Sage Announces Pivotal Phase 3 Trial Status for SAGE-217 in Major Depressive Disorder and Postpartum Depression based on FDA Breakthrough Therapy Meeting

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Expedited SAGE-217 development plan to support potential NDA submission for MDD and PPD

Previously completed placebo-controlled study in MDD considered as pivotal; initiation of one additional Phase 3 pivotal trial anticipated in 2H of 2018

Ongoing study in PPD designated as pivotal; results expected in 4Q 2018

If successfully developed, SAGE-217 has the potential to be the first durable, rapid-acting, oral, short-course treatment for MDD and PPD

Company to host conference call today at 8:00 A.M. ET

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 12, 2018-- Sage Therapeutics (NASDAQ: SAGE), a clinical-stage biopharmaceutical company developing novel medicines to treat life-altering central nervous system (CNS) disorders, today announced its expedited development plan for SAGE-217 following a Breakthrough Therapy meeting with the U.S. Food and Drug Administration (FDA). This development plan is intended to support a potential filing for approval of SAGE-217 in the U.S. for the treatment of major depressive disorder (MDD) and postpartum depression (PPD).

The expedited development plan for SAGE-217 includes a single additional placebo-controlled Phase 3 pivotal trial in patients with MDD and the ongoing placebo-controlled trial in women with PPD, now designated a pivotal trial. Both clinical trials are designed to evaluate the novel concept of episodic dosing, or short course treatment, with SAGE-217 and its effect on the reduction of depressive symptoms compared to placebo. An open-label study will evaluate the potential of episodic treatment for recurrent or new major depressive episodes and provide additional safety data.

Sage plans to initiate the placebo-controlled Phase 3 trial in MDD during the second half of 2018. Further, Sage anticipates announcing top-line data from the placebo-controlled pivotal trial of SAGE-217 in PPD in the fourth quarter of 2018. This expedited pivotal program is supported by the results of a positive placebo-controlled trial in patients with MDD announced in December 2017.

“Sage is excited to receive feedback from the FDA that provides a possible groundbreaking path forward for the development of SAGE-217 for the treatment of depression,” said Jeff Jonas, M.D., chief executive officer of Sage. “In this development program, we are exploring the potential for patients with MDD to feel well within days, with just a 2-week course of treatment – similar to how antibiotics are used today – instead of enduring long-term chronic treatment. We believe a medicine with rapid onset and robust response could be truly paradigm shifting. SAGE-217, if successfully developed and approved, may rewrite the textbook on how the tens of millions of people suffering from MDD are treated, ultimately turning depression into a disorder, not an identity.”

Incorporating feedback from the FDA, the following are the elements of the expected clinical and regulatory path for the SAGE-217 development program moving forward:

- Support from the FDA on a path forward in both MDD and PPD, allowing an expedited development plan.
- Ongoing multi-center, double-blind, placebo-controlled, randomized clinical trial evaluating two weeks of 30mg SAGE-217 treatment compared to placebo in 140 patients with PPD, confirmed as appropriate to support registration for PPD, if both the MDD and PPD trial are successful, and is now designated a pivotal clinical trial.
- One additional Phase 3 placebo-controlled efficacy study planned for SAGE-217 in MDD, evaluating two weeks of 20mg or 30mg SAGE-217 treatment compared to placebo in 450 patients with MDD, with four weeks of additional follow-up.
- Support from FDA in exploring the novel concept of episodic dosing.
- Additional data regarding patient safety and potential treatment of recurrent or new major depressive episodes will be acquired through a long-term open-label study program in which approximately 300 patients will be followed for six months and 100 patients would be followed for a year after initial treatment and episodic retreatment as needed.

Sage received Breakthrough Therapy Designation from the FDA for SAGE-217 in MDD in February 2018. The Breakthrough Therapy Designation is intended to offer a potentially expedited development path and review for promising drug candidates, which includes increased interaction and guidance from the FDA. This regulatory decision was based primarily on the positive results from the placebo-controlled trial of SAGE-217 in 89 adult patients with moderate to severe MDD. In the trial, SAGE-217 met the primary endpoint with a statistically significant mean reduction in the Hamilton Rating Scale for Depression (HAM-D) 17-item total score from baseline at Day 15 in the SAGE-217 group, compared to placebo ($p<0.0001$). Statistically significant improvements were observed in the HAM-D score compared to placebo by the morning following the first dose through Week 4 and the effects of SAGE-217 remained numerically greater than placebo through the end of follow-up at Week 6. SAGE-217 was generally well-tolerated. The most common adverse events in the SAGE-217 group were headache, dizziness, nausea, and somnolence.

Conference Call Information
Sage will host a conference call and webcast today at 8:00 A.M. ET to discuss the expedited development plan for SAGE-217 following a Breakthrough Therapy meeting with the U.S. Food and Drug Administration (FDA). The live webcast can be accessed on the investor page of Sage’s

website at investor.sagerx.com. The conference call can be accessed by dialing 866-450-8683 (toll-free domestic) or 281-542-4847 (international) and use the conference ID 6378326. A replay of the webcast will be available on Sage's website approximately two hours after the completion of the event and will be archived for up to 30 days.

About FDA Breakthrough Therapy Designation
The FDA's Breakthrough Therapy Designation is intended to expedite the development and review of a drug candidate that is planned for use, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. The benefits of Breakthrough Therapy Designation include the same benefits as Fast Track Designation, plus an organizational commitment involving FDA's senior managers with more intensive guidance from the FDA. Breakthrough Therapy Designation does not change the standards for approval.

About Major Depressive Disorder
Major depressive 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. It is estimated that approximately 16 million people in the U.S. suffer from MDD each year. While antidepressants are widely used for treatment, large scale studies have demonstrated the need for additional therapies.

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 the months 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. In the U.S., estimates of new mothers identified with PPD each year vary by state from 8 to 20 percent, with an overall average of 11.5 percent. More than half of these cases may go undiagnosed without proper screening. There are no FDA-approved therapies for PPD and there is a high unmet medical need for improved pharmacological therapy in PPD.

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 CNS, and contributes significantly to regulating CNS function. SAGE-217 is currently being developed for MDD and certain other mood and movement 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, $GABA_A$ and NMDA. Sage's lead program, a proprietary IV formulation of brexanolone (SAGE-547), 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 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 statements as to the potential for expedited development of SAGE-217 in MDD and PPD; our expectations as to the timing of results from the clinical trial of SAGE-217 in PPD and initiation of a Phase 3 clinical trial of SAGE-217 in MDD; our expectations regarding the potential sufficiency of the planned development program, if successful, to support regulatory filing and approval of SAGE-217 in MDD and PPD; our views as to the need for additional treatment options in MDD and the potential of SAGE-217 to represent a potential paradigm shift in the treatment of MDD; our estimates as to the number of patients with MDD and PPD; our statements regarding the potential for expedited development and review as the result of Breakthrough Therapy Designation; and our statements regarding the potential of SAGE-217 and Sage's other product 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 achieve expedited development or review of SAGE-217 despite the results of the Breakthrough Therapy meeting; the FDA may ultimately decide that the design or results of our clinical trials for SAGE-217 are not sufficient for regulatory approval in MDD, PPD or any other indication or do not support episodic treatment of MDD which is the focus of our expedited development plan; we may encounter delays in enrollment and site initiation that may impact our ability to meet our expected time-lines; we may not be successful in our development of SAGE-217 in MDD or PPD or in our development of any of our product candidates in any indication we are currently pursuing or may in the future pursue; success in our non-clinical studies or in earlier stage clinical trials 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 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 and, even if 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 products 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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