Cyclerion Therapeutics Announces Positive Topline Clinical Data for CY6463 in Patients with Cognitive Impairment Associated with Schizophrenia (CIAS)

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Study data demonstrate positive effects of CY6463 on cognition and inflammation after two weeks of dosing in patients with stable schizophrenia on standard of care

Oral, once-daily CY6463 was well tolerated, with no reports of serious adverse events (SAEs) or treatment discontinuation due to adverse events (AEs)

Data demonstrate the translation of sGC multi-dimensional pharmacology and the therapeutic potential of amplifying sGC signaling in the CNS and support the further development of oral, once-daily CY6463

Company to discuss data during live webinar today at 8:00 a.m. EDT

CAMBRIDGE, Mass., July 28, 2022 (GLOBE NEWSWIRE) -- Cyclerion Therapeutics, Inc. (Nasdaq: CYCN), a clinical-stage biopharmaceutical company on a mission to develop treatments that restore cognitive function, today announced positive topline data from its clinical study of CY6463 for the treatment of Cognitive Impairment Associated with Schizophrenia (CIAS) in individuals with stable schizophrenia on a stable, single, atypical antipsychotic regimen. Data from the 14-day, double-blind, randomized, placebo-controlled, multiple-ascending-dose study demonstrate that once-daily CY6463 was safe and well tolerated, with no reports of serious adverse events (SAEs), severe adverse events (AEs), or treatment discontinuation due to AEs. Study data demonstrate a strong effect on cognitive performance after two weeks of 15mg once-daily dosing. A broad positive movement on inflammatory biomarkers was also observed. These signals on exploratory endpoints provide further evidence of the pro-cognitive and anti-inflammatory effects of CY6463 observed in preclinical studies and prior clinical trials.

“Cognitive impairment is a central debilitating, and untreated facet of schizophrenia, and there is a significant need for a treatment option that improves cognition,” said Steven E. Hyman, M.D., Core Member of the Broad Institute, Director of the Stanley Center for Psychiatric Research at the Broad Institute, and new member of Cyclerion’s Board of Directors. “I am encouraged by the promising cognition signals observed after only two weeks of CY6463 dosing in patients with stable schizophrenia. These data demonstrate the therapeutic potential of amplifying sGC signaling in the CNS, including positive effects on cognition and inflammation, and support further development of CY6463 in diseases characterized by cognitive impairment.”

CY6463 is a positive allosteric modulator of soluble guanylate cyclase (sGC) that amplifies endogenous nitric oxide (NO) signaling, a pathway that has been linked to schizophrenia.

The clinical study enrolled 48 participants with stable schizophrenia with no more than moderate positive symptoms and on a stable, single, atypical antipsychotic regimen. Topline results include:

- CY6463 was safe and well tolerated. There were no reports of SAEs, severe AEs, or treatment discontinuation due to AEs. All AEs were transient.
- The pharmacokinetic profile of once-daily CY6463 is consistent with earlier clinical studies in healthy volunteers and MELAS patients, and demonstrated linear, dose-proportional exposure and low intersubject variability.
- The general cognition composite score from the Cogstate Schizophrenia Battery increased with 14 days of once-daily dosing with CY6463 15 mg, compared to placebo, with an effect size of 0.60. An effect size of approximately 0.3 is generally considered clinically relevant in neuropsychiatry.
- Favorable changes were observed in a broad panel of plasma inflammatory biomarkers, including biomarkers with links to schizophrenia and cognition, after 14 days of once-daily dosing with CY6463 15 mg. These anti-inflammatory effects extend results observed in preclinical and earlier clinical studies of CY6463.
- Analysis of data from exploratory EEG assessments (resting state, qEEG, ERP, sleep EEG,) are ongoing. Data from these assessments will be shared in future scientific forums.
- At the two higher dose levels evaluated in this multiple-ascending-dose study (30 and 60 mg), CY6463 was observed to be safe and well tolerated; however, higher doses did not demonstrate an effect on the general cognition composite at Day 14, a finding consistent with preclinical experiments.

“This is the second clinical study successfully demonstrating safety, pharmacokinetics, and therapeutic activity in a patient population where previous drug development has been very challenging,” said Andreas Busch, Ph.D., Chief Scientific Officer at Cyclerion Therapeutics. “These exciting results confirm previous clinical and preclinical findings, adding to a strong data package that supports the advancement of CY6463 in CNS diseases where cognition is impaired, including CIAS and MELAS. We are eager to build on the momentum from these positive data and continue to assess opportunities to accelerate development, refine patient selection, and improve endpoint assessment.”

“The data emerging from this CIAS study, coupled with the recently reported CY6463 MELAS clinical study data, demonstrate positive multi-dimensional therapeutic activity and favorable safety and tolerability in two distinct patient populations,” said Peter Hecht, Ph.D., Chief Executive Officer of Cyclerion. “These data present a path and opportunity forward for Cyclerion’s first-in-class, CNS-penetrant sGC stimulator to yield multiple

breakthrough CNS therapeutics across patient populations in need of novel treatment options. We continue to explore potential partnerships with parties who share our vision for the broad therapeutic potential of sGC in treating CNS disorders."

