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Sage Therapeutics and Collaborators Publish New Pre-clinical Data in Neuropharmacology Demonstrating a Novel Metabotropic Mechanism of Sage Compounds Resulting in Enhanced Effects

In vitro data show short exposure to certain neuroactive steroids, including allopregnanolone and novel Sage tool compound SGE-516, can have sustained effects through enhancement of extrasynaptic $GABA_A$ receptor surface expression

SAGE-547, Sage's proprietary intravenous formulation of allopregnanolone, is in late-stage clinical development for super-refractory status epilepticus, and is being developed for postpartum depression

SGE-516 was designed with similar pharmacology to SAGE-217, Sage's lead oral compound entering Phase 2 development

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 publication in the journal *Neuropharmacology* of pre-clinical data demonstrating new findings relevant to Sage's GABA product candidate portfolio. The paper, titled "Endogenous and synthetic neuroactive steroids evoke sustained increases in the efficacy of GABAergic inhibition via a protein kinase C-dependent mechanism" (Modgil et al., doi: 10.1016/j.neuropharm.2016.10.010), documents in vitro data on a novel mechanism of action that enables certain neuroactive steroids to have sustained effects on extrasynaptic $GABA_A$ receptors, in particular by increasing the number of extrasynaptic receptors on the membrane surface by means of receptor trafficking.

The change in the number of receptors is achieved by inducing a metabotropic mechanism, and the impact of this effect may exert long term enhancement of GABAergic tonic currents. Both allopregnanolone, a naturally occurring neuroactive steroid, and SGE-516, a synthetic next generation neuroactive steroid, were found to induce these changes in vitro, while another synthetic neuroactive steroid, ganaxolone, did not induce this sustained enhancement. While neuroactive steroids are known to possess extrasynaptic activities that may be qualitatively similar, the metabotropic mechanism and related sustained enhancement exhibited in this study are distinct from other well-known activities of the class. Interestingly, not all neuroactive steroids tested produced this increase in receptor trafficking. GABA is the major inhibitory neurotransmitter in the CNS, and mediates downstream neurologic and bodily function via activation of $GABA_A$ receptors.

"Whereas neuroactive steroids are known to allosterically modulate $GABA_A$ receptors, our research findings suggest the ability of neuroactive steroids, specifically allopregnanolone and SGE-516, a synthetic compound designed with an improved pharmacokinetic profile, to exert sustained effects on GABAergic inhibition in vitro by selectively enhancing the trafficking of $GABA_A$ receptors that mediate tonic inhibition," said Stephen Moss, PhD, Professor of Neuroscience, Tufts University School of Medicine. "These findings, which build on our prior research, demonstrate a novel metabotropic pathway that may contribute to the profound effects these neurotransmitters have in animal models on neuronal excitability and behavior. Furthermore, these results indicate that trafficking is not universally stimulated by all $GABA_A$ modulators, such as ganaxolone as demonstrated in this study or propofol as shown in a prior study, which did not demonstrate the ability to metabotropically enhance extrasynaptic receptors in this study."

The research highlighted in this article sought to examine the allosteric and metabotropic properties of allopregnanolone and synthetic neuroactive steroids, SGE-516 and ganaxolone. Allopregnanolone and SGE-516 increased the phosphorylation and surface expression of the β3 subunit-containing extrasynaptic $GABA_A$ receptors in vitro, resulting in increased tonic current. While the allosteric modulation only exists while the neuroactive steroid is present, the PKC-mediated metabotropic enhancement can cause a prolonged increase in inhibitory tone.

"These pre-clinical findings are profoundly relevant for Sage and our portfolio of novel GABA compounds, particularly as reduced expression of extrasynaptic $GABA_A$ receptors has been demonstrated in human and rodent models of status epilepticus, postpartum depression and forms of epilepsy," said Jim Doherty, PhD, Senior Vice President of Research at Sage. "We believe the potential ability of neuroactive steroids, and Sage's compounds in particular, to restore tonic inhibition by increasing the surface expression and trafficking of extrasynaptic $GABA_A$ receptors may provide new ways to

approach the treatment of CNS disorders associated with GABAergic disruption. SGE-516, our novel orally active $GABA_A$ modulator tool compound, used in this study, was designed with similar pharmacology to SAGE-217, our lead oral program entering Phase 2 development, and is an example of Sage's ability to create novel GABA-targeted compounds with improved pharmacokinetic profiles compared to first generation therapies."

Sage is developing a series of novel positive allosteric modulators of synaptic and extrasynaptic $GABA_A$ receptors. Its lead product candidate, SAGE-547 (a proprietary formulation of allopregnanolone), is currently in late-stage development as a treatment for super-refractory status epilepticus (SRSE), and is being developed for postpartum depression (PPD). Sage's lead orally active compound, SAGE-217, is planned to enter Phase 2 clinical development for essential tremor and PPD, as well as proof-of-concept Phase 2 clinical trials in Parkinson's disease and major depressive disorder. Sage is also developing a portfolio of additional novel compounds that target the $GABA_A$ receptors, including SAGE-105, SAGE-324 and SAGE-689.

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 is being developed 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: statements about the potential for the findings from the study described in this release and the likely mechanism of action of Sage's compounds to be relevant to future development or clinical results; our plans with respect to clinical development of our product candidates; and our other statements regarding the potential of Sage's 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: the scientific findings described in this release may not prove to have relevance in humans or to the efficacy and safety of our product candidates in any indication or to our ability to successfully develop our product candidates; 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 and preclinical 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; we may decide that a development pathway for one of our product candidates in one or more indications is no longer feasible or advisable; 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.

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