March 30, 2023

Trevena Reports Fourth Quarter 2022 Results and Provides Business Update

Company announces initial topline OLINVYK data including GI and cognitive outcomes, and length of stay data from ~200 patient real-world clinical outcomes study

TRV045, a novel S1P receptor modulator, continues to advance as a potential treatment for epilepsy, diabetic neuropathic pain and other CNS disorders, with two proof-of-concept studies expected to complete enrollment by mid-2023

Cash balance of $38.3 million at year end 2022

Company to host conference call today, March 30, 2023 at 8:00 a.m. ET

CHESTERBROOK, Pa., March 30, 2023 (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 its financial results for the fourth quarter ended December 31, 2022 and provided an overview of its recent operational highlights.

“We are excited to report initial topline data from the OLINVYK real-world outcomes studies, VOLITION and ARTEMIS. The GI and cognitive results build upon the extensive data set for OLINVYK, and we look forward to reporting respiratory outcome data as soon as it is available,” said Carrie Bourdow, President and CEO of Trevena. “We are also pleased to now have two proof-of-concept studies underway for TRV045, and we expect to report top-line data later this year.”

Fourth Quarter 2022 and Recent Corporate Highlights

- **Initial topline data from new real-world VOLITION study demonstrated over 50% GI complete response and less than 4% incidence of symptoms suggestive of delirium in patients treated with OLINVYK.** The VOLITION study, a 203-patient, real world, open-label, multi-site study led by clinical outcomes research experts from Cleveland Clinic and Wake Forest Baptist Health Medical Center, demonstrated a 52.2% GI complete response rate. A complete GI response was defined as a patient who did not vomit and did not require the use of antiemetics throughout the post-operative period. As reference, in pooled data for the Company’s pivotal Phase 3 studies of OLINVYK, the GI complete response rate was 46.2% (0.35mg) and 39.7% (0.50mg). As reflected in the OLINVYK label, nausea and vomiting were two of the most common adverse events reported in the controlled clinical trials.

  Over 90% of OLINVYK-treated patients in VOLITION reported feeling “alert and calm” from the morning of the first post-operative day and at every observation point thereafter, based on the Richmond Agitation-Sedation Scale, and only 3.9% of

OLINVYK-treated patients exhibited symptoms suggesting delirium at any point in the 48-hour post-operative period, based on the validated 3D-Confusion Assessment Method (3D-CAM) screening tool. Sedation is an established risk of opioids including OLINVYK. Analysis of respiratory data from VOLITION is not yet available, and the Company expects to report these data mid-2023.

- **Initial topline data from electronic medical records (EMR) based study, ARTEMIS, demonstrated a statistically significant 1.6-day reduction in average hospital length of stay vs matched patients treated with other IV opioids at Wake Forest Baptist Health.** OLINVYK-treated patients in VOLITION were matched with comparable patients treated with other IV opioids, undergoing similar surgical procedures at VOLITION study sites during the same period of time that the VOLITION study was enrolled. EMR data analysis is currently available from the single largest contributing site, Wake Forest Baptist Health, representing 96 OLINVYK treated patients and 457 matched patients. Based on this initial data, OLINVYK-treated patients had a statistically significant 1.6-day (~27%) reduction in average overall hospital length of stay compared to matched patients treated with other IV opioids(P=0.0001). There was no statistically significant difference in the average duration of time in the post-anesthesia care unit (PACU), with 2.4 hours observed for both OLINVYK-treated and matched patients (P=0.8174). While an EMR analysis does not provide definitive data of group differences as seen in a prospectively randomized study, the Company believes the EMR data bring a unique perspective to understanding how drugs may perform in the real world.

- **OLINVYK commercial team advances targeted customer outreach.** In the fourth quarter of 2022, the commercial team signed contracts with three new specialty distributors that focus primarily on ambulatory surgery centers (ASCs). Hospital outpatient and ASCs are becoming an increasingly important setting of care. The Company remains flexible and adaptive as it sees a shift in customer inquiries and requests for OLINVYK in the hospital outpatient setting.

