Sage Therapeutics Inc Logo

## Sage Therapeutics Reports Topline Results from Pivotal Phase 3 MOUNTAIN Study of SAGE-217 in Major Depressive Disorder

December 5, 2019

*MOUNTAIN Study did not meet primary endpoint at Day 15*

*Statistical significance on HAM-D scale achieved at Days 3, 8 and 12; preliminary data from long-term follow-up suggest maintenance of effect on depressive symptoms*

*Statistical significance achieved at Days 3, 8, 12 and 15 in patients with measurable drug concentration levels of SAGE-217*

*Statistical significance achieved in patients comparable to those studied in earlier trials with SAGE-217 (HAM-D>24)*

*SAGE-217 was generally well-tolerated with safety profile comparable to placebo*

*Conference call scheduled at 8:30 a.m. EST*

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Dec. 5, 2019-- Sage Therapeutics (NASDAQ: SAGE), a biopharmaceutical company developing novel therapies for people with debilitating brain disorders, today reported topline results from the pivotal Phase 3 MOUNTAIN Study evaluating the effect of SAGE-217 on depressive symptoms in adults with major depressive disorder (MDD). The MOUNTAIN Study did not meet its primary endpoint of a statistically significant reduction from baseline compared to placebo in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 15. SAGE-217 30 mg, given once-daily as an oral treatment, was associated with a mean reduction of 12.6 in HAM-D total score compared to 11.2 for placebo ($p=0.115$). Patients in the SAGE-217 30 mg group achieved statistically significant reductions in the HAM-D total score at Days 3, 8 and 12 ($p<0.018$ for each timepoint). The SAGE-217 development program includes five other pivotal studies, two of which have reported positive data, one in MDD and one in postpartum depression (PPD), and three of which are ongoing.

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Post-hoc analysis revealed that in the MOUNTAIN Study, approximately 9% of patients in the SAGE-217 30 mg group had no measurable drug concentration, consistent with non-compliance in taking SAGE-217. Excluding these patients from the primary analysis set (SAGE-217 30 mg vs. placebo) resulted in statistical significance at all timepoints through, and including, Day 15 ($p<0.048$).

The study enrolled more patients with an overall distribution of milder severity of symptoms than previous studies of SAGE-217. When including only patients with a HAM-D>24 ($n=124$ for SAGE-217 30 mg), a post-hoc analysis demonstrated statistical significance at all timepoints through, and including, Day 15 ($p<0.032$). Analyses utilizing a HAM-D cutoff of 25 or 26 were also statistically significant.

SAGE-217 was generally well-tolerated and showed a similar safety profile as seen in earlier studies. Overall reports of adverse events (AEs) during the 14-day treatment period and 28-day follow-up were similar between SAGE-217 and placebo (30 mg 54.2%, 20 mg 50.0%, placebo 48.9%). The most common AEs (≥5%) in either SAGE-217 group were headache, dizziness, somnolence, fatigue, diarrhea, sedation and nausea.

“This study did not meet the primary endpoint. With that, the data are supportive of the activity of SAGE-217

in MDD given the statistical significance at the majority of timepoints, and in relevant populations," said Jeff Jonas, M.D., chief executive officer at Sage. "Notwithstanding the finding on the primary endpoint, the drug displays good activity on most measures. We understand that drug development is an iterative process. In this study, we've gathered new data on SAGE-217, data we believe support our hypothesis that SAGE-217 has a unique profile with the potential for rapid and robust onset with durable effect."

"These study results reinforce that we have an active drug with safety data that are consistent with the two earlier pivotal trials in MDD and PPD," said Steve Kanes, M.D., Ph.D., chief medical officer at Sage. "As a designated breakthrough therapy, we are evaluating the path forward to more fully inform a potentially expedited pathway to approval, and any amendments we might consider to the ongoing SAGE-217 pivotal program."

**Summary of topline results from the MOUNTAIN Study**
Sage's Phase 3 MOUNTAIN Study evaluated the efficacy, safety and pharmacokinetics of SAGE-217 in adult patients diagnosed with MDD (MADRS total score ≥32 and a HAM-D total score ≥22).

**Effect on depressive symptoms through end of treatment and follow-up**
At Day 15, the primary endpoint and end of dosing, patients randomized to SAGE-217 30 mg demonstrated a reduction in depressive symptoms of 12.6 in the HAM-D total score compared with 11.2 in patients who received placebo (LS Mean Difference from placebo -1.4, p=0.115).

Rapid onset of effect for SAGE-217 30 mg (n=166) was noted beginning at Day 3 and statistical significance from placebo (n=157) was noted at all visits during the treatment period leading up to Day 15 (LS Mean Difference from placebo, p-value): Day 3 (-1.6, p=0.016), Day 8 (-2.1, p=0.008) and Day 12 (-2.1, p=0.018).

Improvements in depressive symptoms were sustained in all treatment groups through Day 42 of the double-blind portion of the study. Change from baseline in HAM-D total score at Day 42 for SAGE-217 30 mg was -11.9 and for placebo was -11.7 (LS Mean Difference from placebo -0.2, p=0.807). Preliminary data suggest maintenance of improvement in depressive symptoms in those patients who have completed long-term follow-up up to 6 months. These data will continue to be collected in the coming months.

The 20 mg dose of SAGE-217 did not separate from placebo in this dose-ranging study.

**Effect on depressive symptoms by performance factors**
Post-hoc analyses were conducted to evaluate the effects of performance factors on the primary outcome at Day 15.

