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Trevena Announces Preclinical TRV045 Data Providing Insight Into Novel Mechanism of Analgesic Effect in Chronic Neuropathic Pain Model and Demonstrating Statistically Significant Anti-Seizure Activity in Epilepsy Models

TRV045 shows potential for sustained, long-term analgesic effect in preclinical model of neuropathic pain, with no evidence of receptor desensitization

TRV045 demonstrates statistically significant, dose-dependent increase in measures of seizure threshold and shows seizure protection in validated preclinical models

TRV045 did not show a statistically significant effect in preliminary preclinical model of epileptogenesis, but results provide direction for additional NIH-initiated studies in epilepsy prevention and treatment

CHESTERBROOK, Pa., June 20, 2024 (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, announced today preclinical data from two separate research collaborations. The first from a series of experiments conducted in collaboration with scientists at Virginia Commonwealth University and presented at the recent annual meeting of the American Society for Pharmacology and Experimental Therapeutics in May 2024. These studies examined the cellular mechanism of analgesic effects of TRV045, a novel S1P1 receptor modulator, in a mouse model of chemotherapy-induced peripheral neuropathy (CIPN). The second set of studies was from a separate, ongoing collaboration, with the NIH-supported Epilepsy Therapy Screening Program (ETSP) which studied the use of TRV045 in three different preclinical models examining its potential effects on acute seizure protection and its potential ability to modify seizure development, or epileptogenesis.

Data in Preclinical Neuropathic Pain Model

“TRV045 showed clear and sustained analgesic-like properties in animal models of neuropathic pain, while showing no evidence of peripheral lymphopenia,” said Dana Selley, PhD, Professor of Pharmacology and Toxicology at Virginia Commonwealth University. “Our studies provide molecular insights into these actions and demonstrate that TRV045 behaves differently from current S1P modulators such as fingolimod at the S1P1 receptor in CNS pain processing centers, where TRV045 caused neither desensitization of receptor function nor downregulation of receptor protein. These data suggest that TRV045 exerts its efficacy

through agonist signaling."

This newly reported preclinical data, presented as a poster at the recent annual meeting of the American Society for Pharmacology and Experimental Therapeutics in May 2024, provides further insight into TRV045's mechanism of action and its potential as a differentiated long-term therapeutic for neuropathic pain. In this study, TRV045 did not cause S1P1R functional desensitization or S1PR1 protein reduction despite repeated dosing over 14 days. In contrast, fingolimod, an approved S1PR modulator, demonstrated both significant S1P1R functional desensitization and protein reduction in this same model. As a result, the Company believes TRV045 may represent a differentiated mechanism to provide sustained S1P1R agonism and analgesic effect, unlike other S1PR modulators, such as fingolimod, that demonstrate initial agonism but long-term functional antagonism due to S1PR desensitization and protein reduction.

In this new study, S1PR1 functional desensitization was measured by S1PR1 stimulated ^{35}SGTPgS binding in membrane homogenates of spinal cord prepared from drug treated mice. Repeated fingolimod (1 mg/kg, once a day for 14 days) dosing decreased such ^{35}SGTPgS binding by approximately 70% compared with vehicle, while repeated TRV045 oral dosing (10 mg/kg, once a day for 14 days) had no effect. S1PR1 protein expression measured by Western immunoblotting indicated that repeated fingolimod treatment caused an approximately 30% reduction in S1P1R protein in spinal cord while repeated TRV045 treatment had no effect. Similar effects were seen in the region of the periaqueductal gray; both of these regions play important roles in pain transmission. We believe these studies indicate that, unlike fingolimod, TRV045 does not cause S1PR1 protein reduction or S1PR1 functional desensitization, suggesting that sustained TRV045 agonism is the underlying mechanism for its analgesic effects.

Trevena has previously reported that, in a validated mouse model of CIPN, oral administration of TRV045 (1 mg/kg, 3 mg/kg, and 10 mg/kg) reduced mechanical and cold stimulus-evoked nociception in a statistically significant, dose-related manner (at the 3 mg/kg and 10 mg/kg doses only). These effects were present after acute single dose administration of TRV045 in both male and female mice and after repeated treatment (once daily for 7 days).

