Cerevel Therapeutics Announces Positive Topline Results for Darigabat in Phase 1 Clinical Trial in Acute Anxiety

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In healthy volunteers, both the 7.5 mg and 25 mg twice-daily doses of darigabat demonstrated a clinically meaningful and statistically significant improvement in the Panic Symptoms List score after eight days of dosing compared with placebo

Darigabat was generally well-tolerated; resulted in no serious adverse events and no treatment-related discontinuations in the trial

Cerevel intends to advance development of darigabat in anxiety-related disorders

Conference call and webcast scheduled for today at 8:00 a.m. EST

CAMBRIDGE, Mass., Feb. 15, 2022 (GLOBE NEWSWIRE) -- Cerevel Therapeutics (Nasdaq: CERE), a company dedicated to unraveling the mysteries of the brain to treat neuroscience diseases, today announced positive results from its Phase 1 healthy volunteer clinical trial to evaluate darigabat, a novel alpha-2/3/5 selective $GABA_A$ receptor positive allosteric modulator (PAM), in acute anxiety. Both the 7.5 mg twice-daily and the 25 mg twice-daily doses of darigabat demonstrated clinically meaningful and statistically significant anxiolytic activity compared with placebo in this proof-of-principle trial. The positive control alprazolam 1 mg twice-daily exhibited placebo-adjusted anxiolytic activity in line with expectations for this trial design.

After eight days of treatment, the darigabat 7.5 mg and 25 mg twice-daily doses demonstrated a 3.9 point (p=0.036) and 4.5 point (p=0.008) placebo-adjusted improvement, respectively, on the primary endpoint of the Panic Symptoms List (PSL-IV) total score. The alprazolam 1 mg twice-daily dose demonstrated a 1.6 point (p=0.286) placebo-adjusted improvement on the PSL-IV total score. These positive results were further supported by the secondary endpoint, change in the Fear Visual Analog Scale (VAS Fear score), which demonstrated a 12.8 point (p=0.026), 7.8 point (p=0.282), and 0.9 point (p=0.876) placebo-adjusted improvement for the darigabat 7.5 mg, 25 mg, and alprazolam 1 mg twice-daily doses, respectively.

“More than 370 million people worldwide suffer from some form of anxiety and there has been a lack of innovation in this field for more than a decade,” said John Krystal M.D., Chair of the Psychiatry Department at Yale University Medical School. “Cerevel’s trial leveraged a well-established translational model of anxiety. With its differentiated alpha-2/3/5 selective mechanism, darigabat could usher in a new generation of anxiolytics that alleviate symptoms while minimizing side effects.”

“The results of this state-of-the-art and well-executed trial demonstrated proof-of-principle for darigabat as a highly-targeted subtype-selective molecule with potential to transform the treatment paradigm in anxiety,” said chief medical officer of Cerevel, Raymond Sanchez, M.D., “While non-selective $GABA_A$ PAMs are widely prescribed across numerous indications, their known tolerability challenges limit them to acute, episodic use, leaving patients seeking better treatment options.” Dr. Sanchez continued, “Today’s results support proceeding with additional trials in anxiety-related disorders with a goal for darigabat to be a daily maintenance treatment for people suffering from inadequately managed anxiety.”

Darigabat was generally well-tolerated in this trial, with no serious adverse events and no treatment-related discontinuations in the darigabat cohorts. Ninety-seven percent of adverse events (AEs) reported in the two darigabat treatment cohorts were considered mild. The remainder were considered moderate and there were no severe AEs in the darigabat treatment arms. The most common AEs included bradyphrenia, dizziness, somnolence, fatigue, and disturbance in attention, and the AEs observed were consistent with previous trials of darigabat in healthy volunteers.

