Sage Therapeutics Announces Positive Results from Placebo-Controlled Trial in a Model of Insomnia Demonstrating Activity on Sleep Parameters and Supporting Development of SAGE-217 as Potential Treatment for Sleep Disorders

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– SAGE-217 met primary endpoint of improved sleep efficiency and demonstrated improvements in maintaining sleep compared to placebo –

– Secondary endpoint measures demonstrated clear dose response with statistical significance in total sleep time and time spent awake after sleep onset –

– Data support further development of SAGE-217 in disorders associated with disruption of normal sleep –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jan. 31, 2018-- Sage Therapeutics (NASDAQ: SAGE), a clinical-stage biopharmaceutical company developing novel medicines to treat life-altering central nervous system (CNS) disorders, today announced positive results from a Phase 1/2, double-blind, placebo-controlled study of SAGE-217 in the treatment of healthy adult volunteers using a 5-hour phase advance model of insomnia using polysomnography. SAGE-217, administered as a single dose at either 30 or 45 mg, significantly improved sleep efficiency (SE), the primary endpoint of the trial, to a median of 85 percent (30 mg; $p<0.0001$) and 88 percent (45 mg; $p<0.0001$), respectively, compared with a median SE of 73 percent for placebo. SAGE-217 also demonstrated statistically significant improvements in total sleep time as well as sleep maintenance as measured by time spent awake after sleep onset, although there was not a significant impact on sleep onset in this model as measured by latency to persistent sleep. SAGE-217 was generally well tolerated and all adverse events (AEs) were mild, with no serious AEs or AEs leading to discontinuation. Based on these positive results, Sage expects to initiate clinical development of SAGE-217 in disorders of sleep in 2018.

“Disturbances of sleep have a profound impact on the quality of life for many individuals, whether occurring as a primary disorder or as associated with other illness,” said Jeff Jonas, M.D., chief executive officer of Sage Therapeutics. “There is a significant need to create an improved patient experience for the treatment of sleep dysfunction, and our work with the GABA mechanism identified an opportunity to develop a potential solution. These findings support the unique potential of SAGE-217 across a variety of psychiatric and neurological disorders with unifying focus on related symptoms, including disorders of mood, sleep and motor function.”

“Key to the experimental medicine capability at Sage is translating insights between compounds and indications for better odds of success across the pipeline,” said Jim Doherty, Ph.D., chief research officer of Sage Therapeutics. “Our evaluation of SAGE-217 in multiple clinical trials, across several indications, suggests that the drug’s mechanism of action may rebalance fundamental brain circuitry, therefore supporting SAGE-217’s development across a broad variety of disorders. These findings suggest that SAGE-217 has the potential to assist sleep maintenance, and we were pleased with the tolerability demonstrated for both doses in this trial.”

Top-line Trial Results

- **Sleep Efficiency (primary endpoint):** the percentage of time in bed spent asleep, as determined by polysomnography.
  - SAGE-217, 30 and 45 mg, administered as a single dose significantly improved Sleep Efficiency (SE) to a median of 84.64% ($p<0.0001$) and 87.55% ($p<0.0001$), respectively compared with a median SE of 72.92% for placebo.
- **Wake After Sleep Onset (secondary endpoint):** total wake time, in minutes, from persistent sleep onset to lights-on, as determined by polysomnography.
  - SAGE-217, 30 and 45 mg, decreased time of wake after sleep onset (WASO) to a median of 55.0 minutes ($p<0.0001$) and 42.5 minutes ($p<0.0001$), respectively, compared with 113.0 minutes for subjects on placebo.
- **Total Sleep Time (secondary endpoint):** duration of total sleep time (non-REM and REM) from lights-off to lights-on during recording with polysomnography.
  - SAGE-217 increased total sleep time, compared with a median of 350.00 min in subjects treated with placebo, to 406.25 ($p<0.0001$) and 420.25 ($p<0.0001$) minutes, respectively for the 30 and 45 mg doses of SAGE-217.
- **Latency to Persistent Sleep (secondary endpoint):** duration in minutes from lights-off to the first epoch of 20 consecutive non-wake epochs, as determined by polysomnography.
  - Compared with placebo, SAGE-217 did not have a significant impact on latency to persistent sleep ($p=0.7049$) with either dose.
- **Safety and Tolerability:** SAGE-217 was generally well tolerated in this study. Adverse event rates were low across all dose groups (4.8% SAGE-217 45 mg, 11.4% SAGE-217 30 mg and 9.8% placebo) and all adverse events (AEs) were mild. There were no serious AEs and no AEs leading to discontinuation.
- **Comprehensive data**, including additional secondary endpoint measures, will be presented at a future scientific conference.

Trial Design

In this double-blind, placebo-controlled crossover study (Treatment Periods 1, 2 and 3), healthy volunteers (n=45) were randomized to receive either 30 mg or 45 mg of SAGE-217 or placebo on three separate visits. Each participant received each dose level and placebo once.

Treatment Period 1 began on Study Day 1 and continued until Study Day 2, using a 5-hour phase advance model of insomnia (lights out and polysomnography recording began five hours (± 30 minutes) prior to participants habitual bedtime). Thirty minutes (±15 minutes) prior to lights out, blinded study drug (SAGE-217 30 mg, SAGE-217 45 mg, or placebo) was administered and participants were required to remain in bed for eight hours. Treatment Period 2 (Visit 4, Study Days 8 to 9) and Treatment Period 3 (Visit 5, Study Days 15 to 16) followed similar procedures.

About SAGE-217

SAGE-217 is a next generation positive allosteric modulator that targets synaptic and extrasynaptic GABA receptors and has a pharmacokinetic profile intended for daily oral dosing. The GABA system is the major inhibitory signaling pathway of the brain and CNS and contributes significantly to regulating CNS function. SAGE-217 is currently being developed in the treatment of MDD and certain other affective disorders, Parkinson's disease and sleep 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 central nervous system (CNS) disorders. Sage has a portfolio of novel product candidates targeting critical CNS receptor systems, GABA and NMDA. Sage's lead program, a proprietary IV formulation of brexanolone (SAGE-547), has completed Phase 3 clinical development for postpartum depression. Sage is developing its next generation modulators, including SAGE-217 and SAGE-718, in various CNS disorders. 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 expectations regarding the potential for SAGE-217 in the treatment of sleep disorders, depression and other diseases and disorders; our statements regarding plans for further development of SAGE-217 and related activities and the potential for successful development; our view of the potential of the GABA mechanism and our product candidates, including SAGE-217, in the treatment of CNS diseases and disorders; and our views as to the unmet need for additional options in the treatment of sleep disorders and the potential of SAGE-217 to meet the unmet need. 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 able to successfully demonstrate the efficacy and safety of SAGE-217 or any of our other product candidates at each stage of development; success in early stage clinical trials may not be repeated or observed in ongoing or future studies of SAGE-217 or any of our other product candidates; ongoing and future clinical results may not support further development or be sufficient to gain regulatory approval to market SAGE-217 or any of our other product candidates; 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 encounter unexpected safety or tolerability issues with SAGE-217 or any of our other product candidates in ongoing or future development; and we may encounter technical and other unexpected hurdles or delays in the development and manufacture 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 on Form 10-Q, and 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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