Cerevel Therapeutics Announces Positive Topline Results for CVL-231 in Phase 1b Clinical Trial in Patients with Schizophrenia

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Both doses of CVL-231 demonstrated a clinically meaningful and statistically significant improvement in PANSS Total score at 6 weeks and were overall well-tolerated compared with placebo

30 mg of CVL-231 once-daily improved PANSS total score at 6 weeks by 12.7 points compared with placebo (p=0.023)

20 mg of CVL-231 twice-daily improved PANSS total score at 6 weeks by 11.1 points compared with placebo (p=0.047)

No meaningful differences in gastrointestinal side effects, extrapyramidal symptoms or weight gain compared with placebo

Cerevel plans to advance CVL-231 to Phase 2 development in schizophrenia and to evaluate the potential for this mechanism in other populations, including dementia-related psychosis

Conference call and webcast scheduled for today at 8:30 a.m. EDT

CAMBRIDGE, Mass., June 29, 2021 (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 1b clinical trial of CVL-231, a novel muscarinic M4-selective Positive Allosteric Modulator (PAM), in adult patients with schizophrenia. CVL-231 was generally well-tolerated, and discontinuation rates were similar between CVL-231 and placebo in the six weeks of dosing, at 22% each. Importantly, both the 30 mg once-daily and the 20 mg twice-daily doses demonstrated clinically meaningful antipsychotic activity with an overall well-tolerated profile compared with placebo. The CVL-231 30 mg once-daily dose resulted in a statistically significant and clinically meaningful mean reduction from baseline of 19.5 points in the Positive and Negative Syndrome Scale (PANSS) total score and a mean reduction of 12.7 points in PANSS versus the placebo group (p=0.023). The CVL-231 20 mg twice-daily dose resulted in a statistically significant and clinically meaningful mean reduction from baseline of 17.9 points in PANSS total score and a mean reduction of 11.1 points in PANSS total score compared with the placebo group (p=0.047). These results were further supported by clinically meaningful reductions in the PANSS Positive and PANSS Negative subscales.

In the previously completed Part A multiple ascending dose (MAD) phase of this study, doses of 5 mg to 40 mg (administered as 20 mg BID) were explored with up to 21 days of administration at target dosage. The Part A MAD safety and tolerability data were supportive of proceeding to 6 weeks of dosing in the subsequent Part B portion of the trial, which is being reported today. The Part B portion was designed, in part, to evaluate tolerability and explore the antipsychotic potential of CVL-231 in patients by measuring the effect on PANSS with selected doses of 30 mg once-daily and 20 mg twice-daily.

“We believe these results are impressive and provide important evidence for the specific activation of the M4 receptor as a potential treatment approach for schizophrenia,” said John M. Kane, M.D., professor and chairman, Department of Psychiatry at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell. “By selectively targeting the M4 receptor, CVL-231 appears to have yielded a robust and clinically meaningful antipsychotic effect while avoiding both the debilitating extrapyramidal side effects commonly seen with dopamine antagonists, as well as the serious gastrointestinal side effects that have limited non-selective muscarinic compounds in the past.”

CVL-231 is an M4-selective PAM being developed as a potential treatment for schizophrenia. CVL-231 is designed as a once-daily medication that selectively targets activation of the M4 receptor in the brain to reduce dopaminergic activity without direct dopamine receptor antagonist activity. CVL-231 has the potential to be a first-in-class once-daily, M4-selective PAM that may provide antipsychotic activity without the need for titration while minimizing gastrointestinal, extrapyramidal, and metabolic side effects seen with other antipsychotic medications. By selectively targeting the M4 receptor, CVL-231 has the potential to avoid the serious gastrointestinal side effects that have commonly been associated with, and have hindered clinical development of, non-selective muscarinic agents.

“We are extremely encouraged with these results, which we believe support our hypothesis that a targeted muscarinic therapy that is highly selective for M4 receptors could deliver clinically meaningful benefit in the treatment of schizophrenia,” said John Renger, Ph.D., chief scientific officer at Cerevel. “By developing a molecule that is several hundred times more selective for M4 receptors over M1, M2, M3, and M5 receptors, we are expanding our understanding of how to best leverage the potential of the muscarinic pathway to effectively treat individuals with schizophrenia, with fewer of the dose-limiting side effects that occur with currently available therapies.”

CVL-231 was generally well-tolerated in the clinical trial. The incidence of treatment emergent adverse events for both dose cohorts were similar to placebo, including heart rate and blood pressure increases. The adverse event (AE) of headache had the highest incidence of reporting across all treatment groups, with placebo at 26%, 30 mg once-daily at 30%, and 26% for the 20 mg twice-daily cohort. Additionally, the rate of nausea was similar between CVL-231 and placebo (4% for placebo and 7% for both 30 mg once-daily and 20 mg twice-daily groups) and rates of other gastrointestinal AEs were very low and similar to placebo. CVL-231 was not associated with a greater incidence of weight gain than placebo and no adverse events related to extrapyramidal symptoms were reported. Serious adverse events reported in the study included COVID-19, accidental overdose, and exacerbation of schizophrenia (one instance of each).

