Trevi Therapeutics Announces Positive Data from Full Set of Subjects in Phase 2 CANAL Trial of Haduvio™ in the Treatment of Chronic Cough in Idiopathic Pulmonary Fibrosis

Data from full set of subjects was statistically significant for the primary efficacy endpoint of daytime cough frequency reduction (p<0.0001)

Magnitude of daytime and 24hr cough frequency reduction were consistent

Key secondary endpoints on patient and clinician reported outcomes were also statistically significant

A summary of data will be presented during the Company's Virtual R&D Day on Monday, September 19, 2022, from 10 AM-11:45 AM ET

NEW HAVEN, Conn., Sept. 19, 2022 /PRNewswire/ -- Trevi Therapeutics, Inc. (Nasdaq: TRVI), a clinical-stage biopharmaceutical company developing an investigational therapy, Haduvio™ (oral nalbuphine ER), for the treatment of chronic cough in adults with idiopathic pulmonary fibrosis (IPF) and prurigo nodularis (PN), today announced positive results from the full set of subjects in its Phase 2 **C**ough **A**nd **NAL**buphine (CANAL) trial of Haduvio for the treatment of chronic cough in IPF. Dr. William Forbes will present the data during the Company's Virtual R&D Day today, Monday, September 19th from 10 AM-11:45 AM ET.

Following the statistically significant efficacy results from the CANAL trial's interim analysis (N=26) conducted in February 2022, the Company concluded enrollment early in March 2022 and allowed enrolled subjects to complete the trial. Topline data from the full set of subjects (N=38) in the Phase 2 CANAL trial was statistically significant for the trial's primary endpoint and showed a 52.5% change compared to placebo (p<0.0001), with a 75.1% reduction in the geometric mean percent change in daytime cough frequency for Haduvio.

"We are pleased to announce the positive results from the full set of subjects from the CANAL trial, which are consistent with the previously announced interim analysis and further demonstrated that Haduvio has the potential to reduce IPF patients' cough," said Jennifer Good, President and CEO of Trevi Therapeutics. "We analyzed the change of 24hr cough frequency as well as daytime cough frequency and observed consistent reductions for both measurements. There are no approved therapies for chronic cough in these patients, and we are excited to continue our development in this indication and look forward to starting our next clinical trial for these patients in the first half of 2023. We would like to thank the CANAL trial participants and investigators for their contribution to this research as we look to improve IPF patients' quality of life."

"It is very promising to see such a significant reduction in chronic cough in IPF patients with nalbuphine ER," said Peter Dicpinigaitis, MD, Professor of Medicine at the Albert Einstein College of Medicine, and Director of the Montefiore Cough Center, in New York. "There is a large unmet need for chronic cough therapies and I believe there is broad potential to improve patients' lives with an oral therapy with a central mechanism of action."

CANAL Primary Efficacy Endpoint Analysis (N=38):

Full Analysis Set	Daytime cough frequency at end of treatment period vs. study baseline
Nalbuphine ER BID	-75.1 %
Placebo BID	-22.6 %
Placebo-adjusted change	52.5% (p<0.0001)

Full Analysis Set includes subjects completing at least 1 treatment period.

Additional Efficacy Analyses:

- Haduvio subjects had a 76.1% reduction in 24hr cough frequency compared to a 25.3% of placebo subjects, a 50.8% placebo-adjusted change (p<0.0001).
- In a post-hoc analysis, 97% of Haduvio subjects had at least a 30% reduction in 24hr cough frequency

compared to 35% of placebo subjects, signifying a clinically meaningful reduction in cough ($p<0.0001$).
- Subjects on Haduvio experienced a statistically significant improvement as measured by their patient reported outcomes compared to placebo over the 3-week treatment period in the EXACT2: Cough Frequency Score ($p=0.001$) and Cough Severity Numerical Rating Scale ($p=0.0001$).
- Based on the Clinical Global Impression of Change rating measuring clinicians' view of change since the start of the trial, 62% of Haduvio subjects improved vs. baseline compared to 19% of placebo subjects ($p=0.01$).

Safety and Tolerability Results:

The safety results of the trial were generally consistent with the known safety profile of Haduvio from previous trials. There were two serious adverse events reported during the trial, neither of which was considered by the investigator to be treatment related. Adverse events most commonly observed during the trial were nausea, fatigue, constipation, dizziness, somnolence, vomiting, headache, anxiety and depression.

To register for the event please click here.

