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Sage Therapeutics Announces Initiation of Phase 2 Clinical Development for SAGE-217 in Mood Disorders

First patient dosed in Phase 2 proof-of-concept trial of SAGE-217 in major depressive disorder and trial sites open for Phase 2 trial of SAGE-217 in postpartum depression

Four Phase 2 clinical programs now underway for SAGE-217 in mood and movement disorders

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Sage Therapeutics (NASDAQ:SAGE), a clinical-stage biopharmaceutical company developing novel medicines to treat life-altering central nervous system (CNS) disorders, today announced the initiation of Phase 2 clinical development for SAGE-217, a novel, internally-developed, next generation oral $GABA_A$ receptor modulator, in two mood disorder clinical programs - postpartum depression (PPD) and major depressive disorder (MDD). Dosing has now been initiated in the MDD study, with dosing expected imminently in the PPD trial. Top-line results from the Part A open-label study in MDD are expected in the first half of 2017, and the PPD study is anticipated to report results in the second half of 2017. Sage also recently initiated Phase 2 clinical trials of SAGE-217 in two movement disorders - essential tremor and Parkinson's disease.

"Sage is focused on developing bespoke next-generation compounds, differentiated from available therapies, that engage powerful mechanisms known to have broad effects on brain networks, such as the GABA receptor," said Jeff Jonas, M.D., Chief Executive Officer of Sage. "Our neuropsych development portfolio now includes seven clinical trials across five indications. We expect 2017 will be a data-rich year with potential significant pipeline expansion for Sage."

"Sage utilizes a novel, efficient and incremental translational approach that is intended to speed discovery and clinical development," said Steve Kanes, M.D., Ph.D., Chief Medical Officer of Sage. "The initiation of two mood disorder clinical trials with SAGE-217 is built on this strategy. Our oral molecule SAGE-217 shares important GABA receptor pharmacology with our intravenous agent SAGE-547. The SAGE-217 clinical program in mood disorders was specifically designed to build upon positive outcomes demonstrated to date in clinical trials in PPD with SAGE-547."

The postpartum depression study is a Phase 2a double-blind, placebo-controlled, randomized study that will evaluate the efficacy, safety, tolerability and pharmacokinetics of SAGE-217 in approximately 32 patients with severe postpartum depression. The primary endpoint of the study will be to evaluate the effect of SAGE-217 compared to placebo following two weeks of treatment as measured by the Hamilton Rating Scale for Depression (HAM-D) total score.

The major depressive disorder program is a two-part Phase 2a clinical trial evaluating the safety, tolerability, pharmacokinetics and efficacy of SAGE-217 in moderate to severe major depressive disorder patients. Part A of the Phase 2a trial will be an open-label, proof-of-concept study evaluating SAGE-217 in approximately 10 patients which, if promising, may lead to the Part B randomized, placebo-controlled phase of the trial. The primary endpoint for the Part A study will be to evaluate the safety and tolerability of SAGE-217. The secondary endpoint will be to evaluate the effect of SAGE-217 compared to placebo following two weeks of treatment as measured by the HAM-D total score.

About SAGE-217

SAGE-217 is a next generation positive allosteric modulator that has been optimized for selectivity to synaptic and extrasynaptic GABA receptors and 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. In a Phase 1 clinical program, SAGE-217 was well-tolerated in single and multiple ascending doses and the results were consistent with the predicted pharmacokinetic and pharmacologic profile. SAGE-217 is currently being developed for certain mood and movement disorders.

About Postpartum Depression

Postpartum depression (PPD) is an affective disorder impacting women after childbirth. 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. It is estimated that PPD affects 500,000 to 750,000 mothers in the US each year.[1,2] A subset of these are severe enough to require hospitalization. There are no approved therapies for PPD and there is a high unmet medical need for improved pharmacological therapy in PPD.

About Major Depressive Disorder

Major depression disorder (MDD) is a common but serious mood disorder in which patients exhibit depressive symptoms, such as a depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two-week period, and demonstrate impaired social, occupational, educational or other important functioning. Approximately 16 million people in the U.S. suffer from MDD each year.[3] While antidepressants are widely used for treatment, large scale studies have demonstrated their limited efficacy.[4,5]

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, and for postpartum depression. Sage is developing its next generation modulators, including SAGE-217 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 our other product candidates and their potential in the treatment of various CNS disorders; the expected initiation and timing of clinical trials and anticipated availability and announcement of data and results; our estimates as to the number of patients with MDD and PPD and our belief as to unmet need in these populations. 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 experience slower than expected clinical site initiation or enrollment in our clinical trials, or the potential need for additional analysis or data or the need to enroll additional patients, leading to possible delays in completion of trials or in the availability of data; we may not be able to generate supportive non-clinical data or to successfully demonstrate the efficacy and safety of our product candidates at each stage of development; success in our non-clinical studies or in earlier stage clinical trials 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 product candidates 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 studies of a product candidate or to obtain marketing approval; we may encounter adverse events at any stage of development that negatively impact further development; the actual size of the MDD and PPD patient populations may be significantly lower than our estimates; 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 products which may delay our timing or increase our expenses and use of cash, 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.

[1] Hamilton BE, Martin JA, Osterman MJK, et al. Births: Final data for 2014. *National Vital Statistics Reports*. National Center for Health Statistics, 2015, 64, 12. Available at http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_12.pdf.

[2] O'Hara MW, McCabe JE. Postpartum depression: Current status and future directions. *The Annual Review of Clinical Psychology*, 2013, 9, 379-407. doi: 10.1146/annurev-clinpsy-050212-185612.

[3] Nat. Inst. of Mental Health website, 2015; Available at https://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml.

[4] Trivedi MH et al. Evaluation of Outcomes with Citalopram for Depression using Measurement-Based Care in STAR*D: Implications for Clinical Practice. *Am J Psychiatry*, 2006,163:1, 28-40. doi: 10.1176/appi.ajp.163.1.28.

[5] Rush AJ et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *Am J. Psychiatry*, 2006,163:11, 1905-1917. doi: 10.1176/ajp.2006.163.11.1905.

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