Sage Therapeutics Announces SAGE-217 Meets Primary and Secondary Endpoints in Phase 3 Clinical Trial in Postpartum Depression

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– Statistically significant reduction observed in depressive symptoms compared to placebo in women with postpartum depression (PPD) –

– Well-tolerated with rapid onset of statistically significant effect (Day 3) through two weeks and maintained for four weeks after treatment –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jan. 7, 2019-- Sage Therapeutics (NASDAQ:SAGE), a biopharmaceutical company developing novel medicines to treat life-altering central nervous system (CNS) disorders, today reported top-line results from the Phase 3 ROBIN Study. This study evaluated the effect of SAGE-217 30 mg on depressive symptoms in women with postpartum depression (PPD). After two weeks of outpatient treatment, patients treated with SAGE-217 had a statistically significant improvement of 17.8 points in the Hamilton Rating Scale for Depression (HAMD-17) score, compared to 13.6 for placebo (primary endpoint, p=0.0029), with statistically significant reductions in HAMD-17 compared to placebo maintained through the end of the four-week follow-up. Remission was achieved in 45% of patients treated with SAGE-217 for two weeks as measured by the HAMD-17 compared with 23% of patients receiving placebo (p=0.0122). Results from secondary endpoints were statistically significant and consistent with the primary endpoint.

SAGE-217 was generally well-tolerated with a safety profile consistent with that seen in earlier SAGE-217 trials. Overall reports of AEs were similar between SAGE-217 (58%) and placebo (51%). Two subjects experienced serious adverse events (SAEs), one subject in each group.

“These are strong and consistent data demonstrating a rapid, stable, and clinically meaningful improvement in PPD depressive symptoms in the SAGE-217 treatment group compared to placebo,” said Jeff Jonas, M.D., chief executive officer of Sage. “This is our fifth consecutive positive study in mood disorders with our investigational medicines that utilize our innovative approach to GABA receptor modulation. Data from the ROBIN Study, along with earlier data from our studies with ZULRESSO in PPD and SAGE-217 in major depressive disorder, all point to the promise that our approach may hold - not only in changing the way PPD and MDD are treated, but also in potentially improving the lives of patients suffering from these mood disorders. The team at Sage has shown what rethinking CNS really means.”

The ROBIN Study is part of a pivotal program studying SAGE-217 as a short-course oral treatment for PPD and major depressive disorder.

Summary of Top-line SAGE-217 Phase 3 PPD Trial Results

Sage’s Phase 3 ROBIN Study evaluated the efficacy, safety and pharmacokinetics of SAGE-217 in 151 adult female patients diagnosed with severe PPD (HAMD-17 ≥26).

Effect on Postpartum Depressive Symptoms:

- Statistically significant differences in the reduction in HAMD-17 total score of SAGE-217 versus

placebo were first observed on Day 3 (-12.5 vs. -9.8; p=0.0255) and the effect was maintained at each timepoint through two weeks of treatment (-17.8 vs. -13.6; p=0.0029), the primary endpoint of the study. The effect was maintained through the four-week follow-up (-19.2 vs. -15.1; p=0.0027).

- After two weeks of treatment with SAGE-217, 45% of patients achieved remission (HAMD-17 ≤7) compared with 23% of patients who received placebo (p=0.0122); at the end of the four-week follow-up, 53% of patients receiving SAGE-217 achieved remission compared with 30% of patients who received placebo (p=0.0102).
- After two weeks of treatment with SAGE-217, 72% of patients achieved a response (50% improvement from baseline HAMD-17 score) compared with 48% of patients who received placebo (p=0.0050); at the end of the four-week follow-up, 75% of patients receiving SAGE-217 achieved a response compared with 57% of patients who received placebo (p=0.0220).
- Statistically significant differences in the reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) score for the SAGE-217 treatment group versus placebo were observed after two weeks of treatment (-22 vs. -18; p=0.0182) and the effect was maintained through the end of the four-week follow-up (-25 vs. -19; p=0.0018).
- Other secondary endpoints, including the Hamilton Anxiety Rating Scale (HAM-A) and Clinical Global Impression – Improvement (CGI-I) Scale, also showed statistically significant improvements in favor of SAGE-217 vs placebo.

