Sage Therapeutics Announces Clinical Updates and Progress Across Neuroscience Pipeline During “Sage FutureCast”

July 24, 2019

Data from Phase 2 open-label study of SAGE-217 in bipolar depression demonstrate rapid improvement compared to baseline; analysis of datasets from previously completed studies reveal encouraging findings relevant to the development of SAGE-217 in treatment-resistant depression and generalized anxiety disorder

Data from Phase 1 study with SAGE-324 show activity in essential tremor; differentiated profile opens potential pathways for development in additional neurological indications

Data from Phase 1 program for SAGE-718, Sage’s lead molecule in its NMDA portfolio, show it was well-tolerated and improved executive function compared to placebo in healthy volunteers

Webcast today at 8:00 a.m. EDT

CAMBRIDGE, Mass. – Jul. 24, 2019 – Today, Sage Therapeutics (NASDAQ: SAGE), a biopharmaceutical company committed to developing novel therapies with the potential to transform the lives of people with debilitating disorders of the brain, will host “Sage FutureCast: An R&D Portfolio Review” and report clinical progress in select depression, neurology, and neuropsychiatry franchise programs.

“Our goal at Sage has always been to step into the void in CNS drug development through an innovative approach we believe to be unique,” said Jeff Jonas, chief executive officer of Sage. “By thinking differently about brain disorders, we’ve built a pipeline with the potential to deliver a broad range of new medicines across multiple indications. The clinical findings presented today are a result of our differentiated approach to discovery and translation. While these are still early data, we believe these data not only meaningfully expand our pipeline opportunities, but more importantly, represent the potential benefits our medicines may provide for patients if we’re successful in our development efforts.”

Clinical Program Updates:
Sage is advancing a portfolio of novel and differentiated product candidates designed to improve brain health by targeting the GABA and NMDA receptor systems. Dysfunction in these systems is known to be at the core of numerous neurological and neuropsychiatric disorders.

Depression Franchise:
SAGE-217, a next-generation positive allosteric modulator (PAM) of GABAA receptors, is being evaluated in Phase 3 clinical development as a treatment for major depressive disorder (MDD), postpartum depression (PPD), and comorbid MDD and insomnia, and is also being evaluated for bipolar depression and additional affective disorders, including treatment-resistant depression (TRD) and generalized anxiety disorder (GAD). SAGE-217 received breakthrough therapy designation from the U.S. Food & Drug Administration (FDA) for the treatment of MDD.

- SAGE-217 in bipolar depression (ARCHWAY Study):
    - Sage’s Phase 2 open-label ARCHWAY Study evaluated the safety and activity of SAGE-217 in 35 adult men and women with moderate to severe bipolar I/II disorder with a major depressive episode. Patients were treated with 30 mg of SAGE-217 once daily for two weeks. The main efficacy measure was Montgomery–Åsberg Depression Rating Scale (MADRS). MADRS baseline total

score was 34.4.

- Results from the trial demonstrated a rapid and durable response to treatment as measured by the MADRS score and a statistically significant improvement compared to baseline at Day 15. The effect was maintained through the end of the follow-up period at Day 42.
    - The average change from baseline in MADRS total score was 15.5 points at Day 15 (n=23; p<0.0001) and 16.4 points at Day 42.
    - At Day 15 (n=23), 43.5% of patients receiving SAGE-217 achieved remission (MADRS =12) with an additional 4% achieving response (=50% reduction in MADRS Total score).
- Roughly one-third of subjects discontinued the study due to a variety of social/personal reasons, which is consistent with discontinuation rates across global studies in bipolar depression. No discontinuations due to adverse events were reported.
- SAGE-217 was generally well-tolerated with a safety profile consistent with $GABA_A$ positive allosteric modulation. The most common adverse events (>5%) were somnolence, headache, diarrhea, and sedation. There were two cases of transient hypomania off-treatment; no mania or serious adverse events (AEs) was reported in the trial.

