Cyclerion Therapeutics Hosted Webinar to Discuss Pipeline Progress

April 27, 2021

Provided updates on development strategy and execution for CY6463, a first-in-class, CNS-penetrant sGC stimulator, including IND clearance from FDA in ADv and ongoing MELAS program

Introduced new CY6463 clinical program in CIAS with key insights from neuropsychiatric key opinion leader, Andreas Reif, M.D.

Announced new development candidate, CY3018, a differentiated, next-generation CNS-penetrant sGC stimulator

CAMBRIDGE, Mass., April 27, 2021 (GLOBE NEWSWIRE) -- Cyclerion Therapeutics, Inc. (Nasdaq: CYCN), a clinical-stage biopharmaceutical company on a mission to develop treatments that restore cognitive function, hosted a webinar today to provide clinical updates for its first-in-class, CNS-penetrant soluble guanylate cyclase (sGC) stimulator CY6463 in Alzheimer's Disease with Vascular pathology (ADv) and Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS). Supported by recent clinical and preclinical data, Cyclerion also discussed the potential for CY6463 to treat Cognitive Impairment Associated with Schizophrenia (CIAS), with key insights from Dr. Andreas Reif on the role of the sGC pathway in the disease. In addition, Cyclerion introduced its latest development candidate CY3018, a differentiated, next-generation, CNS-penetrant sGC stimulator.

"To deliver on our mission to develop treatments that restore cognitive function, we are harnessing the momentum and insights from our preclinical and clinical data on the fundamental role of the NO-sGC-cGMP pathway in central nervous system diseases," said Peter Hecht, Ph.D., Chief Executive Officer of Cyclerion. "Following the science, we see the potential to unlock significant opportunities across a number of patient populations with cognitive impairment, who are in desperate need of new therapeutic options."

Key Webinar Highlights

- **Modulating a fundamental CNS signaling pathway:** sGC stimulators amplify the power of the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate pathway (NO-sGC-cGMP) signaling to address central aspects of disease pathophysiology. Preclinical data from CY6463 and extensive academic work validate the crucial role of the sGC pathway in brain physiology. Clinical data from the recent translational pharmacology study confirm the ability of CY6463 to impact brain oscillations, neuroinflammation and neurophysiological function.

- **CY6463 Updates**

  - **Disease-relevant, biomarker-guided pipeline strategy:** The company is advancing parallel, signal-seeking, exploratory studies in well-defined patient populations with cognitive impairment including neurodegenerative, neuropsychiatric, and mitochondrial diseases. CY6463 targets sGC, a proven druggable target, in critical brain regions and cell types linked to cognition and has demonstrated an impact on multiple biomarkers associated with cognition in previous Phase 1 studies.

  - **ADv clinical trial initiation:** The U.S. Food and Drug Administration (FDA) cleared the Investigational New Drug (IND) application for CY6463 in ADv, and the Company anticipates beginning to enroll patients in a 12-week Phase 2a clinical trial in patients with ADv by mid-2021, barring any COVID-19 related delays. This exploratory study is designed to evaluate safety, tolerability, and pharmacodynamic effects including impact on disease-relevant biomarkers.

  - **MELAS clinical trial advancement:** This study is enrolling more slowly than initially projected, primarily due to COVID-19. Data from the exploratory 29-day open-label Phase 2a pilot study in patients with MELAS are now expected by year end 2021.

  - **Potential to treat CIAS with novel mechanism:** Neuropsychiatric key opinion leader and expert in the neurobiology of nitric oxide and its relation to psychiatric disorders, Andreas Reif, M.D., Chair, Department of Psychiatry, University Hospital Frankfurt, discussed the sGC pathway and its role in cognitive function and CIAS. Reduced NO-sGC-cGMP signaling is linked to cognitive dysfunction in schizophrenia. Stimulation of sGC by CY6463 to amplify NO-sGC-cGMP signaling is a potential first-in-class approach for the treatment of CIAS. Cyclerion is planning to initiate a Phase 1b signal-seeking study in CIAS to evaluate safety and near-term impact on disease-relevant biomarkers.

- **CY3018, a differentiated, next-generation CNS-penetrant sGC stimulator:** Cyclerion shared information on the latest

development candidate, CY3018. Preclinical data show increased CNS-exposure, with significantly increased cerebrospinal fluid (CSF) to plasma ratio, compared to CY6463. This increased CNS distribution is mirrored by a higher level of pharmacological activity in the CNS relative to the periphery. The company is advancing CY3018 through IND-enabling development.

"We are using insights from our preclinical and clinical data to tap into a fundamental CNS signaling pathway with CY6463 – our first-in-class, CNS-penetrant sGC stimulator," said Andy Busch, Ph.D., Chief Scientific Officer at Cyclerion. "We are excited by the data from our CY6463 translational pharmacology study that demonstrated rapid improvement in biomarkers associated with cognition and reflect CY6463's multidimensional pharmacology. These data are leading us to explore opportunities in cognition through the sGC pathway."

Cash, cash equivalents, and restricted cash balance on March 31, 2021 was approximately $45 million, as compared to approximately $58 million on December 31, 2020. As of April 2021, Cyclerion has substantially streamlined its operating model to invest more fully in its priority opportunities in cognition and expects average monthly cash use for the foreseeable future to be approximately 50 percent that of 2020.

Webinar Replay Information
A replay of the event can be accessed by visiting the investors' section of the Cyclerion website at https://ir.cyclerion.com/news-events/event-calendar.

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 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
This press release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Our forward-looking statements are based on current beliefs and expectations of our management team that involve risks, potential changes in circumstances, assumptions, and uncertainties, including statements about the anticipated timing of release of topline results of our clinical trials; the progression of our discovery programs into clinical development; and the business and operations of the Company. We may, in some cases use terms such as "predicts," "believes," "potential," "continue," "anticipates," "estimates," "expects," "plans," "intends," "may," "could," "might," "likely," "will," "should" or other words that convey uncertainty of the future events or outcomes to identify these forward-looking statements. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include those related to the possibility that any results of operations and financial condition of the Company reported are preliminary and subject to final audit and the risks listed under the heading "Risk Factors" and elsewhere in our 2020 Form 10-K filed on February 25, 2021, and our subsequent SEC filings. Investors are cautioned not to place undue reliance on these forward-looking statements. These forward-looking statements (except as otherwise noted) speak only as of the date of this press release, and Cyclerion undertakes no obligation to update these forward-looking statements, except as required by law.

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