Virtual R&D Day Details

The Virtual R&D Day event will feature presentations from key opinion leaders on the current treatment landscape and unmet medical need in patients with chronic cough and prurigo nodularis. Trevi's leadership team will also present data from the CANAL and PRISM trials and provide an update on the Company's development plans for Haduvio. A live webcast, including audio, video, and presentation slides, will be accessible on https://ir.trevitherapeutics.com/ at the time of the meeting. Interested parties unable to watch the live webcast will be able to view and listen to an archived copy of the webcast, including the slides, which will be available on https://ir.trevitherapeutics.com/.

About Chronic Cough in Idiopathic Pulmonary Fibrosis

IPF is a serious, end of life disease where cough is one of the most significant symptoms. There are estimated to be 140,000 IPF patients in the US and more than 1 million patients ex-US, where up to 85% of these patients experience chronic cough. There are no approved therapies for the treatment of chronic cough in IPF, and the cough is often refractory to antitussive therapy. Patients with chronic cough in IPF can cough up to 1,500 times per day, leading to increased feelings of anxiety as it induces breathlessness. Coughing spells or episodes lead to significant fatigue, air hunger, peripheral oxygen desaturation and some patients also experience cough-related urinary incontinence. The social impact of chronic cough in IPF further compounds limited exercise ability, reduced walking distance and the need to use supplemental oxygen. The chronic cough in IPF may be an early clinical marker of disease activity, identify patients at high risk of progression, predict time to death or lung transplant, and may also contribute to enhanced activation of profibrotic mechanisms and disease worsening in IPF.

About CANAL

The Phase 2 **C**ough **A**nd **NAL**buphine (CANAL) trial was a double-blind, randomized, placebo-controlled, 2-treatment, 2-period crossover efficacy and safety study of nalbuphine ER for chronic cough in patients with IPF which took place in the United Kingdom. The study consisted of 2 treatment periods of 3 weeks, with a washout period of 2 weeks after each treatment period. The primary efficacy endpoint was to evaluate the effect of nalbuphine ER tablets on the mean daytime cough frequency at day 22 compared to placebo as measured by an objective cough monitor. More information about the CANAL trial is available at www.clinicaltrials.gov: NCT04030026

About Trevi Therapeutics, Inc.

Trevi Therapeutics, Inc. is a clinical-stage biopharmaceutical company focused on the development and commercialization of the investigational therapy Haduvio for the treatment of chronic cough in adults with idiopathic pulmonary fibrosis and prurigo nodularis. These conditions share a common pathophysiology that is mediated through opioid receptors in the central and peripheral nervous systems.

Founded in 2011, Trevi Therapeutics is headquartered in New Haven, CT.

About Haduvio

Haduvio, an investigational therapy, is an oral extended-release (ER) formulation of nalbuphine. Nalbuphine is a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist that has been approved and marketed as an injectable for pain indications for more than 20 years in the United States and Europe. The κ- and μ-opioid receptors are known to be critical mediators of cough and itch. Nalbuphine's mechanism of action may also

mitigate the risk of abuse associated with μ-opioid agonists because it antagonizes, or blocks, μ-opioid receptors. Trevi intends to propose Haduvio as the trade name for nalbuphine ER. Nalbuphine ER has been granted Fast Track designation by the FDA for the treatment of itch in patients with prurigo nodularis. Its safety and efficacy have not been evaluated by any regulatory authority.

Forward-Looking Statements

Statements contained in this press release regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements are subject to risks and uncertainties and actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, statements regarding Trevi's business plans and objectives, including future plans or expectations for Trevi's product candidates and plans with respect to future clinical trials, and other statements containing the words "believes," "anticipates," "plans," "expects," and similar expressions. Risks that contribute to the uncertain nature of the forward-looking statements include: uncertainties regarding the success, cost and timing of Trevi's product candidate development activities and ongoing and planned clinical trials; uncertainties regarding Trevi's ability to execute on its strategy; uncertainties with respect to regulatory authorities' views as to the data from Trevi's clinical trials and next steps in the development path for Trevi's product candidates in the United States and foreign countries; uncertainties inherent in estimating Trevi's cash runway, future expenses and other financial results, including Trevi's ability to fund future operations, including clinical trials; uncertainties regarding the scope, timing and severity of the COVID-19 pandemic, the impact of the COVID-19 pandemic on Trevi's clinical operations and actions taken in response to the pandemic; as well as other risks and uncertainties set forth in the quarterly report on Form 10-Q for the quarter ended June 30, 2022 filed with the Securities and Exchange Commission and in subsequent filings with the Securities and Exchange Commission. All forward-looking statements contained in this press release speak only as of the date on which they were made. Trevi undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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