Sage Therapeutics Inc Logo

Sage Therapeutics Announces Planned Progression of SAGE-718 to Phase 2 in Huntington's Disease and Presentations at the 2019 Annual Meeting of the American College of Neuropsychopharmacology (ACNP)

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Three poster presentations highlight the role of NMDA receptor dysfunction in Huntington's Disease related cognitive impairment and potential for positive cognitive effects with SAGE-718

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Dec. 10, 2019-- Sage Therapeutics (NASDAQ: SAGE), a biopharmaceutical company committed to developing novel therapies with the potential to transform the lives of people with debilitating disorders of the brain, today announced that it plans to advance SAGE-718, a novel, first-in-class, oxysterol-based positive allosteric modulator (PAM) of N-methyl-D-aspartate (NMDA) receptors, to a Phase 2 placebo-controlled clinical trial in patients with Huntington's disease (HD). The planned progression of SAGE-718 is based on results from Phase 1 studies evaluating the safety and tolerability of SAGE-718, including an open-label cohort of patients with HD.

In the 14-day open-label study of patients with HD, the safety, tolerability, and pharmacokinetic profile of daily SAGE-718 oral solution were evaluated in six patients with early HD. In the study, SAGE-718 was well tolerated, with no serious adverse events or adverse events leading to treatment discontinuation. In addition, patients demonstrated improved performance, compared to baseline, on assessments of executive functioning, with measures relevant to the core cognitive decline seen in people with HD. These results are comparable to improvements in measures of executive function observed in an earlier Phase 1 cohort of individuals without HD. Additional data from the Phase 1 open-label cohort study on the safety and tolerability of SAGE-718 in patients with early HD will be presented at a future congress in 2020.

In addition, the Company is presenting data from three other non-clinical and Phase 1 studies with SAGE-718 at the 58th Annual Meeting of the American College of Neuropsychopharmacology (ACNP). The poster presentations provide supportive evidence for the role of NMDA receptor dysfunction in Huntington's Disease-related cognitive impairment, as well as functional target engagement of SAGE-718, including positive cognitive effects in healthy volunteers.

"There is a critical need for better therapeutics to help patients with cognitive decline, particularly those suffering from conditions such as Huntington's disease," said Mike Quirk, vice president, pharmacology at Sage. "Discovering and developing treatments with the potential to quickly and meaningfully improve the lives of patients is a significant driver of our growing neuropsychiatry franchise. The SAGE-718 data presented at ACNP, together with Phase 1 data from patients with Huntington's Disease, marks an important achievement for our NMDA platform, and supports the progression of SAGE-718 to Phase 2."

Data presentations at ACNP focus on additional studies in HD, including SAGE-718 data:

Poster [M-147]: **Cognitive Deficits in Huntington's Disease and Altered 24(S)-hydroxycholesterol**

24(S)-hydroxycholesterol (24(S)-HC) is an endogenous, brain-specific, cholesterol metabolite that acts as a PAM of the NMDA receptor. Previous work has established that levels of 24(S)-HC are decreased in the plasma and brain in people with HD.

- In this study, plasma samples from the TRACK-HD study, a longitudinal observational study of biological and clinical manifestations of HD, were analyzed.
- Results demonstrated levels of 24(S)-HC declined during the transition from pre-manifest to manifest HD, and that levels correlated with performance on tests of executive dysfunction and emotional

processing.
- These data support a role for 24(S)-HC in cognitive changes in HD and suggest that NMDA hypofunction may contribute to cognitive impairment in HD.

Poster [M-144]: Using a Multimodal Biomarker Approach to Identify Functional Target Engagement of the Novel NMDA Positive Allosteric Modulator SAGE-718

A suite of three clinical studies was designed to evaluate CNS-target engagement of SAGE-718 by electrophysiology and magnetic resonance imaging (MRI), using a low-dose ketamine challenge paradigm in healthy adults in a placebo controlled cross-over design.

- In these studies, SAGE-718 was generally well tolerated with no serious adverse events or adverse events leading to treatment discontinuation.
- A single dose administration of SAGE-718 (3 mg oral solution) attenuated ketamine-induced changes in functional MRI-derived alterations of blood oxygenation levels (BOLD), including attenuation of ketamine-induced increases of BOLD observed in posterior brain regions and decreases observed in anterior brain regions (n=13).
- In a single-click, auditory evoked potential paradigm, the N100-P200 potential waveform was significantly reduced by ketamine under placebo conditions, but not after administration of SAGE-718 (n=18).
- Results from these studies demonstrate that SAGE-718 had effects on functional imaging in healthy volunteers. SAGE-718 also modulated the effects of ketamine on regional and global measures of resting brain activity. These effects are in line with the presumed mechanism of action of SAGE-718 as an NMDA PAM, which supports the hypothesis of functional engagement of the NMDA receptor.

