Sage Therapeutics and Biogen Announce Positive Pivotal Phase 3 Results for Zuranolone, an Investigational Two-Week, Once-Daily Therapeutic Being Evaluated for Major Depressive Disorder

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- *At the Day 15 primary endpoint, zuranolone 50 mg showed a statistically significant and clinically meaningful reduction in depressive symptoms as measured by HAMD-17 (p=0.0141) compared to placebo*
- *Rapid onset of treatment effect was seen in HAMD-17 results at Days 3, 8, and 12*
- *Patients with a response at Day 15 to zuranolone retained on average 86% of their HAMD-17 improvement at Day 42 (4 weeks after dosing ended)*
- *Zuranolone was generally well-tolerated and demonstrated a safety profile consistent with previous clinical studies; trial completion rate was 90.3% in the zuranolone group*
- *Zuranolone is an investigational two-week, once-daily oral drug for MDD that represents a potential new class of drug for the management of this common but serious mental health disorder*

CAMBRIDGE, Mass., June 15, 2021 (GLOBE NEWSWIRE) -- Sage Therapeutics, Inc. (Nasdaq: SAGE) and Biogen Inc. (Nasdaq: BIIB) today announced that the WATERFALL Study in patients with MDD met its primary endpoint with zuranolone (SAGE-217/BIIB125) 50 mg showing statistically significant improvement in depressive symptoms compared with placebo at Day 15 as assessed by the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score. LS means (SE) change from baseline in HAMD-17 total score at Day 15 for patients who received zuranolone 50 mg was -14.1 (0.51) compared with -12.3 (0.50) for patients who received placebo (LS mean difference -1.7 points; p=0.0141).

Monoamine-based antidepressants have been the standard of care for chronic treatment of MDD for the past 60 years. They are treatments administered daily, which require sufficient exposure and continuous use to maintain effect. Zuranolone is a two-week, once-daily oral drug under investigation for the treatment of MDD. It is a molecule that is designed to potentially provide a rapid-acting, sustainable treatment option, and could represent a breakthrough in the current management of depression.

The WATERFALL Study was a pivotal, Phase 3, double-blind, randomized, placebo-controlled study evaluating the efficacy and safety of zuranolone 50 mg in adults 18 to 64 years with MDD (N=543). The WATERFALL Study enrolled patients who had MDD with a HAMD-17 total score ≥24 at screening and Day 1 prior to dosing.

“Sage’s expertise in the modulation of the GABA receptor pathway in the brain, coupled with insights on the treatment wants and needs of clinicians and patients, has resulted in our targeting a unique benefit/risk profile with the development of zuranolone supported to date by the data generated in the WATERFALL Study and the broader Landscape and NEST programs,” said Barry Greene, Chief Executive Officer at Sage Therapeutics. “We dared to imagine a different future for the treatment of MDD where patients have the potential to experience a rapid response that is well-tolerated and that may enable them to stay better with long periods free from depression symptoms, and free from daily chronic treatments and related side effects. In doing so, we aspire to help eliminate stigma associated with brain health disorders so that we can move beyond brain health awareness to brain health action.”

“Together with our collaboration partners at Sage, we are proud to announce highly encouraging results from the Phase 3 WATERFALL Study of zuranolone in major depressive disorder. These results represent hope and positive progress for the more than 250 million patients worldwide who are estimated to live with depression,” said Alfred Sandrock, Jr., M.D., Ph.D., Head of Research and Development at Biogen. “Major depressive disorder is a common co-morbidity of many diseases represented in Biogen’s neuroscience portfolio. We believe zuranolone has the potential to offer a unique, first-in-class therapeutic for depression with a distinct benefit-risk profile to people living with this common but serious mental health condition.”

Zuranolone was generally well-tolerated in the WATERFALL Study and demonstrated a safety profile consistent with previous clinical studies. The rate of treatment emergent adverse events (TEAEs) in the zuranolone group was 60.1% (161/268) vs the placebo group at 44.6% (120/269). The majority of the TEAEs were mild to moderate. The most common TEAEs that were ≥ 5% in patients treated with zuranolone (rates vs placebo) included somnolence 15.3% (vs 3.0%), dizziness 13.8% (vs 2.2%), headache 10.8% (vs 7.8%), and sedation 7.5% (vs 0.4%); these events predominantly occurred during the 14-day treatment period. Throughout the study, a total of two patients each (0.7%) reported serious adverse events (SAEs) in the zuranolone and placebo groups; no death occurred in the study. The percent of patients reporting TEAEs leading to drug discontinuation was 3.4% (9/268) and 1.5% (4/269), in the zuranolone and placebo groups, respectively. No signal for withdrawal symptoms as assessed by the 20-item Physician Withdrawal Checklist (PWC-20), or for increased suicidal ideation or behavior as per the Columbia-Suicide Severity Rating Scale (C-SSRS) were identified.