Safety and Tolerability:

- SAGE-217 was generally well tolerated in the trial. The overall incidence of patients who experienced adverse events was 58% for the SAGE-217 treatment group and 51% for the placebo group.
    - One subject experienced a serious adverse event in the SAGE-217 arm that resolved after dose reduction. One subject experienced a serious adverse event in the placebo arm.
    - There were no reports of loss of consciousness or syncope in either arm of the trial.
    - One subject in the SAGE-217 group discontinued due to an adverse event.
- The most common adverse events (≥5%) in either treatment group were somnolence (12.8% SAGE-217; 8.2% placebo), headache (9.0% SAGE-217; 12.3% placebo), dizziness (7.7% SAGE-217; 5.5% placebo), upper respiratory tract infection (7.7% SAGE-217; 1.4% placebo), diarrhea (6.4% SAGE-217; 2.7% placebo), nausea (3.8% SAGE-217; 8.2% placebo), sedation (5.1% SAGE-217; 0.0% placebo), vomiting (1.3% SAGE-217; 5.5% placebo), abnormal dreams (0.0% SAGE-217; 5.5% placebo) and hyperhidrosis (0.0% SAGE-217; 5.5% placebo).
- There was no signal for increased suicidal ideation or suicidal behavior compared to baseline, as measured by the Columbia Suicide Severity Rating Scale (C-SSRS). There was one report of self-injurious behavior in the placebo arm.

About the ROBIN Study

Sage's Phase 3 ROBIN Study evaluated the efficacy, safety and pharmacokinetics of SAGE-217 in 151 adult female patients diagnosed with severe postpartum depression (PPD). The primary endpoint of the multicenter, randomized, double-blind, parallel-group, placebo-controlled study was to determine if outpatient treatment with SAGE-217 reduces depressive symptoms in subjects with severe PPD compared to placebo as assessed by the change from baseline in the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score at Day 15.

For more information about this trial, please visit https://therobinstudy.com/.

About Postpartum Depression

Postpartum depression (PPD) is a distinct and readily identified major depressive disorder that is the most common medical complication of childbirth, affecting a subset of women typically commencing in the third trimester of pregnancy or within four weeks after giving birth. PPD may have devastating consequences for a woman and for her family, which may include significant functional impairment, depressed mood and/or loss

of interest in her newborn, and associated symptoms of depression such as loss of appetite, difficulty sleeping, motor challenges, lack of concentration, loss of energy and poor self-esteem. Suicide is the leading cause of maternal death following childbirth. Postpartum depression affects approximately one in nine women who have given birth in the U.S. and 400,000 women annually. More than half of these cases may go undiagnosed without proper screening.

About SAGE-217

SAGE-217 is a next generation positive allosteric modulator that has been optimized for selectivity to synaptic and extrasynaptic $GABA_A$ receptors and a pharmacokinetic profile intended for daily oral dosing. The GABA system is the major inhibitory signaling pathway of the brain and central nervous system (CNS), and contributes significantly to regulating CNS function. SAGE-217 is currently being developed for MDD, PPD and certain other mood disorders.

About Sage Therapeutics

Sage Therapeutics is a clinical-stage biopharmaceutical company committed to developing novel medicines to transform the lives of patients with life-altering CNS disorders. Sage's lead product candidate, ZULRESSO™ (brexanolone) injection, has completed Phase 3 clinical development for postpartum depression and a New Drug Application is currently under review with the U.S. Food and Drug Administration. Sage is developing a portfolio of novel product candidates targeting critical CNS receptor systems, including SAGE-217, which is in Phase 3 development in major depressive disorder and postpartum depression. 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 as to the potential of SAGE-217 in PPD and MDD and of ZULRESSO in PPD to change the ways those disorders are treated and to potentially improve lives; our estimates as to the number of patients with PPD; and our other statements regarding the potential of ourproduct candidates. 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 or of any of our other product candidates in any indication we are currently pursuing or may in the future pursue; success in earlier stage clinical trials or in nonclinical studies may not be repeated or observed in ongoing or future studies, and ongoing and future non-clinical and clinical results, including with respect to SAGE-217, may not support further development or be sufficient to gain regulatory approval to market the product; we may not be successful in our efforts to gain FDA approval of ZULRESSO; we may encounter adverse events at any stage of development of our product candidates or in commercialization of our products, if approved, that may negatively impact further development or limit market acceptance of any product we may commercialize; the actual size of the PPD patient population may be significantly lower than our estimates and, even if ZULRESSO or SAGE-217 is approved, it may only be approved or used to treat a subset of the relevant patient populations; and we may encounter technical and other unexpected hurdles in the development and manufacture of SAGE-217 or any of our other product candidates which may delay our timing or change our plans, as well as those risks more fully discussed in the section entitled "Risk Factors" in our most recent Quarterly Report on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. 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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