



September 3, 2015

## **SAGE Therapeutics Announces Results From Successful Exploratory Trial in Essential Tremor**

*Clinically Meaningful Reduction of Tremor Amplitude Observed in Double-Blind, Placebo-Controlled Trial*

*Results Support Future Development of a Daily, Chronic, Oral Treatment*

*Study Represents SAGE's Second Successful Signal-Finding Study*

*Conference Call Scheduled for Sept. 3<sup>rd</sup> at 8:30 a.m. ET*

CAMBRIDGE, Mass., Sept. 3, 2015 (GLOBE NEWSWIRE) -- SAGE Therapeutics (NASDAQ:SAGE) today announced results from a successful exploratory clinical trial of SAGE-547 to evaluate the GABA<sub>A</sub> mechanism of action as a treatment for essential tremor, a debilitating neurological disorder that causes involuntary, rhythmic shaking with no known cause that is estimated to affect more than 10 million people in the United States.

In a randomized, double-blind, placebo-controlled, crossover trial of 25 patients affected by essential tremor, where patients were exposed to the target steady state dose for only two hours, several clinician-rated and accelerometer-rated measures showed significant reductions in tremor. These changes included a significant reduction in accelerometer-measured upper limb kinetic tremor ( $p=0.046$ ) which is one of the major manifestations of tremor impacting morbidity. Overall clinician ratings of large tremor motions, as well as smaller movements such as writing and spiral drawing, also showed improvement ( $p=0.056$ ). In addition, SAGE-547 demonstrated a clinically meaningful reduction of tremor amplitude as measured by accelerometer (at least a 30% reduction from baseline) in 33% of patients, compared with 16% of patients in the placebo arm.

Seventeen of these patients were exposed to higher doses of SAGE-547 in an open-label extension with 44% demonstrating at least a 30% reduction in tremor amplitude from baseline. The most common adverse events at higher doses were fatigue and dizziness. Hypotension led to discontinuation of one patient. No serious adverse events were observed on therapy or during the 30-day follow-up period.

"The information obtained in this exploratory study, including the activity signal supporting the role of the GABA<sub>A</sub> mechanism in essential tremor, greatly increases our confidence in a future program for essential tremor," said Jeff Jonas, M.D., chief executive officer, SAGE Therapeutics. "This study exemplifies SAGE's unique approach to clinical development. By generating efficient, targeted, signal-finding data in humans, SAGE-547 provides us with the unique ability to rapidly explore new indications for our leading library of compounds and to determine where our development efforts are most likely to benefit the many patients who are in need of new and improved treatment options."

### **Trial Design**

The trial was designed as a signal-finding study to evaluate the safety, tolerability, pharmacokinetics and efficacy of the GABA<sub>A</sub> mechanism in patients with essential tremor. The study was powered at 80% for  $p=0.05$ . The goals of the study were to evaluate the feasibility of using the GABA<sub>A</sub> mechanism and, if positive activity signals were obtained, inform the clinical pathway and design of a second-generation SAGE molecule for the chronic treatment of this disorder.

Patients ( $n=25$ ) received either blinded SAGE-547 or placebo in two crossover treatment periods. SAGE-547 was administered as a step-up infusion to a steady state dosage. Seventeen of the 25 patients volunteered to participate in an open-label, dose-escalation extension to study the range of pharmacodynamic effects of the GABA<sub>A</sub> modulator mechanism in conscious patients. Patients were monitored for up to 30 days following treatment.

The study was designed to enroll patients with moderate to severe essential tremor as assessed by a clinician rating scale, The Essential Tremor Rating Scale (TETRAS). Tremor outcome was measured during the trial by TETRAS and accelerometry, a direct physical measure of tremor amplitude and frequency. Patients enrolled in the trial were required to have had diagnosed essential tremor for at least two years and to be off medication, or on a stable dose of medication for their tremor, for at least 28 days prior to screening.

## **Trial Results**

A clear reduction in tremor amplitude, as measured by accelerometer, was observed when comparing administration of SAGE-547 to placebo. Anti-tremor activity of SAGE-547 was observed at non-sedating doses, and peak anti-tremor activity correlated with steady state SAGE-547 levels. The time points showing the greatest reductions in tremor corresponded to peak plasma measurements.

In an open-label, higher dose administration of SAGE-547, a dose-related anti-tremor activity was observed with some sedative effect characterized as sleepiness and fatigue. Tolerance to the sedative effects was noted during drug administration with patients becoming less sedated in the hours they were administered SAGE-547. These data suggest that the anti-tremor effect may be uncoupled from sedation and that tolerance to sedation may occur quickly. These findings are consistent with the extrasynaptic activity of SAGE-547 and are observations that are encouraging for the utility of a second-generation compound.

