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SAGE Therapeutics Achieves 77 Percent Response Rate in Completed Phase 1/2 Clinical Trial of SAGE-547 in Super-Refractory Status Epilepticus

SAGE-547 Demonstrates Favorable Tolerability

Pharmacodynamic Activity Corroborated by Continuous EEG Findings

Phase 3 STATUS Trial Expected to Initiate by Mid-2015

Conference Call Scheduled Today at 8:30 a.m. ET

CAMBRIDGE, Mass., May 14, 2015 (GLOBE NEWSWIRE) -- SAGE Therapeutics (Nasdaq:SAGE) today announced that SAGE-547 demonstrated robust activity, with a 77 percent response rate in evaluable patients with super-refractory status epilepticus (SRSE), in a successfully completed Phase 1/2 clinical trial. SAGE-547 also demonstrated favorable tolerability and a benefit-risk profile supporting development in this acutely ill patient population. SRSE is a critical condition in which the brain is in a state of persistent seizure, where patients are placed in a medically induced coma in an attempt to stabilize them and where conventional and approved therapies fail to awaken the patients. Currently, there are no therapies specifically approved for SRSE.th"We believe these results are unprecedented in the treatment of SRSE and have the potential to be profoundly meaningful for patients affected by this devastating disorder. We believe these data help validate our platform, our unique chemistry capabilities and our approach to drug development based on rare disease indications with high unmet needs and rapid development pathways," said Jeff Jonas, M.D., chief executive officer of SAGE.

Stephen Kanes, M.D., Ph.D., chief medical officer of SAGE, added, "We are extremely pleased by these data, which demonstrate the potential for SAGE-547 as an interventional treatment for patients where all other treatments have failed. Importantly, SAGE-547 also showed clear pharmacodynamic activity as measured by continuous EEG in patients that had previously failed third-line treatment while burst-suppressed under general anesthesia. We would like to thank the patients, their families and the physicians that participated in this trial."

Phase 1/2 Trial Design

The Phase 1/2 open-label clinical trial evaluated the safety, efficacy, tolerability and pharmacokinetics of two IV-administered dose regimen cohorts (target plasma exposures of approximately 200 nM, the standard dose regimen, and approximately 300 nM, the higher dose regimen) of SAGE-547 as an adjunctive therapy for the treatment of patients with SRSE at 18 trial sites in the United States. Patients were administered SAGE-547 intravenously for five days while weaning from third-line IV general anesthesia administered to achieve burst suppression. Patients were then monitored for 30 days from treatment initiation. The trial enrolled 25 total patients. Of these patients, 22 were evaluable for efficacy, 16 at the standard dose regimen and six at the higher dose regimen. Patients were judged to be non-evaluable if their treatment was disrupted or if no weaning attempts from general anesthesia were made.

Phase 1/2 Trial Results

Of the total evaluable patients, 77 percent (17/22) were successfully weaned off their anesthetic agents while SAGE-547 was being administered during the maintenance phase, 81 percent (13/16) of those on the standard dose regimen, and 67 percent (4/6) of those on the higher dose regimen. In addition, 77 percent of the total evaluable patients successfully weaned off SAGE-547 without recurrence of SRSE in the 24-hour period following treatment.

Continuous EEG was evaluated as an exploratory endpoint in 14 patients. SAGE-547 administration was associated with a significant increase in EEG suppression with peak suppression occurring approximately one hour into the loading phase (mean = 19.6, $p < 0.001$; paired t-test comparison of baseline to mean suppression ratio during the one hour after the start of infusion) and terminal suppression being significantly greater than that observed during the pre-SAGE-547 baseline period (mean = 9.8 percent, $p < 0.005$; paired t-test). This effect was seen regardless of underlying third-line agents employed, indicating clear evidence of additive pharmacodynamic activity.

At baseline, all patients were evaluated using the Global Clinical Improvement Scale (CGI-S) and the Glasgow Coma Scale (CGS). At baseline, 23 patients were rated as "most extremely ill" and two were rated as "severely ill." By day 29, the group of patients that were successfully weaned off of third-line IV general anesthesia and SAGE-547 had improved by three points to

"mildly ill," while the non-responder group demonstrated only a one-point improvement. Similarly, this responder group continued to improve over the 29 days of follow-up, demonstrating an overall seven-point improvement in the GCS (mean score of 11 at day 29). Importantly, seven patients had a full (no GCS deficit) score of 15 (41 percent) at day 29. By contrast, of the patients that were not successfully weaned, only one had a GCS rating of 15 at day 29. In the responder group, four patients had recurrence of status epilepticus, with one patient in the one-to-two-week period and three patients in the two-to-four-week period.

