Sage Therapeutics Announces The Lancet Publishes Integrated Data from Pivotal Trials for Brexanolone Injection in Postpartum Depression

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Results from pivotal trials consistently showed treatment with brexanolone injection provided significant and rapid reduction in depressive symptoms within days of initiating therapy

Treatment response was durable over the follow-up period, across three placebo-controlled trials

ZULRESSO™ (brexanolone injection) New Drug Application currently under review with U.S.FDA and, if approved, would be the first medicine indicated for the treatment of postpartum depression

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Aug. 31, 2018-- Sage Therapeutics (NASDAQ: SAGE), a clinical-stage biopharmaceutical company developing novel medicines to treat life-altering central nervous system (CNS) disorders, today announced *The Lancet*has published an integrated analysis across three, double-blind, randomized, placebo-controlled studies of brexanolone injection in women with postpartum depression (PPD). This new analysis, published for the first time, demonstrated significant and clinically meaningful reductions in HAM-D total score, a common measure of depression severity, following treatment with brexanolone 90 µg/kg/h at the primary timepoint of 60 hours compared with placebo. Statistically significant improvement in the HAM-D total score was first observed within 24 hours of initiating treatment and treatment response was durable through the 30-day follow-up. The most common adverse events during treatment across all studies were headache, dizziness and somnolence. The FDA has conditionally accepted the proprietary name ZULRESSO™ for Sage's intravenous formulation of brexanolone.

"Postpartum depression is one of the most common complications of childbirth and it impacts the mother, her children, and the entire family," said Samantha Meltzer-Brody, M.D., M.P.H., Ray M Hayworth and Family Distinguished Professor of Mood and Anxiety Disorders and Director of the UNC Perinatal Psychiatry Program of the UNC Center for Women's Mood Disorders and primary investigator of the study. "I've been treating women with PPD for close to 25 years and the ability to rapidly treat the devastating symptoms of PPD would be a game changer for these women and their families. PPD symptoms vary for each mother, but may include sadness, anxiety, irritability, withdrawing from friends or family, having trouble bonding with her baby and thinking about harming herself and more rarely, her baby. Currently, there are not any pharmacologic treatments specifically approved for PPD. These new brexanolone data represent a significant shift in our understanding of how PPD may be treated in the future."

It is estimated that PPD affects approximately 10-20 percent of women giving birth globally. In the United States, estimates of new mothers identified with PDD each year vary by state from 8-20 percent, with an overall average of 11.5 percent.

"The stigma attached to maternal mental health often prevents mothers from seeking help and these data represent an exciting step forward in developing a treatment for people whose disorders have been ignored," said Steve Kanes, M.D., Ph.D., chief medical officer of Sage and lead author of the paper. "These data show a profound, rapid and durable reduction in PPD symptoms was achieved during the study period among the majority of participants receiving brexanolone. We believe these results validate our clinical approach to drug development and our efforts to bring treatments to areas of significant unmet need. ZULRESSO is currently under review by the FDA as a treatment for postpartum depression and, if approved, has the potential to

significantly improve the treatment options for PPD, which is great news for mothers and families."

The paper, titled "Brexanolone Injection in Post-Partum Depression: Two Multicentre, Double-blind, Randomised, Placebo-controlled Phase 3 Trials," includes integrated results from three pivotal, placebo-controlled trials of brexanolone in women with a range of PPD severities.

An analysis of the integrated comparative efficacy of brexanolone injection 90 µg/kg/hr [BRX90] versus placebo groups across two Phase 3 studies (studies 1 & 2) and one Phase 2 study completed in 2017 was conducted; as a unique dose group, brexanolone injection 60 µg/kg/hr [BRX60] in study 2 was not included in the integrated efficacy analysis but was included in integrated analyses of safety.