- SAGE-217 in patients who didn't respond to a single anti-depressant:
    - Sage conducted a post hoc analysis of 51 patients from the MDD-201B and ROBIN (PPD) studies with ongoing symptoms of depression despite receiving standard anti-depressant pharmacotherapy. Of the 51 total patients with major depressive disorder or postpartum depression, 28 received SAGE-217 and 23 received placebo.
    - Results from the analysis demonstrated a rapid and durable response to treatment and reduction in depressive symptoms in the SAGE-217-treated group compared to placebo in patients with ongoing symptoms of depression despite receiving standard anti-depressant therapy.
        - At Day 15, patients receiving SAGE-217 experienced a 7.2-point greater reduction (p=0.004) in Hamilton Rating Scale for Depression (HAM-D-17) compared to patients receiving placebo.
        - At the last study visit (Day 42 or 45), patients receiving SAGE-217 experienced a 4.9-point greater reduction (p=0.07) in HAM-D-17 compared to patients receiving placebo.
    - Based on outcomes of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, improvements observed in SAGE-217 studies suggest opportunity to address unmet need for rapid treatment response in patients with treatment-resistant depression.
    - Findings from this analysis, if replicated in further development, suggest SAGE-217 may have utility as an oral medication for people who are struggling with depression, regardless of their resistance to standard therapies.

- SAGE-217 in patients with anxiety:
    - Sage evaluated response on the Hamilton Anxiety Rating Scale (HAM-A), a secondary endpoint, in all patients randomized in the MDD-201B and ROBIN

(PPD) studies of SAGE-217. This analysis evaluated 240 patients, 89 patients from the MDD-201B study with major depressive disorder and 151 patients from the ROBIN Study with postpartum depression.

- Findings demonstrated rapid onset of activity and durable effect past initial treatment, with a clinically meaningful anxiolytic effect within days in the SAGE-217-treated group compared to placebo.
    - At Day 15, patients receiving SAGE-217 experienced a 4.6-point greater reduction (p=0.0008) in HAM-A score and 3.9-point greater reduction (p=0.006) in HAM-A score compared to placebo in the MDD-201B study and ROBIN Study, respectively.
    - At Day 42 (last visit), patients receiving SAGE-217 experienced a 2.3-point greater reduction (p=0.20) in HAM-A score compared to placebo in the MDD-201B study; at Day 45 (last visit), patients receiving SAGE-217 experienced on average a 5-point greater reduction (p=0.0002) in HAM-A score compared to placebo in the ROBIN Study.

- Sage plans to evaluate SAGE-217 in patients with TRD and will discuss plans for how to sequence opportunities in bipolar depression, TRD and GAD during the FutureCast webinar.

Neurology Franchise:

SAGE-324, a next-generation PAM of $GABA_A$ receptors, is in development as a potential therapy for neurological conditions, such as essential tremor (ET) and epileptiform disorders.

- SAGE-324 pharmacokinetics and tolerability:
    - Sage conducted single-ascending dose (SAD) and multiple-ascending dose (MAD) studies of SAGE-324 in healthy volunteers. Results demonstrate a pharmacokinetic (PK) profile suitable for chronic dosing in indications amenable to the GABA PAM mechanism.
    - Little variability was observed in steady state plasma concentrations over the dose interval, which may provide consistent trough concentrations while minimizing peak-related tolerability issues.
    - SAGE-324 demonstrated a long half-life of approximately 90 – 120 hours. This attribute supports the low peak to trough ratio and provides flexibility in dosing paradigms, making SAGE-324 well-suited for development in neurological conditions where stable plasma levels are a clinical challenge.
    - SAGE-324 was generally well tolerated. The most common (>5%) adverse events were feeling of relaxation, dizziness, and somnolence.
    - Data with respect to tolerability in context with EEG biomarker data suggest that the therapeutic index with respect to sedation for SAGE-324 is potentially broader than for SAGE-217, making it an asset that may have utility in indications where sleep consolidation is not desirable.

- SAGE-324 in ET:
    - Sage conducted a Phase 1b single dose, open-label study evaluating SAGE-324 in six patients with ET. Patients were administered a non-optimized single dose of SAGE-324 that was below the maximum tolerated dose. Data demonstrated a reduction in tremor from baseline, with a maximum mean reduction in

accelerometer upper limb total score of 48%.

