September 6, 2023

Trevena Announces Preliminary TRV045 Data from Two Proof-of-Concept Studies Evaluating S1PR Mechanism of Action and CNS Target Engagement

TRV045 Demonstrated Statistically Significant Analgesic Effect in Capsaicin-induced Model of Neuropathic Pain in Target Engagement POC Study

TMS POC Study Provided Statistically Significant Evidence of CNS Activity of TRV045 on Day 4 as Measured by EEG Power Spectral Analysis

No SAEs and No Study Drug-Related Discontinuations were reported; Full Safety and Tolerability Data Expected in early 4Q 2023

Company to Hold Conference Call on Wednesday, September 6 at 8 a.m. Eastern

CHESTERBROOK, Pa., Sept. 06, 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 announced preliminary topline data from two Phase 1 proof-of-concept studies of TRV045, a novel sphingosine-1-phosphate receptor modulator selective for the S1P receptor subtype 1.

“We’re very excited about the progress we’ve made with TRV045 and I’m pleased that both proof-of-concept studies demonstrated CNS target engagement. This dataset marks another significant milestone for Trevena and our ongoing commitment to focus on innovative new therapies,” said Carrie Bourdow, President and CEO of Trevena. “As a novel, non-opioid therapy, we believe TRV045 has the potential to make a meaningful difference in the lives of patients and we look forward to advancing TRV045, on our own or with a strategic partner, for potential treatment of neuropathic pain and other CNS disorders.”

Data from both studies demonstrated CNS penetration and target engagement, as well as plasma exposures in the anticipated active dose range, supporting the therapeutic potential of TRV045. In a capsaicin-induced neuropathic pain model, a validated model of neuropathic pain, TRV045 showed a statistically significant, dose-dependent treatment effect. In the transcranial magnetic stimulation (TMS) proof-of-concept study, TRV045 demonstrated statistically significant changes in the power spectral density in several bands.

“These preliminary studies strongly suggest to me that this compound has an impact on the central processing of pain, and is potentially working by reducing neural hyperexcitability,” said Daniel Clauw, MD, Professor of Anesthesiology, Medicine and Psychiatry at the University of Michigan. “There is a clear need for innovative new medications for the treatment of chronic pain. TRV045’s novel mechanism of action, accompanied by the early data suggesting it is well tolerated, make this an exciting new potential therapeutic

approach."

Target Engagement (PainCart®) POC Study

The Target Engagement POC study was a randomized, double-blind, placebo-controlled, single dose four-way cross-over study (n=25 subjects) designed to evaluate evidence of target engagement for TRV045, using a select battery of pharmacodynamic outcomes. The study used the validated PainCart® 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. Each subject received three different single doses of TRV045 (50mg, 150mg and 300mg) and placebo on four separate visits across the study duration. Plasma exposures of TRV045 in this study were comparable to levels seen in the previously reported Phase 1, FIH study and reached the anticipated targeted active dose range.

TRV045 demonstrated a statistically significant, dose-dependent reduction in mechanical allodynia following topical capsaicin application at 150mg and 300mg v. placebo. Allodynia was assessed by cutaneous pain sensation upon mechanical stimulation with Von Frey hair filaments, a validated model of neuropathic pain. The difference was measured for each dose of TRV045 compared to placebo as the change from baseline in both the secondary area of allodynic sensation and the total area of allodynia across 10 hours following the dose of study medication. The change from baseline in painful surface area at the final 10 hour timepoint is shown below, along with the associated P-values for each treatment difference across the entire 10 hour period of observation. Differences were evident for both the 150mg and 300mg doses beginning at hour 2 and continuing through the entire period of study observation at hour 10.

Outcome	Treatment	Change from Baseline in Painful Surface Area at Final 10 Hour Timepoint (mm^2)*	P-Value for Overall Treatment Difference v Placebo
Total Allodynic Area (mm^2)	Placebo	-67.19	
	TRV045 50mg	-211.61	0.1844
	TRV045 150mg	-389.45	0.0002
	TRV045 300mg	-731.78	0.0001
Secondary Allodynic Area (mm^2)	Placebo	-15.79	
	TRV045 50mg	-54.98	0.5313
	TRV045 150mg	-186.14	0.0022
	TRV045 300mg	-393.05	0.0023

* Least squares (LS) mean change from baseline

TRV045 further demonstrated a dose-dependent trend in change from baseline in the cold pressor test, and also demonstrated trends in reduction to heat pain detection threshold on both unexposed and capsaicin-treated forearm skin, on heat pain detection threshold on unexposed skin on the upper back, and pain tolerance in the electrical burst stimulation test,

though these endpoints did not achieve statistical significance. TRV045 did not show a statistically significant difference or trend compared to placebo in other pain modalities.

