Trevi Therapeutics Reports Statistically Significant Result on Interim Analysis from the Ph2 CANAL Trial of Nalbuphine ER in the Treatment of Chronic Cough in Idiopathic Pulmonary Fibrosis

Interim analysis showed primary efficacy endpoint of cough reduction was highly statistically significant (p<0.0001) for Haduvio (nalbuphine ER)
Enrollment to be stopped due to strength of the interim data with plans to accelerate development
Interim data will be presented by management and they will be joined by the lead investigator, Dr. Toby Maher, on a conference call and webcast on February 24, 2022 at 8:30 a.m. EST

NEW HAVEN, Conn., Feb. 24, 2022 /PRNewswire/ -- Trevi Therapeutics, Inc. (Nasdaq: TRVI) today announced positive interim analysis results of the Phase 2 **C**ough **A**nd **NAL**buphine (CANAL) trial of its investigational therapy Haduvio™ (nalbuphine ER) in idiopathic pulmonary fibrosis patients (IPF) suffering from chronic cough, establishing proof of concept. Further patient recruitment in the trial will stop based on the strength and consistency of the data.

Trevi Therapeutics' Ph2 CANAL study's interim analysis achieved statistical significance

The Company conducted a statistical analysis to assess the probability of success of CANAL based on the interim data. The results of that analysis revealed that there was a 100% chance of success on existing data and the Company has moved to end screening and conclude enrollment into CANAL. The interim analysis (N=26) was statistically significant on the primary efficacy endpoint, demonstrating a 52% placebo-adjusted reduction in the geometric mean percent change in daytime cough events (p<0.0001, conditional power 100%) for Haduvio. The interim analysis was conducted by an independent statistical team according to the pre-specified endpoint in the protocol.

"We are excited about the clinically and highly statistically significant results of Haduvio in the CANAL trial and the potential to treat chronic cough in IPF patients," said Dr. Bill Forbes, Chief Development Officer at Trevi Therapeutics. "Chronic cough in patients with IPF is a serious complication of a terminal disease with no approved therapies. Based on these significant results and consistency of the data, we are ending recruitment into the CANAL trial to focus on accelerating Haduvio into the next phase of development for chronic cough in patients with IPF."

"These are extremely encouraging results that show the potential of nalbuphine ER to significantly improve the debilitating chronic cough which often severely impacts quality-of-life in many patients with IPF," said Dr. Toby Maher, MD, Professor of Medicine and Director of Interstitial Lung Disease at Keck School of Medicine,University of Southern California. "Chronic cough in IPF is unusually challenging as it is often refractory to antitussive medications and is typically not modified by currently approved anti-fibrotic therapies. Chronic cough is a frequent symptom affecting IPF patients which contributes to emotional, physical, and psychological distress."

CANAL Interim Primary Efficacy Endpoint Analysis: (as of January 28, 2022)

N=26, Full Analysis Set	**Daytime cough frequency at end of treatment period vs. study baseline**	**p-value**
Nalbuphine ER BID	-77.3%	p<0.0001
Placebo BID	-25.7%	
Placebo-adjusted change	*-51.6%*	

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

Supplemental Efficacy Analyses: (as of January 28, 2022)
The supplemental efficacy analyses from the CANAL interim data support the strong results seen in the primary efficacy endpoint. The supplemental analyses showed consistency when analyzed for completers of both treatment periods in the crossover design, against treatment period baseline, and baseline cough counts.

Secondary endpoints of patient reported outcome measure changes were consistent with the improvement in daytime cough frequency results.

Arithmetic mean change in daytime cough frequency

	Full Analysis Set		Completers	
	vs. Study Baseline	vs. Treatment Period Baseline	vs. Study Baseline	vs. Treatment Period Baseline
All cough counts				
Number of subjects, N	26	26	18	18
Mean baseline coughs/hr	31	31	31	31
Nalbuphine ER	-67.7%	-65.9%	-67.0%	-65.0%
Placebo	-15.9%	+12.2%	-11.9%	+25.6%
Placebo adjusted change	***-51.8%***	***-78.1%***	***-55.1%***	***-90.6%***
Coughs/hr ≥20.5 (50% ITT)				
Number of subjects, N	13	13	9	9
Mean baseline coughs/hr	50	50	50	50
Nalbuphine ER	-71.7%	-70.5%	-71.8%	-70.5%
Placebo	-23.7%	-0.7%	-25.1%	+5.5%
Placebo adjusted change	***-48.0%***	***-69.9%***	***-46.7%***	***-76.1%***

Full Analysis Set includes subjects completing at least 1 treatment period. Completers include subjects completing both treatment periods.

Safety and Tolerability Results:
Nalbuphine ER has been well-tolerated in the CANAL trial and has been studied in more than 1,000 subjects across indications. The safety profile remains consistent with prior studies with no new safety signals. One SAE has been reported in the CANAL trial to date and was not considered to be treatment related.

Next Steps:
Based on the positive interim analysis for the Ph2 CANAL trial, Trevi has determined to stop further recruitment into the CANAL trial and plans to initiate discussions with Health Authorities regarding the next study. The Company plans to report data from the full CANAL trial early in the third quarter 2022 and will include the patients enrolled in January and February of this year, which we expect to total approximately 40 subjects.

Conference Call Details
To participate in the live conference call by phone, please dial (888) 317 6003 (domestic) or (412) 317 6061 (international) and provide access code 2766160. A live audio webcast and presentation will be accessible from the 'Investors & News' section on the Company's website at www.trevitherapeutics.com. An archived replay of the webcast and the presentation will also be available for 30 days on the Company's website following the event.

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 130,000 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 520 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 is 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 taking place in the United Kingdom. The study consists of 2 treatment periods of 3 weeks, with a washout period of 2 weeks after each treatment period. The primary efficacy endpoint is 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 to treat serious neurologically mediated conditions. Trevi is conducting a Phase 2b/3 clinical trial of Haduvio for the treatment of chronic pruritus associated with prurigo nodularis (PN) and a Phase 2 trial for chronic cough in patients with idiopathic pulmonary fibrosis (IPF). 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 itch, cough and certain movement disorders. 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. Parenteral nalbuphine is not currently classified as a controlled substance by the DEA in the United States or by regulatory authorities in most of Europe. Trevi intends to propose Haduvio as the trade name for nalbuphine ER. Nalbuphine ER (Haduvio) is an investigational therapy that has been granted Fast Track designation by the FDA for the proposed indication of reduction of moderate to severe pruritus 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, the expected timing of reporting full data from Trevi's Phase 2 CANAL trial of Haduvio in IPF patients with chronic cough; Trevi's business plans and objectives, including future plans or expectations for Trevi's product candidates; 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 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; uncertainties regarding Trevi's ability to execute on its strategy; the risk that interim results from a clinical trial may not necessarily be predictive of the results of the completed trial or other future or ongoing clinical trials; potential regulatory developments 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 continue as a going concern, comply with its obligations under its loan facility and fund future operations; as well as other risks and uncertainties set forth in the quarterly report on Form 10-Q for the quarter ended September 30, 2021 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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https://ir.trevitherapeutics.com/2022-02-24-Trevi-Therapeutics-Reports-Statistically-Significant-Result-on-Interim-Analysis-from-the-Ph2-CANAL-Trial-of-Nalbuphine-ER-in-the-Treatment-of-Chronic-Cough-in-Idiopathic-Pulmonary-Fibrosis