“I’m really excited about these breakthrough data: we know MDD is episodic and zuranolone has the potential to treat episodically. The LANDSCAPE clinical studies are all helpful taken together because they provide data on both short- and long-term use of zuranolone,” said Anita H. Clayton, M.D., Chair of Psychiatry and Neurobehavioral Sciences, University of Virginia School of Medicine. “These data suggest that this treatment, if approved, has the potential to work fast with a short-course of therapy that is well-tolerated, with the effect maintained over the long-term. This will empower my patients to think differently about their depression and treatment, and to rapidly return to their life. Depression is not an identity, it’s an episodic disorder that we hope in the future to be able to treat quickly with treatments that are well-tolerated and with benefits that last.”

“MDD is a pressing mental health concern and, unlike physical health concerns where innovation is commonplace, many of the treatments for MDD were first approved more than two decades ago,” said Paul Gionfriddo, President and CEO of Mental Health America (MHA). “We welcome today’s news, and the potential for a new and innovative treatment that could change the way we treat depression.”

Zuranolone has been granted Breakthrough Therapy Designation by the U.S. Food & Drug Administration, and the Companies intend to discuss next steps with the Agency. Full data from the WATERFALL Study will be shared at future scientific forums.

Detailed Topline Results from the WATERFALL Study

- The WATERFALL Study enrolled 543 patients with MDD. The patients were treated with zuranolone 50 mg or placebo once nightly for 14 days.
- The primary endpoint of the study was the change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 15; the first secondary endpoint was the change from baseline in the Clinical Global Impression-Severity of Illness (CGI-S) at Day 15
- The mean (SD) baseline HAMD-17 score at entry into the study was 26.8 (2.60) in the zuranolone 50 mg treatment group (n=268) and 26.9 (2.67) in the placebo group (n=269).
- 90.3% of patients who received zuranolone, and 87.4% of patients who received placebo, completed the study
- Results for the primary endpoint and several topline secondary efficacy endpoints during the treatment period are outlined in the following table and all favor zuranolone:

Outcome*	Day 3	Day 8	Day 12	Day 15
HAMD-17: LS mean difference (p value)	-3.0 (<0.0001)^	-2.6 (<0.0001)^	-2.5 (0.0003)	-1.7 (0.0141)*
CGI-Severity: LS mean difference (p value)	-0.4 (<0.0001)	-0.4 (0.0001)	-0.3 (0.0014)	-0.2 (0.1193)^
CGI-Improvement Response: Odds ratio (p value)	1.8 (0.0032)	1.9 (0.0005)	1.6 (0.0101)	1.5 (0.0191)
MADRS: LS mean difference (p value)	Not measured per protocol	-3.4 (0.0003)	Not measured per protocol	-2.4 (0.0238)
HAM-A: LS mean difference (p value)	Not measured per protocol	-1.7 (0.0011)	Not measured per protocol	-1.4 (0.0199)

Except for HAMD-17 at Day 15 (primary) which was statistically significant and CGI-S (first secondary endpoint) which was not significant at Day 15, all p-values in the table are nominal and not adjusted for multiple comparisons.
**Pre-specified primary endpoint*
^Pre-specified key secondary endpoints
LS = least squares; LS mean difference = difference in LS means of change from baseline between zuranolone and placebo groups

Patients with a response at Day 15 in the zuranolone group retained on average 86.1% of their HAMD-17 improvement at Day 42 (4 weeks after dosing ended). A similar maintenance of response was also observed with the MADRS scale, where people who responded to zuranolone at Day 15 maintained 87.6% of that response at Day 42. While not statistically significant, a numerical advantage in favor of zuranolone was demonstrated at Day 42.

