Cyclerion Therapeutics Announces Positive Topline Clinical Data for CY6463 in MELAS Patients at UMDF Mitochondrial Medicine 2022 Symposium

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Data from an eight-patient, open-label study demonstrate improvements across multiple biomarkers of mitochondrial function, inflammation, cerebral blood flow, and functional connectivity

CY6463 was well tolerated, with no reports of serious adverse events (SAEs) or treatment discontinuation due to adverse events (AEs); oral, once-daily administration provided expected CNS exposure

Data support further development of CY6463 in CNS diseases with mitochondrial dysfunction

CAMBRIDGE, Mass., June 10, 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 in its signal-seeking clinical study of CY6463, for the potential treatment of Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS). Chad Glasser, Pharm.D., Director of Clinical Research at Cyclerion Therapeutics, will present results from this clinical study today during the *Clinical Trial Updates Panel* at the United Mitochondrial Disease Foundation (UMDF) Mitochondrial Medicine 2022 Symposium, taking place June 8-11, 2022, in Phoenix, Arizona.

CY6463 is a positive allosteric modulator of soluble guanylate cyclase (sGC), which amplifies endogenous NO signaling, a pathway that has been linked to mitochondrial biogenesis and function. In this open-label, single-arm study of the oral, once-daily sGC stimulator in eight MELAS patients, improvements were seen across a range of biomarkers, including mitochondrial disease-associated biomarkers such as lactate and GDF-15, a broad panel of inflammatory biomarkers, cerebral blood flow, and functional connectivity between neural networks. These positive effects after 29 days of dosing were supported by correlations across several endpoints and were more pronounced in patients with greater baseline disease burden. A return toward baseline levels after discontinuation of CY6463 dosing across several biomarkers was also observed.

CY6463 was well tolerated with no adverse events leading to treatment discontinuation, and pharmacokinetics (PK) were consistent with the Phase 1 study in healthy volunteers. The positive data from this study further support the potential of CY6463, the first and only CNS-penetrant sGC stimulator in clinical development, to provide therapeutic benefit to people living with MELAS.

“MELAS patients currently have no approved treatment options for a devastating orphan disease that affects multiple organs, including the CNS, skeletal muscle, and eyes,” said Peter Hecht, Ph.D., Chief Executive Officer of Cyclerion. “We are excited by the strength of these data and consistency across disease domains, which support the further advancement of CY6463 as a potential treatment option.”

Study Highlights:

- The single-arm, open-label study enrolled eight participants who spanned a range of disease burden; 6 of the 8 (75%) were also taking a daily regimen of oral arginine or citrulline, precursors to nitric oxide that are current standard of care for MELAS patients.
- CY6463 was well tolerated; there were no reports of serious adverse events (SAEs) or treatment discontinuation due to adverse events (AEs).
- The PK profile and concentrations in the cerebrospinal fluid (CSF) and plasma were consistent with exposures observed in Phase 1 healthy volunteer studies.
- Effects were observed across multiple domains of disease activity:
    - Improvements in biomarkers associated with mitochondrial function including lactate and GDF-15. These changes correlated with each other and with CY6463 plasma concentrations
    - Improvements across a broad panel of inflammatory biomarkers
    - Increases in cerebral blood flow across all brain regions. These changes correlated with clinical improvement as assessed by the patient global impression of change (PGIC) scale
    - Increases in functional connectivity between brain regions and activation of occipital brain regions in response to the visual stimulus as measured by fMRI BOLD

“In this study we saw positive impacts on important biomarkers associated with MELAS and other mitochondrial disease following 29 days of once-daily dosing with CY6463,” said Andreas Busch, Ph.D., Chief Scientific Officer at Cyclerion Therapeutics. “These findings are exciting as we think about the potential of our mechanism in mitochondrial disease and more broadly about the effects of CY6463 on mitochondrial function, which is relevant to numerous CNS diseases, including schizophrenia and Alzheimer’s Disease.”

A video presentation of the topline data is available on the Investor page of the Cyclerion website. Additional data from the MELAS clinical study will be shared in the coming weeks.

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 the Study

The Phase 2a study was an open-label, single-arm study of oral, once-daily CY6463 in eight adults aged 18 or older with MELAS. The primary objective of the study was to assess the safety and tolerability of a 15 milligram, once-daily, oral dose of CY6463 over 29 days. The secondary objectives included pharmacokinetics, and exploratory pharmacodynamic effects, with the goal of identifying which biomarkers to carry forward into additional studies. The study was not powered for hypothesis testing.

About MELAS

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) is a devastating orphan disease affecting multiple organ systems, including the CNS, with no approved therapies. It is the most common form of primary mitochondrial diseases (PMD). MELAS is phenotypically and genetically defined by a mutation in mitochondrial tRNA. It is estimated that about 1 in 4,300 individuals has a mitochondrial disease, and ~80% of individuals with mitochondrial disease have CNS symptoms. The unmet need in MELAS is immense, symptoms include, chronic fatigue, muscle weakness, and pain in addition to neurological manifestations. Life expectancy is estimated at ~17 years from onset of CNS symptoms. The disease impedes the individual's ability to live independently, leads to social isolation, and overall reduced quality of life.

About Cyclerion Therapeutics

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

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 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, 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, including in particular single-arm open-label studies involving a number of patients that is not statistically significant such as described in this release, not necessarily being indicative of or supported by the final results of our ongoing or subsequent clinical trials; our ability to fund additional clinical trials to continue the advancement of our product candidates; the timing of and our ability to 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; 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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