Of the 25 patients enrolled, three patients reported at least one adverse event on blinded SAGE-547, compared to five patients reporting at least one adverse event while on placebo. Of the 17 patients in the open-label, higher dose SAGE-547 portion, eight patients reported at least one adverse event. The only adverse events reported more than once across all SAGE-547 treatment periods were fatigue and dizziness, predominantly at the higher dose of SAGE-547. There was one discontinuation in the higher dose SAGE-547 portion due to hypotension, with recovery following drug discontinuation. There were no reports of serious adverse events.

"Given the step-up infusion administration of SAGE-547, we were able to detect a strong activity signal despite being at possible therapeutic levels for only a few hours in these chronically ill patients," said Stephen Kanen, M.D., Ph.D., chief medical officer, SAGE Therapeutics. "In addition, the uncoupling of drug activity from sedation that was observed in this study has been demonstrated by our GABA<sub>A</sub> molecules in preclinical animal models, suggesting a predictable mechanism and the translatable utility of our animal models and research."

Dr. Kanen added, "We have also developed and continue to research innovative methods of measuring tremor activity that we believe may provide even greater utility in studying this disorder as we move forward."

## **Next Steps**

As ongoing analysis of the data proceeds, SAGE intends to move forward with a Phase 2 program for essential tremor using a second-generation GABA<sub>A</sub> modulator, such as SAGE-217, which has demonstrated many of the optimal properties for daily, chronic, oral therapy in pre-clinical models. The Company plans to submit the detailed results of this trial, and further exploratory analyses, for publication and presentations at future medical meetings.

## **Conference Call Information**

SAGE will host a conference call and webcast on Thursday, September 3, 2015 at 8:30 a.m. ET to discuss the results of the essential tremor exploratory clinical trial. 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 30465758. An accompanying presentation will be made available on SAGE's website. A replay of the webcast will also be available on SAGE's website approximately two hours after the completion of the event.

## **About SAGE-547**

SAGE-547 is a potent allosteric modulator of both synaptic and extrasynaptic GABA<sub>A</sub> receptors, a major inhibitory neurotransmitter system broadly accepted as impacting many neurological and psychiatric disorders. SAGE-547 is an intravenous agent in Phase 3 clinical development as an adjunctive therapy for the treatment of super-refractory status epilepticus (SRSE). SAGE-547 has been granted Fast Track and orphan drug designations by the U.S. Food and Drug Administration (FDA) for the treatment of SRSE. The active pharmaceutical ingredient has been contributed under agreement by the Regents of the University of California and the University of California, Davis.

## **About Essential Tremor**

Essential tremor is a common neurological condition that affects an estimated 10 million Americans and millions more worldwide. Essential tremor causes a rhythmic trembling of the hands, head, voice, legs or trunk. Symptoms generally evolve over time and are both visible and persistent following onset, which commonly occurs either between 15-20 or 50-70 years of age. First-line treatments for essential tremor include the anticonvulsant primidone and the  $\beta$ -adrenergic blocker propranolol. All current treatments for essential tremor are only moderately effective, reducing, though not resolving, tremor amplitudes in about 50% of the patients. In addition, one out of three patients abandons treatment due to side effects or poor efficacy.

## About SAGE Therapeutics

SAGE Therapeutics is a clinical-stage biopharmaceutical company committed to developing and commercializing novel medicines to treat life-altering central nervous system, or CNS, disorders. SAGE's lead program, SAGE-547, is in Phase 3 clinical development for super-refractory status epilepticus (SRSE) and is the first of several compounds the Company is developing in its portfolio of potential CNS medicines. SAGE's proprietary chemistry platform has generated multiple new compounds that target GABA<sub>A</sub> and NMDA receptors, which are broadly accepted as impacting many psychiatric and neurological disorders. For more information, please visit [www.sagerx.com](http://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, SAGE-217 or another product candidate as a treatment for essential tremor, statements concerning the potential safety and efficacy of SAGE-547, SAGE-217 or another product candidate as a treatment for essential tremor, SAGE's ability to identify an optimized product candidate for future study in essential tremor, and SAGE's plans to commence a Phase 2 clinical trial of a product candidate for the treatment of essential tremor, 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 the data reported from this exploratory clinical trial of SAGE-547 in patients with essential tremor may not be repeated or observed in future trials involving SAGE-547, SAGE-217, or another product candidate. 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 product 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 most recent quarterly report on Form 10-Q, 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.*

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Source: SAGE Therapeutics

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