Overall, tolerability to SAGE-547 was demonstrated in the context of the serious nature of SRSE. Overall, 64 percent of patients experienced at least one serious adverse event, though none were drug-related as determined by the Safety Review Committee. Individual serious adverse events reported in at least two patients were respiratory failure, pulmonary embolism, sepsis, convulsion and renal failure. Independent of treatment response, six patient deaths occurred within the study period, all driven by underlying medical conditions. A total of 207 adverse events were reported in 23 patients. The most common adverse events (reported in four or more patients) were fever, hypotension, diarrhea, peripheral edema, anemia and blood urea nitrogen (BUN) increase. One case each of fever and BUN increase were deemed related to SAGE-547 by the investigator.

Phase 1/2 Trial Subject Profile

The trial employed broad inclusion criteria, primarily excluding patients only with major damage to the brain, such as anoxic injury, devastating stroke or the presence of a large lesion. A status epilepticus patient who failed therapy with first- and second-line antiepileptic agents and had failed to be weaned from third-line IV general anesthesia administered over 24 hours was eligible to be included in the trial.

Of the 25 total patients enrolled in the trial, 11 males and eight females with a mean age of 44 were enrolled in the standard dose cohort, while five males and one female with a mean age of 42 were enrolled in the higher dose cohort. The mean duration of status epilepticus prior to treatment with SAGE-547 was eight days overall, with a mean duration of nine days in the standard dose cohort and seven days in the higher dose cohort.

Of the 25 total patients, the underlying etiology of SRSE was attributed to infections in six patients, brain hemorrhage in four patients, worsening of seizures in three patients, unknown causes in three patients, primary or metastatic brain tumors in two patients and toxic ingestion in two patients. SRSE was caused by each of the following in one case: anti-NMDA encephalitis, stroke, sickle cell anemia, PRES and Lupus.

Responses were unrelated to underlying condition, age, gender, status epilepticus severity at baseline as determined by Status Epilepticus Severity Score (STESS), duration of status epilepticus prior to enrollment and concomitant treatment.

The Phase 1/2 clinical trial results will be presented on May 15, 2015, by Stephen Kanes, M.D., Ph.D., chief medical officer of SAGE, at the Antiepileptic Drug and Device Trials XIII Conference.

Phase 3 Development Program

SAGE plans to initiate the STATUS Trial, a Phase 3 randomized, double-blind, placebo-controlled clinical trial of SAGE-547 for the treatment of patients with SRSE, by mid-2015. SAGE has begun enrollment in its Phase 3 open-label expanded access protocol, designated Study 302. Study 302 will make SAGE-547 available to patients in the United States, aged two years or older, who are affected with SRSE and is designed to evaluate the safety of SAGE-547. The results from the STATUS Trial, along with other results from the SAGE-547 development program, may form the basis of a New Drug Application (NDA) submission for SAGE-547.

Conference Call Information

SAGE will host a conference call and webcast today at 8:30 a.m. ET to discuss the results of the SAGE-547 Phase 1/2 clinical trial and the first quarter 2015 financial results. The event will be available on the investor page of SAGE's website at http://investor.sagerx.com/ or by dialing 1-866-450-8683 (toll-free domestic) or 1-281-542-4847 (international) and using the conference ID 44443636. A replay of the webcast will be available on SAGE's website approximately two hours after the completion of the event.

About SAGE-547

SAGE-547 is an allosteric modulator of both synaptic and extra-synaptic $GABA_A$ receptors. $GABA_A$ receptors are widely regarded as validated drug targets for a variety of disorders, with decades of research and multiple approved drugs targeting these receptor systems. SAGE-547 is an intravenous agent entering Phase 3 clinical development as an adjunctive therapy, a therapy combined with current therapeutic approaches, for the treatment of super-refractory status epilepticus (SRSE), as well as in exploratory Phase 2a clinical trials for the treatment of essential tremor and as an adjunctive therapy for the treatment of severe postpartum depression. SAGE plans to begin enrollment of its planned Phase 3 clinical trial, called the STATUS Trial, in

mid-2015. SAGE-547 has been granted both Fast Track and orphan drug designations by the U.S. Food and Drug Administration (FDA) for the treatment of SRSE. The active pharmaceutical ingredient, treatment IND and support for emergency-use patients have been contributed under agreement by the Regents of the University of California and the University of California Davis.

About Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition that occurs in approximately 150,000 people each year in the U.S., of which 30,000 SE patients die.[i] We estimate that there are 35,000 patients with SE in the U.S. that are hospitalized in the intensive care unit (ICU) each year. An SE patient is first treated with benzodiazepines, and if no response, is then treated with other, second-line, anti-seizure drugs. If the seizure persists after the second-line therapy, the patient is diagnosed as having refractory SE (RSE), admitted to the ICU and placed into a medically induced coma.

Currently, there are no therapies that have been specifically approved for RSE; however, physicians typically use anesthetic agents to induce the coma and stop the seizure immediately. After a period of 24 hours, an attempt is made to wean the patient from the anesthetic agents to evaluate whether or not the seizure condition has resolved. Unfortunately, not all patients respond to weaning attempts, in which case the patient must be maintained in the medically induced coma. At this point, the patient is diagnosed as having SRSE. Currently, there are no therapies specifically approved for SRSE.

About SAGE Therapeutics

SAGE Therapeutics is a clinical-stage biopharmaceutical company committed to developing and commercializing novel medicines to treat life-threatening, rare central nervous system, or CNS, disorders. SAGE's lead program, SAGE-547, is entering Phase 3 clinical development for super-refractory status epilepticus, or SRSE, and is the first of several compounds the Company is developing in its portfolio of potential anti-seizure medicines. SAGE's proprietary chemistry platform has generated multiple new compounds that target $GABA_A$ and NMDA receptors, which are broadly accepted as impacting many psychiatric and neurological disorders. For more information, please visit www.sagerx.com.

Forward-Looking Statements

Various statements in this release concerning SAGE's future expectations, plans and prospects, including without limitation, SAGE's expectations regarding SAGE-547 as a treatment for SRSE, essential tremor and severe postpartum depression, statements concerning the potential safety and efficacy of SAGE-547 and durability of response, the final protocol design, statistical power and timing of a planned Phase 3 clinical trial and an open-label, expanded access protocol for SAGE-547, and whether the results from the planned Phase 3 clinical trial together with other available clinical data for SAGE-547 will be sufficient to support submission of an NDA for this product candidate, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. In particular, it should be noted that FDA typically requires at least two well-controlled studies be completed prior to submission of an NDA. Whether a single Phase 3 trial of SAGE-547 will be sufficient to support submission of an NDA is typically a review issue to be discussed with FDA following completion of the trial. In addition, it should be noted that there is limited data concerning the safety and efficacy of SAGE-547. These data may not be repeated or observed in ongoing or future studies involving SAGE-547 or SAGE's other product candidates. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including, without limitation, SAGE's ability to successfully demonstrate the efficacy and safety of its drug candidates, the pre-clinical and clinical results for its product candidates, which may not support further development of product candidates, actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials, obtaining, maintaining and protecting intellectual property, SAGE's ability to enforce its patents against infringers and defend its patent portfolio against challenges from third parties, competition from others developing products for similar uses, SAGE's ability to manage operating expenses, SAGE's ability to obtain additional funding to support its business activities and establish and maintain strategic business alliances and new business initiatives, SAGE's dependence on third parties for development, manufacture, marketing, sales and distribution of products, the outcome of litigation, and unexpected expenditures, as well as those risks more fully discussed in the section entitled "Risk Factors" in SAGE's annual report on Form 10-K for the fiscal year ended December 31, 2014, as well as discussions of potential risks, uncertainties, and other important factors in SAGE's subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent SAGE's views only as of today and should not be relied upon as representing its views as of any subsequent date. SAGE explicitly disclaims any obligation to update any forward-looking statements.

[i] DeLorenzo, Robert J., Pellock, John M., Towne, Alan R., Boggs, Jane G. Epidemiology of Status Epilepticus. *J Clin Neuro* 1995; 12(4): 316-325.

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