Cyclerion Therapeutics Provides Additional Positive CY6463 MELAS Clinical Data at a Webinar Hosted by United Mitochondrial Disease Foundation

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Data for CY6463, a first-in-class, CNS-penetrant, sGC stimulator, demonstrate safety and positive effects across biomarkers of disease in MELAS patients

Company leadership discussed key insights for patients with MELAS with clinician-researcher, Amel Karaa, M.D., and Philip Yeske, Ph.D. of UMDF

CAMBRIDGE, Mass., June 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 participated in a webinar hosted by the United Mitochondrial Disease Foundation (UMDF). The Company shared additional positive clinical data from its signal-seeking study of CY6463, a first-in-class, CNS-penetrant sGC stimulator, in patients with Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS). Data from the 8-participant, open-label study demonstrate CY6463 was well tolerated, with no reports of serious adverse events (SAEs) or treatment discontinuation due to adverse events (AEs), and showed improvements across multiple mitochondrial disease-associated biomarkers, inflammatory biomarkers, cerebral blood flow, and functional connectivity between neural networks.

The webinar included MELAS and mitochondrial disease community insights from Philip Yeske, Ph.D., Science & Alliance Officer of UMDF, and the perspective of MELAS clinician-researcher, Amel Karaa, M.D., Assistant Professor and Director of the Mitochondrial Disease Program and Lysosomal Disorders Program at Harvard Medical School and Massachusetts General Hospital, and recent president of the Mitochondrial Medicine Society, on the implications and potential impact of these data for patients with MELAS.

“With no approved therapies for this devastating progressive orphan disease that affects multiple organ systems, including the CNS, MELAS patients living with debilitating symptoms are in desperate need of therapeutic options,” said Dr. Karaa. “I am excited and encouraged by these data and am convinced that further study and development should be undertaken to pursue CY6463 as a potential treatment for MELAS.”

“UMDF was pleased to partner with Dr. Karaa and Cyclerion to provide MELAS patients, their loved ones, researchers and medical experts, who know the most about this debilitating mitochondrial disease, with an opportunity to understand the study data,” said Brian Harman, President and Chief Executive Officer of UMDF. “We will continue to lift up the voices of the mitochondrial disease community and do everything in our power to chart a course toward future treatments through awareness, education, and support.”

Key Webinar Highlights
Dr. Yeske and Dr. Karaa provided key insights into the MELAS patient burden of disease and treatment options, and Cyclerion’s Christopher Winrow, Ph.D., Vice President, Translational Medicine & Development Program Lead, and Chad Glasser, Pharm.D., Director of Clinical Research, discussed the results from the Phase 2a study, including:

- The single-arm, open-label study enrolled eight participants who spanned a range of disease severity; 6 of the 8 (75%) were also taking a daily regimen of oral arginine or citrulline, precursors to nitric oxide that are often prescribed as 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 pharmacokinetic 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 objective domains of disease activity in 6 of the 8 participants enrolled following 29 days of CY6463 dosing:
    - Improvements in at least 1 plasma biomarker associated with mitochondrial dysfunction were observed in 7 of the 8 participants.
        - Reductions in lactate were observed in 6 of the 8 participants with a mean percentage change of 24% and a range of 7% to 46%
        - Reductions in GDF-15 concentrations were observed in 4 of the 8 participants with the greatest reductions (up to 39%) observed in participants with higher concentrations of GDF-15 at baseline
        - Changes across these biomarkers, including FGF-21, an additional biomarker of mitochondrial dysfunction, were also strongly correlated with each other and with CY6463 plasma concentrations at the end of treatment
    - Approximately two thirds of a panel of 40 plasma biomarkers of inflammation were decreased from baseline following dosing with CY6463. The largest effect sizes were observed in serum amyloid P, Beta2-microglobulin. Effects were also observed in tumor necrosis factor receptor 2 and vascular cell adhesion protein 1, which are known to be implicated in mitochondrial disease. Overall, the greatest reductions in these biomarkers were observed in participants with the highest concentrations at baseline.

- Increases from baseline in cerebral blood flow were observed for 5 of the 8 participants, ranging from 19% to 60% (mean change of 42%). Changes in cerebral blood flow were strongly correlated with clinical improvement as assessed by the Patient Global Impression of Change (PGIC) scale (r value of -0.84).
- Increases from baseline in functional connectivity between brain regions associated with sensorimotor processing and executive function were observed via resting state functional MRI (fMRI). fMRI BOLD response to visual stimulation, which is known to be markedly reduced in symptomatic MELAS patients compared to healthy controls, also improved following CY6463 dosing for 29 days as shown by increased activation of occipital brain regions in response to the visual stimulus compared to screening. Minimal change was observed between screening and pre-dose on day 1.

“In a disease category with no approved therapies, we are pleased to gather additional evidence that targeting a fundamental CNS signaling pathway with CY6463 could potentially help people with MELAS,” said Peter Hecht, Ph.D., Chief Executive Officer of Cyclerion. “We are eager to work with mitochondrial disease experts and the Food and Drug Administration (FDA) to design a development program to further advance CY6463 as a potential treatment for MELAS as quickly as possible.”

Webinar Replay Information
A replay of the event can be accessed on both the UMDF and Cyclerion websites at https://www.umdf.org/mito-university or https://ir.cyclerion.com/news-events/event-calendar.

About MELAS
Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) is one of the most complex orphan diseases affecting multiple organ systems, including the CNS, with different degrees of severity, and no approved therapies. MELAS is caused by some of the most common mitochondrial DNA mutations affecting the mitochondrial tRNA, and results in large clusters of familial cases of primary mitochondrial diseases (PMD). 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 can affect virtually any organ and cause intense 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 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 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 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 (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 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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