“Novel approaches for treating schizophrenia have been challenging to identify for decades, and patients and caregivers are seeking new therapies without the debilitating side effects that lead to poor compliance and relapse,” said Raymond Sanchez, M.D., chief medical officer at Cerevel. “We are working to develop CVL-231 to be a once-daily formulation with improved tolerability, and without the need for titration, which could potentially improve adherence and avoid the vicious cycle of relapse with the exacerbation of symptoms so often seen with this illness.”

Pharmacodynamic Results Summary

Week 6 (Day 42)	Placebo (N=27)	CVL-231 30 mg QD (N=27)	CVL-231 20 mg BID (N=27)	Combined CVL-231 (N=54)
PANSS Total Score				
LS Mean Change from Baseline	-6.8	-19.5	-17.9	-18.7
Difference vs Placebo (p-value)		-12.7 p = 0.023	-11.1 p = 0.047	-11.9 p = 0.014
PANSS Positive Score				
LS Mean Change from Baseline	-2.5	-6.8	-4.9	-5.8
Difference vs Placebo (p-value)		-4.3 p = 0.016	-2.4 p = 0.166	-3.3 p = 0.028
PANSS Negative Score				
LS Mean Change from Baseline	0.1	-3.0	-3.6	-3.3
Difference vs Placebo (p-value)		-3.1 p = 0.009	-3.7 p = 0.002	-3.4 p = 0.001

Additional data from the trial will be presented at an upcoming scientific meeting.

The results of this trial support the advancement of CVL-231 into a Phase 2 program in schizophrenia. Cerevel also plans to explore additional related indications including dementia-related psychosis.

“Consistent with the scientific approach we have taken across our broad neuroscience portfolio, CVL-231 leverages our differentiated understanding of neurocircuitry and the power of targeted receptor selectivity in the development of innovative medicines for patients in need,” said Tony Coles, M.D., chairperson and chief executive officer of Cerevel. “We are extremely encouraged by the data from this trial and believe CVL-231 has the potential to be a truly transformative therapy in schizophrenia, a disease area that has not seen the significant advancement in therapies that patients and physicians have been seeking for decades. Today’s data readout marks an exciting and important milestone in our journey to become the premier neuroscience company.”

About the Trial

The Phase 1b clinical trial was a two-part multiple ascending dose (MAD) trial to evaluate the safety, tolerability, pharmacokinetics (PK) and preliminary pharmacodynamics (PD) of repeated daily doses of CVL-231 in patients with a primary diagnosis of schizophrenia per the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). In Part A, the objectives were to characterize physiological effects, identify any dose-limiting tolerability effects, and to identify the maximum tolerated dose of CVL-231 in patients with stable schizophrenia symptoms. In Part A, fifty patients across five CVL-231 cohorts were evaluated versus placebo, and the emerging data from Part A informed the doses and dosing schedules for Part B. Part B was a randomized, double-blind, three-arm, placebo-controlled trial with the objective of further evaluating safety, PK and preliminary PD. In Part B, 81 patients with baseline PANSS total scores of at least 80 and experiencing acute exacerbation of psychosis were randomized 1:1:1 to CVL-231 at a dose of 20 mg BID, 30 mg QD, or placebo for a total of 6 weeks. The trial was 59% powered to detect a seven point difference from placebo on the PANSS total score. The measures used for evaluation included change from baseline in PANSS total score and subscales (negative, positive and general psychopathology), as well as other measures.

About Schizophrenia

Schizophrenia is a serious, complex and debilitating mental health disorder characterized by a constellation of symptoms, including delusions, hallucinations, disorganized speech or behavior, slowed speech and blunted affect. Schizophrenia is also often associated with significant cognitive impairment, which further limits a patient’s ability to be gainfully employed and maintain relationships. Diagnosis of schizophrenia is usually made in young adulthood and the disease follows a chronic and indolent course characterized by periods of remission and relapse. Only 20% of patients report favorable treatment outcomes and medication adherence is poor, with a compliance rate of about 60% and a discontinuation rate of 74% within 18 months.[1,2] Patients who discontinue their medication suffer from high relapse rates of 77% at one year and 90% at two years.[3] People with schizophrenia have a 10 to 25-year reduction in life expectancy compared to the general population.[4] An estimated 20 million people worldwide suffer from schizophrenia.[5]

Conference Call Information

Cerevel will host a conference call and webcast today, June 29, at 8:30 a.m. EDT to discuss the results of the Phase 1b trial of CVL-231 in schizophrenia. To access the call, please dial 833-665-0655 (domestic) or 702-495-1044 (international) and refer to conference ID 9584017. 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 five 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 substance use disorder. 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 advancement of CVL-231 into a Phase 2 program in schizophrenia and plans to explore additional related indications. 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 May 17, 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.

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