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Trevena Announces Positive Topline OLINVYK Cognitive Function Data and Provides General Business Update

OLINVYK demonstrated statistically significant reduced impact on neurocognitive functioning vs IV morphine on primary endpoint

Successfully negotiated OLINVYK contract with a large group purchasing organization (GPO) serving over 50% of US acute care providers and 20% of US ambulatory care providers

Novel S1P receptor modulator TRV045 for diabetic neuropathic pain on track for completion of Phase 1 in 2H 2022

Strategic allocation of resources and cost reductions reinforce key focus areas and extends cash runway to mid-2023

CHESTERBROOK, Pa., July 28, 2022 (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 reported positive topline results from its post-approval study designed to assess the impact on cognitive function in subjects treated with OLINVYK compared to IV morphine. The Company also provided a general business update including recent realignment of resources and cost reductions, as well as progress on the US commercial launch of OLINVYK and the Company's pipeline assets.

"We are pleased to announce the positive topline cognitive function data and a major contract win for OLINVYK," said Carrie Bourdow, President and CEO of Trevena. "We also remain focused on advancing the clinical studies for TRV045, our novel S1P receptor modulator, and our recent corporate realignment will help us increase financial flexibility to drive forward our strategic priorities."

Cognitive Function Study

OLINVYK was studied in a randomized, double-blind, placebo-controlled, dose-ranging design, in collaboration with the Netherlands-based Center for Human Drug Research. Subjects received single intravenous doses of OLINVYK 1 mg and 3 mg, or morphine 5 mg and 10 mg, or placebo, using a partial-block crossover design. A comprehensive battery of neurocognitive and motor assessments was obtained following each blinded dose, which included measures of Sedation/Reaction Time, Visual Tracking, Higher-order Cognitive Processing, Motor Function and Eye-Hand Coordination. Twenty-three healthy subjects participated in the study, including 13 males and 10 females, with a median age of 26.

Overall, OLINVYK showed evidence of a reduced impact on neurocognitive function

compared to IV morphine.

Key Findings:

- **Primary Endpoint.** OLINVYK showed a statistically significant reduction in sedation versus IV morphine, measured by saccadic eye movement peak velocity, a sensitive laboratory measure of sedating action of medications. The prespecified mixed-model repeated measures ANOVA highlighted a difference between treatments (main effect of treatment, $P < 0.0001$), driven by a reduced impact of OLINVYK versus IV morphine ($P = 0.0236$).
- **Secondary Endpoints.** On several of the prespecified secondary outcome measures, OLINVYK showed a statistically significant difference or trend compared to IV morphine, despite the relatively small sample size, across a range of neurocognitive measures and motor performance:
 - *Reaction Time.* Reduced impact on saccadic eye movement reaction time (main effect, $P = 0.0201$) (OLINVYK vs IV morphine, $P = 0.0273$)
 - *Postural Stability (Motor Function).* Reduced body sway, a measure of motor function (main effect, $P = 0.0314$) (OLINVYK vs IV morphine, $P = 0.0951$)
 - *Eye-Hand Coordination.* Reduced performance accuracy on the adaptive tracking test, a measure of eye-hand coordination (main effect, $P = 0.0011$), (OLINVYK vs IV morphine, $P = 0.1303$)
 - *Target Engagement (Pupillometry and Analgesia).* Across the dose ranges studied, both OLINVYK and IV morphine demonstrated expected effects on opioid-induced pupillary constriction, and analgesia in response to cold pain testing

Other secondary outcome measures, including visual tracking and higher-order cognitive processing did not show statistical differences between OLINVYK and IV morphine. No serious adverse events were observed in the study, and adverse events were generally assessed as mild.

“Neurocognitive function including sedation and postural instability may have important consequences in the clinical care setting with the use of opioid medications.” said Mark Demitrack, M.D. Chief Medical Officer of Trevena. “Mitigating the impact of these adverse events may have important implications for length of stay and other health economic outcomes.”

Trevena General Business Updates

- **Executed a contract in July with a leading hospital group purchasing organization (GPO), which will allow for broad OLINVYK access for member hospitals.** The hospital GPO has coverage across US academic medical centers, acute care hospitals and ambulatory surgical centers.
- **Implemented a realignment of Company resources in July to maintain focus on key value drivers and extend cash runway to mid-2023.** The Company implemented a ~25% reduction in full-time employees and terminated its contract sales force agreement with Syneos. Trevena maintains a focused internal commercial and medical affairs team supporting OLINVYK. The Company effected other general

expense reductions that the Company believes will collectively help reduce operating expenses and extend the cash runway to mid-2023. The Company believes these decisions allow Trevena to continue to sufficiently resource its key strategic priorities of driving commercial adoption of OLINVYK and developing TRV045.

- **Continued to advance Phase 1 study of TRV045, our novel S1P receptor modulator, for diabetic neuropathic pain; on track for completion 2H 22.** TRV045 is a novel, selective sphingosine-1 phosphate subtype 1 (S1P1) receptor modulator being developed as a potential treatment for acute and chronic neuropathic pain secondary to diabetic peripheral neuropathy. Through a preclinical collaboration with the National Institutes of Health, Trevena is also exploring TRV045 as a potential treatment for epilepsy, with possible application in refractory epilepsy and other rare or orphan seizure disorders.
- **Maintained approximately \$49.5 million in cash and equivalents at June 30, 2022** which the Company believes will be sufficient to fund the Company's operating expenses and capital expenditure requirements to mid-2023. There were no net sales of OLINVYK for the quarter ended June 30, 2022. The cash balance includes net proceeds in April from the first \$15 million tranche of the royalty-based financing agreement with an affiliate of R Bridge Healthcare Fund.

About OLINVYK[®] (oliceridine) injection

OLINVYK is a new chemical entity approved by the FDA in August 2020. OLINVYK contains oliceridine, an opioid, which is a Schedule II controlled substance with a high potential for abuse similar to other opioids. 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 is available in 1 mg/1 mL and 2 mg/2 mL single-dose vials, and a 30 mg/30 mL single-patient-use vial for patient-controlled analgesia (PCA). Approved PCA doses are 0.35 mg and 0.5 mg and doses greater than 3 mg should not be administered. The cumulative daily dose should not exceed 27 mg. Please see Important Safety Information, including the BOXED WARNING, and full prescribing information 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 an opioid agonist 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 II controlled substance, 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 may 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 CO₂ retention, such as those with evidence of increased intracranial pressure or brain tumors, as a reduction in respiratory drive and the resultant CO₂ 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 $\geq 10\%$) adverse reactions in Phase 3 controlled clinical trials were nausea, vomiting, dizziness, headache, constipation, pruritus, and hypoxia.

MEDICAL INFORMATION

For medical inquiries or to report an adverse event, other safety-related information or product complaints for a company product, please contact the Trevena Medical Information Contact Center at **1-844-465-4686** or email MedInfo@Trevena.com.

You are encouraged to report suspected adverse events of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

[Please see Full Prescribing Information, including Boxed Warning.](#)

About Trevena

Trevena, Inc. is a biopharmaceutical company focused on the development and commercialization of innovative medicines for patients with CNS disorders. The Company has one approved product in the United States, 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's novel pipeline is based on Nobel Prize winning research and includes three differentiated investigational drug candidates: TRV045 for diabetic neuropathic pain and epilepsy, TRV250 for the acute treatment of migraine and TRV734 for maintenance treatment of opioid use disorder.

For more information, please visit www.Trevena.com

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 and other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "suggest," "target," "potential," "will," "would," "could," "should," "continue," and 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 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 discussions with FDA; 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 approved product; 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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