- **Jiangsu Nhwa, Trevena's partner in China, expects a regulatory decision for OLINVYK in the first half of this year**. We continue to work closely with NHWA in support of potential approval of OLINVYK in China. If approved, Trevena would be eligible to receive a $3 million milestone payment from NHWA and would expect an additional $15 million of non-dilutive funding from R-Bridge Healthcare payable upon first commercial sale in China.

- **Initiated two proof-of-concept studies for TRV045, a novel S1P receptor modulator selective for the S1P receptor subtype 1.** The Company advanced the clinical development program for TRV045, its novel S1P receptor modulator, initiating two proof-of-concept studies. These studies will help inform the Company's future development path for TRV045 which has shown promising anti-inflammatory data in nonclinical models suggesting a potential disease-modifying role in CNS disorders.

    - ***TRV045 Target Engagement Study.*** The first study is a randomized, double-blind, placebo-controlled, four-way cross-over study designed to test the mechanism of action and measure evidence of target engagement for TRV045. The study will use a validated set of analgesic tests to evaluate potential central

and peripheral nervous system effects and to provide insight into the potential anti-inflammatory actions of TRV045.

- ***TRV045 Transcranial Magnetic Stimulation Study***. The second study is a randomized, double-blind, placebo-controlled, two-way cross-over, multiple dose study designed to evaluate the pharmacodynamic effects of TRV045 on the cortical excitability in healthy male adults. The study will use Transcranial Magnetic Stimulation Electromyography (TMS-EMG) and Electroencephalography (TMS-EEG) to measure the potential effect of TRV045 on brain function, relevant to epilepsy and other CNS disorders.

Both studies are expected to complete enrollment by mid-2023, and the Company expects to report top-line data in 3Q 2023

Financial Results for Fourth Quarter 2022

For the fourth quarter of 2022, the Company reported a net loss attributable to common stockholders of $7.0 million, or $0.73 per share, compared to $14.0 million, or $2.12 per share in the fourth quarter of 2021. For the full year ended December 31, 2022, net loss attributable to common stockholders was $53.7 million, or $7.59 per share, compared to $51.6 million, or $7.90 per share.

Cash and cash equivalents were $38.3 million as of December 31, 2022, which the Company believes will be sufficient to fund the Company's operating expenses and capital expenditure requirements into the fourth quarter of 2023.

Conference Call and Webcast Information

The Company will host a conference call and webcast with the investment community on March 30, 2023, at 8:00 a.m. Eastern Time featuring remarks by Carrie Bourdow, President and Chief Executive Officer, Patricia Drake, Chief Commercial Officer, Mark Demitrack, M.D., Senior Vice President and Chief Medical Officer, and Barry Shin, Chief Financial Officer.

Title:	Trevena Fourth Quarter 2022 Financial Results Conference Call & Webcast
Date:	Thursday, March 30, 2023
Time:	8:00 a.m. ET
Conference Call Details:	Toll-Free: 1-877-704-4453 International: 1-201-389-0920 Conference ID: 13736610

The conference call will be webcast live from the Company's website and will be available via the following links:

Webcast:

https://viavid.webcasts.com/starthere.jsp?ei=1600316&tp_key=4a1d148855

https://www.trevena.com/investors/events-presentations/ir-calendar

The webcast should be accessed 15 minutes prior to the conference call start time. A replay of the webcast will be available following the conclusion of the live broadcast and will be accessible on the Company's website.

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 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.

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 TRV045

TRV045 is a novel, selective sphingosine-1-phosphate subtype 1 ($S1P_1$) receptor modulator being developed as a potential treatment for acute and chronic neuropathic pain secondary to diabetic peripheral neuropathy. Through a collaboration with the National Institutes of Health, Trevena is also exploring TRV045 as a potential treatment for epilepsy.