Trevena has previously observed that TRV045, unlike other known S1P-targeted compounds, exerted these analgesic effects in the absence of any reduction in circulating peripheral lymphocytes, suggesting that TRV045's analgesic effects may not be due to receptor down-regulation.

Data in Preclinical Epilepsy Models

"The data observed with TRV045 in the ETSP study program showed a clear and strong anticonvulsant effect across a range of animal models. Current pharmacotherapy options in epilepsy are limited by incomplete anti-seizure medication efficacy and tolerance", said Alexander Rotenberg, MD, PhD, Professor of Neurology at Boston Children's Hospital and Harvard Medical School. "With its unique mechanism of action, TRV045 has the potential to open an important new approach to epilepsy treatment."

In a preclinical study using a validated model of seizure induction in mice, known as the intravenous Pentylenetetrazol (ivPTZ) Seizure Threshold Test, one of four doses of TRV045

(5, 10, 20 or 30mg/kg) or vehicle was orally administered to ten mice per dosage level. At one hour after test drug administration, 0.5% PTZ solution, a known seizure-inducing compound, was administered via iv infusion. Outcome measures included time to the first myoclonic (whole-body) twitch, and time to generalized clonus (seizure).

At the 30mg/kg dose, TRV045 demonstrated a statistically significant increase in time to first myoclonic twitch (31.6 seconds TRV045 vs 26.0 seconds vehicle, p=0.02). This dose of TRV045 also demonstrated an increase in time to generalized clonus (33.9 seconds TRV045, vs 28.7 seconds vehicle, p=0.056).

A separate study used a validated model of acute anti-seizure effect in rats, the maximal electroshock (MES) model. In this test, 60 Hz of alternating current (150 mA) is delivered for 0.2 sec by corneal electrodes after application of local anesthesia. Protection from MES-induced seizures is shown by abolition of the hindlimb tonic extensor component of the seizure episode. Rats (N=8 per group) were tested at four doses of TRV045, administered by intra-peritoneal (IP) injection (10, 15, 20 and 30 mg/kg). There was a dose-dependent protection observed across the dose range, reaching 7 of 8 rats protected at the 30 mg/kg dose level, and an estimated effective dose for 50% of the population (ED50) of 18 mg/kg.

Finally, TRV045 was screened in a preliminary study to evaluate the potential for TRV045 to exert an antiepileptogenic effect, or to prevent the emergence of epilepsy. In this model, rats underwent repeated low-dose IP injection of kainic acid to induce status epilepticus (SE), which leads to the development of spontaneous recurring seizures weeks later. Administration of test compounds immediately after the induction of SE, and before the development of spontaneous seizures, provides insight into the potential disruption of the process of seizure development, or epileptogenesis. One hour after SE induction, 24 rats were randomized into two equal sized groups and injected with a dose of either TRV045 (15 mg/kg, IP) or vehicle solution three times per day for 7 days. All animals were then surgically fitted with EEG monitoring devices to assess later spontaneous seizure activity through automated assessment. At two time intervals, weeks 4-6 and weeks 8-10 following induction of SE, seizure activity was then measured. At the latest time interval, weeks 8-10, two animals in the TRV045 group (17%) were seizure free, while no animals in the vehicle group reached this endpoint. However, there was no statistically significant difference in the outcomes of seizure frequency, seizure burden or seizure severity between TRV045 and vehicle treated groups at either observation interval.

Taken together, the results of these studies are consistent with prior data indicating that TRV045 showed an anti-seizure effect in validated animal models of pharmaco-resistant epilepsy. Based on these data, the ETSP plans to initiate additional studies of the anti-seizure potential of TRV045. Although the initial assessment of the potential anti-epileptogenic effect of TRV045 did not demonstrate a statistically significant difference on the outcomes studied here, these results will assist in subsequent considerations of other dose and treatment duration in future seizure prevention studies.

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 TRV045

TRV045 is a novel, highly 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.

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 expectations surrounding the continued advancement of the Company's product pipeline; the potential safety and efficacy of the Company's product candidates and their regulatory and clinical development; the Company's intention to pursue strategic alternatives for OLINVYK and the ability of any such strategic alternative to provide shareholder value; the expected financial and operational impacts of the Company's decision to reduce commercial support for OLINVYK; 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 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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