June 7, 2016

Sage Reports Positive Top-line Results from Phase 1 Clinical Program of SAGE-217

SAGE-217 was well-tolerated in single and multiple ascending doses

Results consistent with predicted pharmacokinetic and pharmacologic profile

Initiation of Phase 2 clinical trials planned for second half 2016

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Sage Therapeutics (NASDAQ:SAGE) today announced positive top-line results from its Phase 1 clinical program of SAGE-217, a novel, internally-developed orally active compound intended to enhance GABA receptor mediated inhibition in the brain. In the trial, SAGE-217 was found to be generally well-tolerated with no serious adverse events reported during the treatment and follow-up periods. Assessment of electrical activity in the brain using an electroencephalogram (EEG) showed clear evidence of target engagement ($GABA_A$ receptor modulation) starting at the lowest dose tested (15 mg). The observed EEG effect was sustained throughout the 7-day dosing period without diminution. In addition, rates of moderate to deep sedation defined by a structured rating scale (MOAA/S < 3) were comparable to placebo until the maximum tolerated dose (MTD) was reached, in both the single and multiple ascending dose phases of the study. The presence of sedation was associated with maximum drug exposure.

This Smart News Release features multimedia. View the full release here:
http://www.businesswire.com/news/home/20160607006570/en/

Sage is developing SAGE-217 for the treatment of several $GABA_A$ dysfunction-related disorders, including essential tremor and seizures associated with rare epilepsy disorders. In addition, SAGE-217 is under evaluation for potential use in postpartum depression (PPD). The company plans to announce additional details from the trial and complete data outcomes at the 13th Eilat Conference on New Antiepileptic Drugs and Devices in Madrid, Spain (June 26-29, 2016).

"SAGE-217 is an example of Sage's distinct approach to drug development and our ability to custom-tailor next-generation neuromodulators," said Jeff Jonas, M.D., Chief Executive Officer of Sage. "Leveraging insights into the brain's complexity and our knowledge of GABA modulation, Sage has developed a rich and growing library of proprietary compounds with the potential to address a variety of brain disorders. Our goal for SAGE 217 was to generate a highly potent, oral, extrasynaptic positive allosteric modulator of GABA, suitable for further development allowing once-daily dosing, and these data suggest our team was successful in this goal."

The primary objectives of the study were to assess the safety and tolerability, pharmacokinetic profile, and target engagement of SAGE-217 in healthy subjects in single (SAD) and multiple (MAD) ascending doses. The SAD and MAD studies were double-blind, placebo-controlled trials evaluating an oral solution formulation of SAGE-217 in single- and 7-day multiple ascending dose protocols. Both trials successfully met their primary endpoints.

"The performance of SAGE-217 in this Phase 1 program matched our expectations from preclinical studies, and we are quite pleased with the pharmacokinetic and pharmacodynamic profile that was demonstrated. When our solid formulation is introduced into studies, we believe this will provide multiple options for future development depending on the pharmacodynamic profile desired," said Jim Doherty, Ph.D., Senior Vice President of Research of Sage. "Based on the substantial amount of encouraging safety data that was generated, as well as demonstration of a profile useful for daily oral dosing, we are moving forward with plans for initiation of multiple Phase 2 trials of SAGE-217 later this year."

Summary of Preliminary SAGE-217 Phase 1 Study Results

- *Single Ascending Dose (SAD) Study:* In the SAD study, SAGE-217 was administered as an oral solution at doses between 0.25 and 66 mg in nine double-blind placebo controlled cohorts (randomized 6:2) enrolling a total of 72 healthy volunteers. Based on pre-specified dose escalation stopping criteria, the maximum tolerated dose (MTD) was established at 55 mg.

- *Multiple Ascending Dose (MAD) Study:* In the MAD study, three double-blind placebo controlled cohorts (randomized 9:3) with doses of 15 mg, 30 and 35 mg were tested against placebo over 7 days in 36 healthy volunteers. Those in the 30 mg cohort were tested both in the morning, and following a one-week washout period, tested for another 7 days with dosing in the evening. Based on pre-specified stopping criteria, the MTD for this study was established at 30 mg/day.
- *Safety, Tolerability and Pharmacokinetics:*
  SAGE-217 was generally well tolerated. In both trials, doses were escalated until the expected onset of deep sedation. At predicted efficacious doses, observed sedation was mild, transient and associated with daily peak exposure. Most adverse events were reported as mild or moderate in intensity. There were no serious adverse events reported in either trial. The 30 mg dosing administered in the evening was accompanied by lower mean sedation scores in the first 2 hours after dosing than were observed following morning administration.

  The pharmacokinetic profile obtained in both SAD and MAD of SAGE-217 is consistent with once daily dosing, displaying dose linearity over the multiple-dose range studied (15-35 mg), with a half-life ranging from 16 - 21 hours.

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 once-daily oral dosing. The GABAergic system is the major inhibitory signaling pathway of the brain and CNS and contributes significantly to regulating CNS function. SAGE is developing SAGE-217 for seizures associated with select neurological disorders, including orphan epilepsies, and other $GABA_A$ dysfunction-related disorders, such as essential tremor. Pending the outcome of the ongoing proof-of-concept clinical trial of SAGE-547 in severe PPD, the Company plans to commence development of SAGE-217 in the treatment of PPD, leveraging the fact that SAGE-217 shares important GABA receptor pharmacology with SAGE-547.

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, SAGE-547, is in Phase 3 clinical development for super-refractory status epilepticus, a rare and severe seizure disorder. Sage is developing its next generation modulators, including SAGE-217, SAGE-689 and SAGE-718, with a focus on acute and chronic 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 development of SAGE-217 and commencement of planned clinical trials, and statements related to our view of the potential of SAGE-217 and our other product candidates and of our development approach. 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 our product candidates at each stage of development; success in early stage clinical trials or non-clinical studies may not be repeated or observed in ongoing or future studies involving the same compound or other product candidates; and ongoing and future pre-clinical and clinical results may not support further development of a product candidate or be sufficient to gain regulatory approval to market any product; decisions or actions of regulatory agencies may affect the initiation, timing, progress and cost of clinical trials, and our ability to proceed with further clinical trials of a product candidate in a particular indication or at all or our ability to obtain marketing approval; 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; and we may encounter technical and other unexpected hurdles in the development and manufacture of our 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, 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.

View source version on businesswire.com: http://www.businesswire.com/news/home/20160607006570/en/

Investor Contact:
Sage Therapeutics
Paul Cox, 617-299-8377

paul.cox@sagerx.com
or
Media Contact:
Suda Communications LLC
Maureen L. Suda, 585-387-9248
maureen.suda@sagerx.com

Source: Sage Therapeutics