TMS POC Study

The TMS POC study was a randomized, double-blind, placebo-controlled, multiple dose, two-way cross-over study (n=25 subjects) designed to evaluate the pharmacodynamic effects of TRV045 (250mg) on cortical excitability in healthy male adults, using both EEG and EMG to measure the impact of TRV045 on the electrical excitation of the brain. The goal of the study was to provide further insight into TRV045 CNS target engagement and mechanism of action for the potential treatment of epilepsy and other CNS disorders. Each subject received one of two treatment sequences in random order: TRV045 at a dose of 250mg, followed by placebo; or placebo followed by 250mg of TRV045, each treatment sequence given once daily for four consecutive days. Plasma exposures of TRV045 in this study were comparable to levels seen in the previously reported Phase 1, FIH study and reached the anticipated targeted active dose range.

Among the EEG-related endpoints measured in the study, resting state EEG obtained before and after administration of TRV045, demonstrated statistically significant increases in the power spectral density on day 4 in several of the middle to higher frequency bands including alpha, beta and gamma waves. The changes in alpha waves are generally considered to be associated with conscious arousal and alertness, while beta waves are thought to be associated with GABA-mediated inhibitory cortical neurotransmission, and gamma waves are generally associated with cognitive processing, learning and memory. Alpha waves demonstrated this statistically significant increase in power in the frontal region (P=0.0164), as well as both left parietal (P=0.0047), and right parietal (P=0.0418) regions. This statistically significant increase in power was observed in the frontal region for beta waves (P=0.0235) and gamma waves (P=0.0343).

With respect to slow brain waves, which are generally associated with sedation or sleep, TRV045 showed a statistically significant decrease in the delta brain waves on day 4 in the right parietal region (P=0.0432), and no significant difference in theta brain waves at any of the three observed regions.

Among the EMG-related endpoints measured in the study, TRV045 demonstrated evidence of reduction in cortical excitability, as measured by change in peak motor-evoked potential (MEP) amplitude, on Day 1 comparable in magnitude to the reduction in cortical excitability reported in similar test conditions in the same laboratory for approved anti-epileptic drugs, though this result did not achieve statistical significance. There was no difference in mean peak MEP amplitude on Day 4, and no difference in resting motor threshold (RMT) on Day 1 or Day 4 or other EMG-related endpoints.

There were no serious adverse events reported, and no drug-related discontinuations from either study. Full safety and tolerability data for these studies are not yet available. This data is expected in early 4Q 2023. In the previously reported Phase 1 study of TRV045, the only adverse event assessed by study investigators as probably or definitely related to drug was headache in four subjects across all three parts of the study (n=53, n=27, n=9).

Subjects in both studies were enrolled outside of the United States, and the studies were not conducted under the Investigational New Drug Application for TRV045.

Conference Call and Webcast Information
The Company will host a conference call and webcast with the investment community on September 6, 2023 at 8:00 a.m. Eastern Time featuring remarks by Carrie Bourdow, President and Chief Executive Officer, Mark Demitrack, M.D., Senior Vice President and Chief Medical Officer, and Barry Shin, Chief Financial Officer.

Title:	Trevena Business Update Conference Call & Webcast
Date:	Wednesday, September 6, 2023
Time:	8:00 a.m. ET
Conference Call Details:	Toll-Free:1-877-704-4453 International:1-201-389-0920 Conference ID: 13740836

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=1630911&tp_key=ea5c342481 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 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 Epilepsy

Epilepsy, one of the most common neurological diseases in the world, is a chronic disorder characterized by recurrent seizures. Epilepsy is defined as having two or more unprovoked seizures separated by at least 24 hours or after one seizure with a high risk of more.

A seizure is a sudden surge of electrical activity in the brain caused by complex chemical changes that occur in nerve cells. Usually, there is a balance of cells that either encourage or stop other brain cells from sending messages. A seizure occurs when there may be too much or too little electrical activity in the brain causing an imbalance. Seizures are a symptom of many different disorders that can affect the brain. Nearly 50 million people suffer from epilepsy worldwide, including 3 million adults and 470,000 children in the U.S. 150,000 new cases of epilepsy are reported in the United States each year. According to the CDC, 56% of adults living with diagnosed epilepsy continue to have seizures.

About Diabetic Neuropathic Pain

Diabetic neuropathy is a common complication of both type 1 and type 2 diabetes, with pain in the extremities being one of the main symptoms. Other symptoms may include numbness, tingling, allodynia and hyperalgesia. Diabetic neuropathic pain is usually characterized as moderate to severe in nature and can substantially affect patients' quality of life as well as their social and psychological well-being.

Approximately 25% of people with diabetes are affected by DNP, equaling over 5 million people in the U.S. During their lifetime, approximately 50% to 70% of diabetic patients may experience symptoms of DNP.

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; 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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