Safety and tolerability:

- Adverse events were consistent with the safety profile of zuranolone seen to date in clinical studies.
- The incidence of treatment emergent adverse events (TEAEs) in the zuranolone group was 60.1% (161/268) vs the placebo group at 44.6% (120/269).
- The majority of the TEAEs were mild to moderate, with 8 (3.0%) and 3 (1.1%) being severe in the zuranolone and placebo groups respectively.
- The most common TEAEs observed in ≥5% of patients in either treatment group are listed below and occurred predominantly during the 14-day treatment period. These events were non-serious, and most were mild to moderate.

AE (≥5%)	Zuranolone 50 mg	Placebo
Somnolence, n (%)	41 (15.3)	8 (3.0)
Dizziness, n (%)	37 (13.8)	6 (2.2)
Headache, n (%)	29 (10.8)	21 (7.8)
Sedation, n (%)	20 (7.5)	1 (0.4)
Diarrhea, n (%)	8 (3.0)	14 (5.2)

- Discontinuation rates of the study drug due to AEs in patients receiving zuranolone were 3.4% (9/268) compared to 1.5% (4/269) in those receiving placebo.
- Throughout the study, a total number of 4 patients reported serious adverse events (SAEs), 2 (0.7%) each in the zuranolone and placebo groups.
- No deaths occurred in the study.
- No signal in increased suicidal ideation or behavior, as assessed by the C-SSRS, was observed throughout the study in patients receiving zuranolone 50 mg or placebo.
- No signal in withdrawal effects, as assessed by the PWC-20, was observed after discontinuation of zuranolone.
- No loss of consciousness, or adverse effects such as weight gain, sexual dysfunction, or euphoria were reported.

About the WATERFALL Study
The WATERFALL Study was a double-blind, placebo-controlled pivotal Phase 3 study evaluating the efficacy and safety of zuranolone in adults with major depressive disorder. In the study, 543 patients were enrolled. Patients were randomized to receive zuranolone 50 mg, or placebo, once-nightly for two weeks. The primary endpoint of the study was the change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 15. Secondary endpoints included the change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Rating Scale (HAM-A) total score, among others.

About Zuranolone
Zuranolone (SAGE-217/BIIB125) is a once-daily, two-week drug in development for the treatment of major depressive disorder (MDD) and postpartum depression (PPD). Zuranolone is an investigational oral neuroactive steroid (NAS) GABA-A receptor positive allosteric modulator (PAM). The GABA system is the major inhibitory signaling pathway of the brain and central nervous system and contributes significantly to regulating brain function.

Zuranolone has been granted Breakthrough Therapy Designation by the U.S. Food & Drug Administration.

Zuranolone is being evaluated as a potential rapid-acting, 2-week treatment for PPD and MDD in the NEST and LANDSCAPE clinical trial programs. The programs are designed to generate data to support a potential NDA filing as efficiently as possible. If successful, LANDSCAPE and NEST may support paths to approval with three distinct opportunities to address patient needs: PPD, acute rapid response therapy (RRT) in MDD when co-initiated with a new standard antidepressant, and as-needed treatment of MDD.

Zuranolone is being evaluated as a potential rapid-acting, 2-week treatment for PPD and MDD in the NEST and LANDSCAPE clinical trial programs. The two development programs include multiple studies examining use of zuranolone in several thousand patients with a variety of dosing, clinical endpoints, and treatment paradigms. The LANDSCAPE Program includes six studies of zuranolone in patients with MDD. Data have been reported from three studies of zuranolone 30 mg in patients with MDD (MDD-201, MOUNTAIN Study and the 30 mg cohort from the ongoing SHORELINE Study), and one study of zuranolone 50 mg in patients with MDD (WATERFALL Study). Two additional studies evaluating zuranolone 50 mg in patients with MDD are expected to read out by the end of 2021 (CORAL Study and a 50mg cohort of the SHORELINE Study).

The NEST Program includes two placebo-controlled studies of zuranolone in patients with PPD. Positive data from the ROBIN Study (zuranolone 30 mg) have been previously reported. The SKYLARK Study (zuranolone 50 mg) is anticipated to readout by the end of 2021.

About Major Depressive Disorder (MDD)
Major depressive disorder (MDD) is a common but serious mood disorder in which people experience depressive symptoms that impair their social, occupational, educational or other important functioning, such as a depressed mood or loss of interest or pleasure in daily activities, consistently for at least a two-week period. It is estimated that approximately 17 million people in the U.S. and more than 250 million people worldwide suffer from MDD each year. While antidepressants are widely used to treat MDD, large-scale studies have demonstrated the need for additional therapies with a differentiated profile.

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.