Darigabat is an alpha-2/3/5 selective $GABA_A$ receptor PAM being developed as a potential treatment for anxiety and epilepsy. By selectively targeting the alpha 2, 3 and 5 subunits of the $GABA_A$ receptor and sparing the alpha 1 subunit, darigabat may have the potential to achieve anxiolytic activity while minimizing the debilitating side effects that limit the use of currently approved benzodiazepines, which are non-selective $GABA_A$ receptor PAMs. These side effects include sedation, cognitive impairment, efficacy tolerance, and abuse potential.

“Cerevel’s differentiated approach to neuroscience – which is grounded in a deep understanding of the brain’s neurocircuitry, targeted receptor subtype selectivity and receptor pharmacology – has once again yielded an important result for the advancement of the understanding and treatment of neuroscience diseases,” said Tony Coles, M.D., chairperson and chief executive officer of Cerevel. “The success of this clinical trial highlights the importance of our innovative, deliberate and thoughtful approach to discovery and clinical development, trial design and execution in achieving results.”

Results Summary

The chart below summarizes the observed placebo-adjusted anxiolytic effect on the primary and secondary endpoints. On both endpoints, a reduction in the score indicates anxiolytic effect.

Day 8 (vs. pbo)	Darigabat 7.5 mg BID (N=18)	Darigabat 25 mg BID (N=18)	Alprazolam 1mg BID (N=18)
Δ in PSL-IV total score	-3.9 pts (p=0.036)	-4.5 pts (p=0.008)	-1.6 pts (p=0.286)
Δ in Fear VAS score	-12.8 pts (p=0.026)	-7.8 pts (p=0.282)	-0.9 pts (p=0.876)

The data presentation can be found on the Cerevel Therapeutics website here. Additional data from the trial will be presented at future scientific

conferences.

Darigabat is also being studied as a potential treatment for epilepsy, for which non-selective $GABA_A$ receptor PAMs are used acutely as anticonvulsants. Cerevel is currently conducting REALIZE, a Phase 2 proof-of-concept trial of darigabat in focal epilepsy, which is expected to read out in the second half of 2022. Additionally, Cerevel is conducting an open label extension trial of darigabat in focal epilepsy.

About the Phase 1 Healthy Volunteer Clinical Trial in Acute Anxiety
The Phase 1 proof-of-principle trial was a three-cohort, randomized, double-blind, placebo- and active-controlled, crossover trial in healthy volunteers. The primary objective of the trial was to evaluate the anxiolytic effects of multiple doses of darigabat using an experimental medicine model of carbon-dioxide (CO_2) inhalation that is associated with symptoms of anxiety/panic in healthy volunteers. This model is known to be sensitive to the effects of drugs approved for the treatment of anxiety, including benzodiazepines and selective serotonin reuptake inhibitors (SSRIs).

This trial was designed with a maximum duration of approximately thirteen weeks and consisted of a screening/baseline period, a treatment period and a follow-up period. During the screening/baseline period, subjects were exposed to the CO_2 challenge, and only subjects who were sensitive to the anxiogenic effects of 35% CO_2 double-breath inhalation at screening were eligible for randomization during the treatment period. Each treatment period consisted of eight days of dosing followed by the CO_2 challenge performed after dosing on Day 8. Adverse events were reported via participant queries approximately four times daily. The trial was conducted as a two-period, two-sequence crossover design comparing multiple doses of high-dose darigabat (25 mg BID), low-dose darigabat (7.5 mg BID), and alprazolam (1 mg BID) against placebo. Three cohorts of 18 subjects, for a total of 54 subjects, completed the trial. The primary endpoint of the trial was the change in the Panic Symptoms List (PSL-IV) total score, which includes 13 symptoms scored across a range of 0 (absent) to 4 (very intense) and is commonly used to assess panic/anxiety.