Change from baseline in HAM-D total score at Day 15, SAGE-217 30 mg vs. placebo:

- Patients with SAGE-217 measurable drug concentrations (n=151) (excluding 30 mg patients with no measurable drug concentration consistent with noncompliance): SAGE-217 30 mg (-13.0) vs. placebo (-11.2); LS Mean Difference -1.8, p=0.048.
- Patients with HAM-D≥24 (n=124): SAGE-217 30 mg (-13.7) vs. placebo (-11.4); LS Mean Difference -2.3, p=0.032.
- Patients with SAGE-217 measurable drug concentrations and HAM-D≥24 (n=115): SAGE-217 30 mg (-14.0) vs. placebo (-11.4); LS Mean Difference -2.6; p=0.017.

**Safety and tolerability**
SAGE-217 was generally well tolerated in the trial. The overall incidence of patients who experienced AEs during the 14-day treatment period and 28-day follow up was 54.2% for SAGE-217 30 mg, 50.0% for SAGE-217 20 mg and 48.9% for placebo.

- Two patients receiving SAGE-217 30 mg experienced serious adverse events (SAEs) during treatment: one suicide attempt on Day 5 in a patient with a longstanding history of MDD and a past

suicide attempt, and one report of a bile duct stone after Day 2 requiring removal in a patient with a prior bile duct repair. In addition, three patients, one in each treatment group, reported SAEs during follow-up, all occurring at least one week following cessation of treatment: syncope and associated injuries which occurred with dehydration and orthostatic hypotension during exercise in a patient with a history of bradycardia (SAGE-217 30 mg, Day 28), multiple SAEs related to medical complications of cocaine ingestion (SAGE-217 20 mg, Day 39) and suicidal ideation (placebo, Day 22).

- The number of subjects having treatment emergent AEs leading to study drug discontinuation were similar in each treatment group (SAGE-217 30 mg 2.1%, SAGE-217 20 mg 1.6% and placebo 3.2%).
- The most common AEs (≥5%) in any group (SAGE-217 30 mg, SAGE-217 20 mg and placebo) during the 14-day treatment period and the 28-day follow up were:
    - Headache (30 mg 6.3%, 20 mg 11.2%, placebo 7.4%)
    - Dizziness (30 mg 5.7%, 20 mg 7.4%, placebo 3.7%)
    - Somnolence (30 mg 6.8%, 20 mg 5.9%, placebo 4.2%)
    - Fatigue (30 mg 6.8%, 20 mg 1.6%, placebo 2.6%)
    - Diarrhea (30 mg 6.3%, 20 mg 5.9%, placebo 5.3%)
    - Sedation (30 mg 4.7%, 20 mg 5.9%, placebo 3.2%)
    - Nausea (30 mg 3.6%, 20 mg 5.3%, placebo 4.7%)
- There were no AEs of loss of consciousness.
- There was no signal for increased suicidal ideation or suicidal behavior compared to baseline, as measured by Columbia Suicide Severity Rating Scale (C-SSRS).

Sage plans to present additional results from the MOUNTAIN Study at an upcoming medical congress.

**About the MOUNTAIN Study**
The MOUNTAIN Study is a double-blind, placebo-controlled pivotal Phase 3 study evaluating the efficacy and safety of SAGE-217 in adults with major depressive disorder (MDD). In the study, 581 patients were randomized to receive SAGE-217, 20 mg or 30 mg, or placebo, once-nightly for two-weeks. The primary endpoint of the study is the change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 15. Secondary endpoints include the change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Rating Scale (HAM-A) total score, among others.

**About Major Depressive Disorder**
Major depressive disorder (MDD), commonly referred to as depression, is a brain health disorder that affects an estimated 17 million adults in the U.S. each year. It is one of the largest contributors to disability in the U.S. and worldwide and is characterized by symptoms of depressed mood and/or loss of interest in pleasurable activities. MDD causes significant impairment in daily life and can limit a person’s ability to fulfill work, school, family, or social responsibilities; enjoy leisure activities; or maintain health and hygiene. While antidepressants are widely used to treat MDD, large-scale studies have demonstrated that there is an unmet need in the treatment of MDD as well as the need for new therapeutic options.

**About SAGE-217**
SAGE-217 is an investigational, oral, novel medicine in development for depression. SAGE-217 is an investigational oral neuroactive steroid (NAS) $GABA_A$ receptor positive allosteric modulator (PAM). The GABA system is the major inhibitory signaling pathway of the brain and central nervous system (CNS), and contributes significantly to regulating CNS function.

The clinical program evaluating SAGE-217 in depression is progressing. To date, two positive pivotal studies have been completed, one in MDD (MDD-201) and one in postpartum depression (ROBIN Study). Ongoing studies include the REDWOOD, SHORELINE and RAINFOREST studies.

**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 the potential of SAGE-217 in the treatment of depression; our views as to the potential profile and benefit of SAGE-217; our plans and expectations related to ongoing development of SAGE-217, the potential pathway for approval and next steps; and our plans, goals, opportunity and potential for our programs 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-217 in depression or of 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; ongoing and future clinical or nonclinical results may generate results that are different than we expect or may not support further development or be sufficient to gain regulatory approval of SAGE-217 or any of our other product candidates; the FDA may decide that the development program for SAGE-217, or any of our product candidates, is not sufficient for a new drug application filing or approval and may require completion of additional clinical trials or nonclinical studies; we may decide that a development pathway for one of our 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 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; 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-217 or any of 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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