About Biogen
At Biogen, our mission is clear: we are pioneers in neuroscience. Biogen discovers, develops and delivers worldwide innovative therapies for people living with serious neurological and neurodegenerative diseases as well as related therapeutic adjacencies. One of the world's first global biotechnology companies, Biogen was founded in 1978 by Charles Weissmann, Heinz Schaller, Kenneth Murray and Nobel Prize winners Walter Gilbert and Phillip Sharp. Today Biogen has the leading portfolio of medicines to treat multiple sclerosis, has introduced the first approved treatment for spinal muscular atrophy, commercializes biosimilars of advanced biologics and is focused on advancing research programs in multiple sclerosis and neuroimmunology, Alzheimer's disease and dementia, neuromuscular disorders, movement disorders, ophthalmology, neuropsychiatry, immunology, acute neurology and neuropathic pain.

We routinely post information that may be important to investors on our website at www.biogen.com. Follow us on social media – Twitter, LinkedIn, Facebook, YouTube.

Forward-Looking Statements

Sage Therapeutics Safe Harbor
Various statements in this release concern Sage's future expectations, plans and prospects, including without limitation statements regarding: the potential for future regulatory approval of zuranolone; our planned timing for reporting of data from ongoing clinical trials; the potential profile and benefit of zuranolone in MDD and PPD; plans for discussions of next steps with the FDA; regulatory filing plans and potential pathways and opportunities; planned next steps for the program; our estimates as to the number of patients with MDD; and the goals, opportunity and potential for zuranolone and 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: success in earlier clinical trials may not be repeated or observed in ongoing or future studies, and ongoing and future non-clinical and clinical results may not meet their primary or key secondary endpoints or be sufficient to file for or gain regulatory approval to market a product without further development work or may not support further development at all; unexpected concerns may arise from additional data, analysis or results from any of our completed studies; we may encounter adverse results or adverse events at any stage of development that negatively impact further development or that require additional nonclinical and clinical work which may not yield positive results; we may encounter delays in conduct of our clinical trials, including slower than expected site initiation or enrollment, that may impact our ability to meet our expected time-lines; the FDA may ultimately decide that the design, conduct or results of our completed and planned clinical trials for zuranolone, even if positive, are not sufficient for regulatory filing or approval in the indications that are the focus of our development plan and may require additional trials or data which may significantly delay our efforts to obtain approval and may not be successful; other decisions or actions of the FDA or other regulatory agencies may affect the zuranolone program and our plans, progress or results; the actual size of the MDD patient population may be significantly lower than our estimates and, even if zuranolone is approved, it may only be approved or used to treat a subset of the relevant patient populations; we may encounter technical and other unexpected hurdles in the development and manufacture of zuranolone or our other product candidates 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.

Biogen Safe Harbor
This news release contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to the potential, benefits, safety and efficacy of zuranolone (SAGE-217/BIIB125); the potential clinical effects of zuranolone; results from the Phase 3 WATERFALL Study of zuranolone; the clinical development program for zuranolone; clinical development programs, clinical trials and data readouts and presentations for zuranolone; the potential treatment of MDD and PPD; the potential of Biogen's commercial business and pipeline programs, including zuranolone; the anticipated benefits and potential of Biogen's collaboration arrangement with Sage; and risks and uncertainties associated with drug development and commercialization. These forward-looking statements may be accompanied by words such as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "potential," "possible," "will," "would" and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements, or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including without limitation, uncertainty of success in the development and potential commercialization of zuranolone; unexpected concerns may arise from additional data, analysis or results obtained during the WATERFALL Study or the other clinical studies of zuranolone; regulatory authorities may require additional information or further studies, or may fail or refuse to approve or may delay approval of Biogen's drug candidates, including zuranolone; the occurrence of adverse safety events; the risks of other unexpected hurdles, costs or delays; failure to protect and enforce data, intellectual property and other proprietary rights and uncertainties relating to intellectual property claims and challenges; product liability claims; third party collaboration risks; and the direct and indirect impacts of the ongoing COVID-19 pandemic on our business, results of operations and financial condition. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from Biogen's expectations in any forward-looking statement. Investors should consider this cautionary statement as well as the risk factors identified in Biogen's most recent annual or quarterly report and in other reports Biogen has filed with the U.S. Securities and Exchange Commission. These statements are based on Biogen's current beliefs and expectations and speak only as of the date of this news release. Biogen does not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

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