Webinar Information
The Company will discuss these positive topline clinical data during a live webinar on Thursday, July 28th at 8:00 a.m. EDT, including a live Q&A. The live event can be accessed by visiting the investors' section of the Cyclerion website at https://ir.cyclerion.com/news-events/event-calendar. An archived replay will also be available on the Cyclerion website.

About the CIAS Study

The CIAS trial (NCT04972227) was an in-center, randomized, placebo-controlled, multiple-ascending-dose study of oral, once-daily CY6463 in 48 adults aged 18-50 who were diagnosed with stable schizophrenia with no more than moderate positive symptoms and on a stable, single, atypical antipsychotic regimen. The primary objective of the study was to assess the safety and tolerability of 15, 30 and 60 milligram, once-daily, oral doses of CY6463 over 14 days. The secondary objectives included pharmacokinetics and exploratory pharmacodynamic effects. The study was not powered for hypothesis testing.

About Schizophrenia and CIAS

Schizophrenia is a chronic brain disorder that affects how patients think, feel, and behave, which may result in hallucinations, delusions and/or disordered behavior that impairs daily functioning. Cognitive impairment is a core, debilitating, and untreated symptom of schizophrenia, with nearly all patients suffering from some cognitive deficits. There are currently no approved therapies that specifically improve cognitive deficits.

About CY6463

CY6463 is the first CNS-penetrant sGC stimulator to be developed as a symptomatic and potentially disease-modifying therapy for serious CNS diseases. The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway is a fundamental mechanism that precisely controls key aspects of physiology throughout the body. In the CNS, the NO-sGC-cGMP pathway regulates diverse and critical biological functions including neuronal function, neuroinflammation, cellular bioenergetics, and vascular dynamics. Although it has been successfully targeted with several drugs in the periphery, this mechanism has yet to be fully leveraged therapeutically in the CNS, where impaired NO-sGC-cGMP signaling is believed to play an important role in the pathogenesis of many neurodegenerative and neuropsychiatric diseases and other disorders associated with cognitive impairment. As an sGC stimulator, CY6463 acts as a positive allosteric modulator to sensitize the sGC enzyme to NO, increase the production of cGMP, and thereby amplify endogenous NO signaling. By compensating for deficient NO-sGC-cGMP signaling, CY6463 and other sGC stimulators may have broad therapeutic potential as a treatment to improve cognition and function in people with serious CNS diseases.

About Cyclerion Therapeutics
Cyclerion Therapeutics is a clinical-stage biopharmaceutical company on a mission to develop treatments that restore cognitive function. Cyclerion's lead molecule is CY6463, a novel, first-in-class, CNS-penetrant, sGC stimulator that modulates a key node in a fundamental CNS signaling network. The multidimensional pharmacology elicited by the stimulation of sGC has the potential to impact a broad range of CNS diseases. CY6463 has shown rapid improvement in biomarkers associated with cognitive function and is currently in clinical development for Alzheimer's Disease with Vascular pathology (ADv) and Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS) and Cognitive Impairment Associated with Schizophrenia (CIAS). Cyclerion is also advancing CY3018, a next generation sGC stimulator.

For more information about Cyclerion, please visit https://www.cyclerion.com/ and follow us on Twitter (@Cyclerion) and LinkedIn (http://www.linkedin.com/company/cyclerion).

Forward Looking Statement
Certain matters discussed in this press release are "forward-looking statements". We may, in some cases, use terms such as "predicts," "believes," "potential," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should", "positive" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company's statements regarding the potential for CY6463 in the treatment of CNS diseases, including CIAS and MELAS, the potential for any successful development of CY6463, the sufficiency of our resources and other abilities to pursue the development of CNS, and other trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, our ability to continue with sufficient liquidity and capital resources to pursue our business plan regarding CY6463 or any other product (including without limitation our ability to fund additional clinical trials); our ability to successfully demonstrate the efficacy, safety and therapeutic effectiveness of CY6463; the success, timing and cost of our ongoing or future clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation and completion of the trials, futility analyses and receipt of interim results, which are not necessarily indicative of or supported by the final results of our ongoing or subsequent clinical trials; any results of clinical studies not necessarily being indicative of or supported by the final results of our ongoing or subsequent clinical trials;; the timing of and our ability to pursue, obtain and maintain U.S. Food and Drug Administration ("FDA") or other regulatory authority approval of, or other action with respect to, our product candidates; the potential for the CY6463 clinical trial to provide a basis for approval for treatment of MELAS and CIAS; the Company's ability to successfully defend its intellectual property or obtain necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company's research and development programs and collaborations; the success of the Company's license agreements; the acceptance by the market of the Company's product candidates, if approved; and other factors, including general economic conditions and regulatory developments, not within the Company's control. The factors discussed herein could cause actual results and developments to be materially different from those expressed in or implied by such statements. The forward-looking statements are made only as of the date of this press release and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

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