-756-4313 Conference ID: 4976734
Webcast:	https://www.trevena.com/investors/events-presentations/ir-calendar

OLINVYK Efficacy and Safety Data

The efficacy of OLINVYK was established in two randomized, double-blind, placebo- and morphine-controlled studies which enrolled 790 patients with moderate to severe acute pain (pain intensity of ≥4 on a 0-10 numeric rating scale) after orthopedic surgery-bunionectomy or plastic surgery-abdominoplasty.

In each study, patients were randomized to one of three OLINVYK treatment regimens, a placebo-control regimen, or a morphine-control regimen. The loading dose for all OLINVYK treatment regimens was 1.5 mg; demand doses were 0.1, 0.35, or 0.5 mg, according to the assigned treatment group; supplemental doses were 0.75 mg. A lockout interval of 6 minutes was used for all PCA regimens. Etodolac 200 mg was available as rescue medication. Patients using the approved OLINVYK doses of 0.35 and 0.5 mg had a statistically

significantly greater SPID-48/24 than patients using placebo.

The most common adverse reactions (≥10%) in these controlled trials were nausea, vomiting, dizziness, headache, constipation, pruritus, and hypoxia. When stratified by the 27 mg daily dosing limit, discontinuation of OLINVYK due to adverse reactions occurred in 4% of patients who received a daily dose ≤27 mg, and less than 1% of patients who received a daily dose >27 mg.

In an open-label safety study of patients with moderate to severe acute pain following a surgical procedure or due to a medical condition, a total of 768 patients received at least one dose of OLINVYK. OLINVYK was administered via clinician-administered bolus dosing, PCA, or a combination of the two. Bolus dosing was initiated at 1 to 2 mg, with supplemental doses of 1 to 3 mg every 1 to 3 hours, as needed, based on individual patient need and previous response to OLINVYK. If OLINVYK was administered via PCA, the loading dose was 1.5 mg, the demand dose was 0.5 mg, and the lockout interval was 6 minutes. Supplemental doses of 1 mg were given as needed, taking into account the patient's utilization of PCA demand doses, individual patient need, and previous response to OLINVYK.

The most frequent condition treated in the open-label safety study was postsurgical acute pain, and included (in order of decreasing frequency): orthopedic, gynecologic, colorectal, general, plastic, urologic, neurologic (including spinal), bariatric, and cardiothoracic surgical procedures. Of the 768 patients treated with OLINVYK, 32% were age 65 years or older and 78% had a Body Mass Index ≥ 25 kg/m^2. OLINVYK was administered as needed; 55% of patients received OLINVYK via clinician bolus administration only, and 45% of patients received OLINVYK via PCA self-administration or a combination of clinician bolus- and PCA self-administration. Discontinuation of OLINVYK in this study due to adverse drug reactions occurred in 3% of patients who received a daily dose ≤27 mg and 1% of patients who received a daily dose >27 mg.

Full Prescribing Information, including the Boxed Warning, is available at www.OLINVYK.com.

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANTS

Addiction, Abuse, and Misuse

OLINVYK exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk before prescribing OLINVYK, and monitor all patients regularly for the development of behaviors or conditions.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of OLINVYK. Monitor for respiratory depression, especially during initiation of OLINVYK or following a

dose increase.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of OLINVYK during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Risk From Concomitant Use With Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

INDICATIONS AND USAGE

OLINVYK is a new chemical entity indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve OLINVYK for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

The cumulative total daily dose should not exceed 27 mg, as total daily doses greater than 27 mg may increase the risk for QTc interval prolongation.

CONTRAINDICATIONS

OLINVYK is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Known hypersensitivity to oliceridine (e.g., anaphylaxis)

WARNINGS AND PRECAUTIONS

- OLINVYK contains oliceridine, a Schedule [*controlled substance schedule pending*],

that exposes users to the risks of addiction, abuse, and misuse. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OLINVYK. Assess risk, counsel, and monitor all patients receiving opioids.