S1P receptors are located throughout the body, including the central nervous system, where they are believed to play a role in modulating neurotransmission and membrane excitability.

Trevena's discovery efforts have identified a family of compounds that are highly selective for the $S1P_1$ receptor. TRV045 reversed thermal hyperalgesia, a measure of neuropathic pain, in nonclinical models of diabetic peripheral neuropathy and chemotherapy-induced peripheral neuropathy. TRV045 was not associated with lymphopenia and produced no changes in blood pressure, heart rate, or respiratory function at or above pharmacologically active doses in nonclinical studies. TRV045 is an investigational product and is not yet

approved by the FDA.

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

About Jiangsu Nhwa:

Jiangsu Nhwa Pharmaceutical Co., Ltd. (SZ002262), founded in 1978, is a leading CNS company in China. Over the past 40 years, Nhwa is exclusively dedicated to developing innovative and differentiated pipeline in the areas of anesthesia, analgesia, psychiatry and neurology via in-house R&D and global partnership.

As a fully integrated pharmaceutical company with more than 4000 employees, Nhwa has comprehensive capabilities in research, clinical development, manufacturing and commercialization of CNS drugs. In recent years, Nhwa has further strengthened its leadership in CNS field in China by providing the services of precision diagnosis of CNS disorders (Shanghai N-yuen Biotechnology Company), and investing the largest Chinese CNS internet health platform (Happy Mood).

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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TREVENA,INC.

Condensed Statements of Operations

(Unaudited, in thousands except share and per share data)

	Three Months Ended Dec 31,		Year Ended Dec 31,	
	2022	**2021**	**2022**	**2021**
Product revenue	$ -	$ minus(1)	$ minus(438)	$ 498
License revenue	-	-	20	69
Total revenue	-	minus(1)	minus(418)	567
Operating expenses:				
Cost of goods sold	228	334	3,018	954
Selling, general and administrative	5,723	9,761	34,728	38,112

Research and development	3,396	3,937	18,211	13,426
Total operating expenses	9,347	14,032	55,957	52,492
Loss from operations	minus(9,347)	minus(14,033)	minus(56,375)	minus(51,925)
Other income	2,342	80	2,705	337
Loss before income tax expense	minus(7,005)	minus(13,953)	minus(53,670)	minus(51,588)
Unrealized gain on marketable securities	-	-	1	-
Net loss	$minus(7,005)	$minus(13,953)	$minus(53,669)	$minus(51,588)
Per share information:				
Net loss per share of common stock, basic and diluted	minus($0.73)	minus($2.12)	minus($7.59)	minus($7.90)
Weighted average shares outstanding, basic and diluted	9,594,072	6,586,251	7,072,362	6,529,074

TREVENA,INC.

Condensed Balance Sheets

(Unaudited, in thousands)

	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 38,320	$ 66,923
Inventories	906	2,352
Prepaid expenses and other current assets	1,782	1,448
Total current assets	41,008	70,723
Restricted cash	1,960	1,311
Property and equipment, net	1,488	1,841
Right-of-use lease assets	4,224	4,706
Other assets	-	1,543
Total assets	$ 48,680	$ 80,124
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable, net	$ 2,372	$ 4,547
Accrued expenses and other current liabilities	5,461	3,847
Current portion of lease liabilities	899	792

Total current liabilities	8,732	9,186
Loans payable, net	13,430	-
Leases, net of current portion	5,436	6,309
Warrant liability	5,483	-
Total liabilities	33,081	15,495
Common stock	8	7
Additional paid-in capital	563,362	558,724
Accumulated deficit	minus(547,772)	minus(494,102)
Accumulated other comprehensive income (loss)	1	-
Total stockholders' equity	15,599	64,629
Total liabilities and stockholders' equity	$ 48,680	$ 80,124

Source: Trevena, Inc.