About Anxiety
Anxiety disorders are the most common form of mental illness in the United States, affecting over 45 million adults or approximately 15% of the U.S. population[1]. Globally, more than 370 million people are impacted by an anxiety disorder of some kind[2]. The most common types of anxiety disorders include obsessive-compulsive, post-traumatic stress, social anxiety, panic and generalized anxiety[3]. The social impact of anxiety disorders includes increased risk of suicide, reduced achievement in work and school, increased risk of absenteeism, co-morbid depression, potential for substance abuse and higher healthcare costs[4].

Conference Call Information
Cerevel will host a conference call and webcast today, February 15, at 8:00 a.m. EST to discuss the results of the Phase 1 trial of darigabat in acute anxiety. To access the call, please dial 833-665-0655 (domestic) or 702-495-1044 (international) and refer to conference ID 5044015. The live webcast and accompanying slides can be accessed on the investor relations section of the Cerevel Therapeutics website here. A replay will be available in the same section of the company's website for approximately 90 days.

About Cerevel Therapeutics
Cerevel Therapeutics is dedicated to unraveling the mysteries of the brain to treat neuroscience diseases. The company is tackling diseases with a targeted approach to neuroscience that combines expertise in neurocircuitry with a focus on receptor selectivity. Cerevel Therapeutics has a diversified pipeline comprising six clinical-stage investigational therapies and several pre-clinical compounds with the potential to treat a range of neuroscience diseases, including Parkinson's, epilepsy, schizophrenia, and dementia-related apathy. Headquartered in Cambridge, Mass., Cerevel Therapeutics is advancing its current research and development programs while exploring new modalities through internal research efforts, external collaborations, or potential acquisitions. For more information, visit www.cerevel.com.

Special Note Regarding Forward-Looking Statements
This press release contains forward-looking statements that are based on management's beliefs and assumptions and on information currently available to management. In some cases, you can identify forward-looking statements by the following words: "may," "will," "could," "would," "should," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "project," "potential," "continue," "ongoing" or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. These statements involve risks, uncertainties and other factors that may cause actual results, levels of activity, performance, or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this press release, we caution you that these statements are based on a combination of facts and factors currently known by us and our projections of the future, about which we cannot be certain. Forward-looking statements in this press release include, but are not limited to, statements about the potential attributes and benefits of our product candidates, including the ability of darigabat to achieve anxiolytic activity while minimizing side effects, to be a daily maintenance treatment and to transform the treatment paradigm in anxiety; the format and timing of our product development activities and clinical trials, including the timing of the Phase 2 proof-of-concept trial of darigabat in focal epilepsy and advancing development of darigabat in anxiety-related disorders; the ability to compete with other companies currently marketing or engaged in the development of treatments for relevant indications; the size and growth potential of the markets for product candidates and ability to serve those markets; and the rate and degree of market acceptance of product candidates, if approved. We cannot assure you that the forward-looking statements in this press release will prove to be accurate. Furthermore, if the forward-looking statements prove to be inaccurate, the inaccuracy may be material. Actual performance and results may differ materially from those projected or suggested in the forward-looking statements due to various risks and uncertainties, including, among others: clinical trial results may not be favorable; uncertainties inherent in the product development process (including with respect to the timing of results and whether such results will be predictive of future results); the impact of COVID-19 on the timing, progress and results of ongoing or planned clinical trials; other impacts of COVID-19, including operational disruptions or delays or to our ability to raise additional capital; whether and when, if at all, our product candidates will receive approval from the FDA or other regulatory authorities, and for which, if any, indications; competition from other biotechnology companies; uncertainties regarding intellectual property protection; and other risks identified in our SEC filings, including those under the heading "Risk Factors" in our Quarterly Report on Form 10-Q filed with the SEC on November 10, 2021 and our subsequent SEC filings. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. The forward-looking statements in this press release represent our views as of the date of this press release. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we have no current intention of doing so except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this press release.

Media Contact:
Anna Robinson
Cerevel Therapeutics
anna.robinson@cerevel.com

Investor Contact:
Matthew Calistri
Cerevel Therapeutics
matthew.calistri@cerevel.com

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