Poster [M-143]: Cognitive Performance After Repeated Administration of the NMDA Positive Allosteric Modulator SAGE-718 in Healthy Volunteers

In a double-blind, placebo-controlled study, the effects of 10-day repeated exposure of SAGE-718 on core cognitive battery were investigated in healthy volunteers. Healthy volunteers (n=40) were randomized to receive either SAGE-718 1 mg (n=19) plus ketamine or placebo (n=21) plus ketamine, and computerized testing was used to measure performance on key cognitive domains, including attention, working memory, processing speed, executive function, and motor reaction time.

- Statistically significant improvements were observed compared to placebo on tests of higher-order working memory (Two-Back Test) and complex problem solving (Groton Maze Test).
- SAGE-718 was generally well tolerated with no serious adverse events or adverse events leading to study withdrawal or discontinuation.
- Improvements in executive performance, as reflected by significant improvements on the Two-Back and Groton Maze tests, suggest that SAGE-718 is potentially distinct from other cognitive-enhancing compounds and supports further investigation of SAGE-718 for the treatment of conditions characterized by states of relative NMDA hypofunction, particularly those manifesting with executive deficits.

About SAGE-718 and NMDA Receptors

SAGE-718 is a novel, oral, first-in-class, oxysterol-based positive allosteric modulator (PAM) of N-methyl-D-aspartate (NMDA) receptors. SAGE-718 is the lead compound from Sage's NMDA modulator platform.

NMDA receptors are glutamate-gated cation channels that play a critical role in the health and regulation of neurons, and are involved in learning, memory and neuroplasticity. Positive modulation of NMDA receptors may have potential benefit in the treatment of conditions associated with NMDA hypofunction and disorders associated with a high prevalence of anti-NMDA antibodies, as well as in disorders associated with

reductions in plasma cerebrosterol, such as Huntington's disease and Alzheimer's disease.

About Sage Therapeutics

Sage Therapeutics is a biopharmaceutical company committed to developing novel therapies with the potential to transform the lives of people with debilitating disorders of the brain. We are pursuing new pathways with the goal of improving brain health, and our depression, neurology and neuropsychiatry franchise programs aim to change how brain disorders are thought about and treated. Our mission is to make medicines that matter so people can get better, sooner. For more information, please visit www.sagerx.com.

Forward-Looking Statements

Various statements in this release concern Sage's future expectations, plans and prospects, including without limitation: our views and expectations regarding our development plans for SAGE-718; our belief in the potential of SAGE-718 in various indications; the potential profile and benefit of SAGE-718; and the goals, opportunity and potential for our other product candidates and business. These statements constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. These forward-looking statements are neither promises nor guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, which could cause actual results to differ materially from those contemplated in these forward-looking statements, including the risks that: we may not be successful in our development of SAGE-718 or any of our other current or future product candidates in any indication we are currently pursuing or may in the future pursue; success in earlier clinical trials or nonclinical studies may not be repeated or observed in ongoing or future studies of SAGE-718 or any of our other product candidates; ongoing and future clinical or nonclinical results may generate results that are different than we expect or may not support further development; we may decide that a development pathway for SAGE-718 or any of our other product candidates in one or more indications is no longer feasible or advisable or that the unmet need no longer exists; decisions or actions of the FDA or other regulatory agencies may affect our plans for development of SAGE-718, including the initiation, timing, design, size, progress and cost of clinical trials and our ability to proceed with further development; we may experience slower than expected initiation or enrollment in ongoing or future clinical trials; we may encounter unexpected safety or tolerability issues with SAGE-718 or any of our other product candidates; the internal and external costs required for our ongoing and planned research and development efforts, and to build our organization in connection with such activities, and the resulting expense increases and use of cash, may be higher than expected which may cause us to change or curtail some of our plans; and we may encounter technical and other unexpected hurdles in the development of SAGE-718 or our other product candidates; as well as those risks more fully discussed in the section entitled "Risk Factors" in our most recent quarterly report filed with the Securities and Exchange Commission (SEC), and discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. In addition, any forward-looking statements represent our views only as of today, and should not be relied upon as representing our views as of any subsequent date. We explicitly disclaim any obligation to update any forward-looking statements.

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