- Sage evaluated plasma concentration of SAGE-324 over 24 hours and observed a clear pharmacokinetic/pharmacodynamic relationship.

- Sage plans to initiate a Phase 2 study evaluating SAGE-324 in essential tremor in 2H 2019. This study will also inform clinical expansion into adjacent opportunities in neurological conditions such as epileptiform disorders and Parkinson's.

Neuropsychiatry Franchise:

SAGE-718, a first-in-class NMDA receptor PAM, is in development as a potential therapy for cognitive disorders associated with NMDA receptor dysfunction.

- Five Phase 1 healthy volunteer studies with SAGE-718 have been completed, including SAD, MAD, and three target engagement biomarker studies.
  - SAGE-718 demonstrated linear pharmacokinetics, a long half-life consistent with once-daily dosing, and was generally safe and well-tolerated.
  - A suite of three target engagement studies with SAGE-718 were recently completed:
    - Results of an integrated analysis in healthy volunteers demonstrate SAGE-718 had effects on electrophysiological, functional neuroimaging, and cognitive measures consistent with CNS activity.
    - Healthy volunteers dosed with SAGE-718 also received low-dose ketamine as a selective antagonist of the NMDA receptor (used here to induce a state of relative NMDA hypofunction). Among the findings, SAGE-718 was found to modulate the effects of ketamine on regional and global measures of resting brain activity, indicating functional interaction with NMDA receptors and potential NMDA PAM activity.
    - 19 healthy volunteers administered SAGE-718 once-daily for 10 days exhibited significantly better performance on tests of working memory and complex problem solving compared to 20 healthy volunteers administered placebo, at times reaching statistical significance ($p<0.05$).
      - If these data are replicated in further development, SAGE-718 may demonstrate a distinct profile from currently available cognitive-enhancing agents, and the potential to improve higher-order cognitive processes more closely linked to real-world functioning.
  - In the SAD and MAD studies, SAGE-718 demonstrated a long half-life consistent with once-daily dosing and was well-tolerated. The most commonly reported adverse event was mild orthostatic hypotension, which occurred in 2 subjects.

- Sage plans to move forward to evaluate SAGE-718 in Phase 2 development programs in neurodegenerative disorders and other conditions where executive function is impaired. Additional timing for these studies will be provided in 2H 2019.

About Sage Therapeutics

Sage Therapeutics is a biopharmaceutical company committed to developing novel therapies with the

potential to transform the lives of people with debilitating disorders of the brain. We are pursuing new pathways with the goal of improving brain health and our depression, neurology and neuropsychiatry franchise programs aim to change how brain disorders are thought about and treated. Our mission is to make medicines that matter so people can get better, sooner. 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 views and expectations regarding our development plans, goals and strategy and the potential timing and results of our development efforts; our belief in the potential of our product candidates in various indications; the potential profile and benefit of our product candidates; and the goals, opportunity and potential for our business. These statements constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. 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 be successful in our development of any of our current or future product candidates in any indication we are currently pursuing or may in the future pursue; success in earlier stage clinical trials or nonclinical studies may not be repeated or observed in ongoing or future studies of any of our product candidates; ongoing and future clinical or nonclinical results may generate results that are different than we expect or may not support further development or be sufficient to gain regulatory approval of our product candidates; 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; the FDA may decide that the development program for any of our product candidates, even if positive, is not sufficient for a new drug application filing or approval; decisions or actions of the FDA or other regulatory agencies may affect the initiation, timing, design, size, progress and cost of clinical trials and our ability to proceed with further development; we may experience slower than expected initiation or enrollment in ongoing or future clinical trials; we may encounter unexpected safety or tolerability issues with our product candidates; the internal and external costs required for our ongoing and planned research and development efforts, and to build our organization in connection with such activities, and the resulting expense increases and use of cash, may be higher than expected which may cause us to change or curtail some of our plans; and we may encounter technical and other unexpected hurdles in the development of our product candidates; as well as those risks more fully discussed in the section entitled "Risk Factors" in our most recent quarterly report filed with the Securities and Exchange Commission (SEC), and discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. 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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