- Serious, life-threatening respiratory depression has been reported with the use of opioids, even when used as recommended, especially in patients with chronic pulmonary disease, or in elderly, cachectic and debilitated patients. The risk is greatest during initiation of OLINVYK therapy, following a dose increase, or when used with other drugs that depress respiration. Proper dosing of OLINVYK is essential, especially when converting patients from another opioid product to avoid overdose. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status.
- Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia with risk increasing in a dose-dependent fashion. In patients who present with CSA, consider decreasing the dose of opioid using best practices for opioid taper.
- Prolonged use of opioids during pregnancy can result in withdrawal in the neonate that can be life-threatening. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using OLINVYK for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of OLINVYK with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, or alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate, prescribe the lowest effective dose, and minimize the duration.
- OLINVYK was shown to have mild QTc interval prolongation in thorough QT studies where patients were dosed up to 27 mg. Total cumulative daily doses exceeding 27 mg per day were not studied and may increase the risk for QTc interval prolongation. Therefore, the cumulative total daily dose of OLINVYK should not exceed 27 mg.
- Increased plasma concentrations of OLINVYK may occur in patients with decreased Cytochrome P450 (CYP) 2D6 function or normal metabolizers taking moderate or strong CYP2D6 inhibitors; also in patients taking a moderate or strong CYP3A4 inhibitor, in patients with decreased CYP2D6 function who are also receiving a moderate or strong CYP3A4 inhibitor, or with discontinuation of a CYP3A4 inducer. These patients may require less frequent dosing and should be closely monitored for respiratory depression and sedation at frequent intervals. Concomitant use of OLINVYK with CYP3A4 inducers or discontinuation of a moderate or strong CYP3A4 inhibitor can lower the expected concentration, which may decrease efficacy, and may require supplemental doses.
- Cases of adrenal insufficiency have been reported with opioid use (usually greater than one month). Presentation and symptoms may be nonspecific and include nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If confirmed, treat with physiologic replacement doses of corticosteroids and wean patient from the opioid.
- OLINVYK may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or

concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension. In patients with circulatory shock, avoid the use of OLINVYK as it may cause vasodilation that can further reduce cardiac output and blood pressure.

- Avoid the use of OLINVYK in patients with impaired consciousness or coma. OLINVYK should be used with caution in patients who may be susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure or brain tumors, as a reduction in respiratory drive and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy.
- As with all opioids, OLINVYK may cause spasm of the sphincter of Oddi, and may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.
- OLINVYK may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in vulnerable patients. Monitor patients with a history of seizure disorders for worsened seizure control.
- Do not abruptly discontinue OLINVYK in a patient physically dependent on opioids. Gradually taper the dosage to avoid a withdrawal syndrome and return of pain. Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving OLINVYK, as they may reduce the analgesic effect and/or precipitate withdrawal symptoms.
- OLINVYK may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.
- Although self-administration of opioids by patient-controlled analgesia (PCA) may allow each patient to individually titrate to an acceptable level of analgesia, PCA administration has resulted in adverse outcomes and episodes of respiratory depression. Health care providers and family members monitoring patients receiving PCA analgesia should be instructed in the need for appropriate monitoring for excessive sedation, respiratory depression, or other adverse effects of opioid medications.

ADVERSE REACTIONS

Adverse reactions are described in greater detail in the Prescribing Information.

The most common (incidence ≥10%) adverse reactions in Phase 3 controlled clinical trials were nausea, vomiting, dizziness, headache, constipation, pruritus, and hypoxia.

About OLINVYK™ (oliceridine) injection

OLINVYK is a new chemical entity approved by the FDA in August 2020. It is indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. OLINVYK will not be available for distribution until the United States Drug Enforcement Administration assigns it to its schedule of controlled substances. For more information, please visit www.OLINVYK.com.

About Trevena

Trevena, Inc. is a biopharmaceutical company focused on the development and commercialization of novel medicines for patients with CNS disorders. The Company has one approved product in the U.S., OLINVYK™ (oliceridine) injection, indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. The Company also has four novel and differentiated investigational drug candidates: TRV250 for the acute treatment of migraine, TRV734 for maintenance treatment of opioid use disorder, and TRV027 for acute lung injury / abnormal blood clotting in COVID-19 patients. The Company has also identified TRV045, a novel S1P receptor modulator that may offer a new, non-opioid approach to treating a variety of CNS disorders.

Forward-Looking Statements

Any statements in this press release about future expectations, plans and prospects for the Company, including statements about the Company's strategy, future operations, clinical development and trials of its therapeutic candidates, plans for potential future product candidates, commercialization of approved drug products and other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "might," "plan," "objective," "predict," "project," "suggest," "target," "potential," "will," "would," "could," "should," "continue," "ongoing," or the negative of these terms or similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: the commercialization of any approved drug product, the status, timing, costs, results and interpretation of the Company's clinical trials or any future trials of any of the Company's investigational drug candidates; the uncertainties inherent in conducting clinical trials; expectations for regulatory interactions, submissions and approvals, including the Company's assessment of the discussions with the FDA or other regulatory agencies about any and all of its programs; uncertainties related to the commercialization of OLINVYK; available funding; uncertainties related to the Company's intellectual property; uncertainties related to the ongoing COVID-19 pandemic, other matters that could affect the availability or commercial potential of the Company's therapeutic candidates; and other factors discussed in the Risk Factors set forth in the Company's Annual Report on Form 10-K and Quarterly Reports on Form 10-Q filed with the Securities and Exchange Commission (SEC) and in other filings the Company makes with the SEC from time to time. In addition, the forward-looking statements included in this press release represent the Company's views only as of the date hereof. The Company anticipates that subsequent events and developments may cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so, except as may be required by law.

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Source: Trevena Inc.