Mean pre-dose HAM-D total scores for the integrated BRX90 arms and placebo arms were 25.5 and 25.7, respectively. At the 60-hour primary timepoint, there were significantly larger mean reductions from baseline in HAM-D total scores with BRX90 relative to placebo (-17.0 vs. -12.8; $p<0.0001$). These treatment differences at Hour 60 were maintained at Day 30 (BRX90, -16.9; placebo, -14.3; $p=0.0213$). Brexanolone injection showed similar results in subjects with and without a concomitant antidepressant use, with both subgroups demonstrating significant differences in change from baseline HAM-D total score versus placebo at Hour 60 (no antidepressant: BRX90, -16.9; placebo, -12.6; $p<0.0001$; concomitant antidepressant: BRX90, -17.4; placebo, -13.0; $p=0.0282$). Additionally, brexanolone injection had higher rates of remission (defined as HAM-D total score ≤7; BRX90, 50.0%; placebo, 26.4%; $p<0.0001$) and response (defined as ≥50% reduction in HAM-D total score; BRX90, 74.5%; placebo, 5.7%; $p=0.0003$) than placebo at Hour 60.

Across all brexanolone injection subjects, including subjects who received BRX60, there were two (1%) brexanolone subjects with at least one serious adverse event (vs. no placebo subjects), and there were three (2%) brexanolone subjects with at least one severe adverse event compared with two (2%) placebo subjects. There were no deaths. There was a similar percentage of subjects with at least one adverse event between treatments (50% on brexanolone injection vs. 51% on placebo). The most common (≥10% of subjects) AEs during brexanolone injection administration were headache, dizziness, and somnolence.

About Postpartum Depression
Postpartum depression (PPD) is a distinct and readily identified major depressive disorder that is the most common medical complication of childbirth, affecting a subset of women typically commencing in the third trimester of pregnancy or within four weeks after giving birth. PPD may have devastating consequences for a woman and for her family, which may include significant functional impairment, depressed mood and/or loss of interest in her newborn, and associated symptoms of depression such as loss of appetite, difficulty sleeping, motor challenges, lack of concentration, loss of energy and poor self-esteem. Suicide is the leading cause of maternal death following childbirth. In the U.S., estimates of new mothers identified with PPD each year vary by state from 8 to 20 percent, with an overall average of 11.5 percent. More than half of these cases may go undiagnosed without proper screening. There are no FDA approved therapies for PPD and there is a high unmet medical need for improved pharmacological therapy in PPD.

About the Hamilton Rating Scale for Depression (HAM-D)
HAM-D is a validated rating scale used to provide an assessment of depression, and as a guide to evaluate recovery. This scale is an accepted regulatory endpoint for depression. The scale is used to rate the severity of a patient's depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation, anxiety, weight loss, and somatic symptoms.

About ZULRESSO™ (brexanolone injection)
Brexanolone is an allosteric modulator of both synaptic and extrasynaptic $GABA_A$ receptors. Allosteric modulation of neurotransmitter receptor activity results in varying degrees of desired activity rather than complete activation or inhibition of the receptor. ZULRESSO (brexanolone injection) has completed Phase 3 clinical development for postpartum depression and a New Drug Application is currently under review with the U.S. Food and Drug Administration. ZULRESSO for the treatment of PPD has been granted

Breakthrough Therapy Designation by the FDA and PRIority MEdicines (PRIME) designation from the European Medicines Agency (EMA).

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 CNS disorders. Sage's lead product candidate, ZULRESSO (brexanolone injection), has completed Phase 3 clinical development for postpartum depression and a New Drug Application is currently under review with the U.S. Food and Drug Administration. Sage is developing a portfolio of novel product candidates targeting critical CNS receptor systems, including SAGE-217, which is in Phase 3 development in major depressive disorder and postpartum depression. 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 expectations regarding the potential for approval of our NDA for brexanolone IV in the treatment of PPD; our views as to the potential of brexanolone IV to represent a paradigm shift in the treatment of PDD, and to improve treatment options; our estimates of the prevalence of PPD; and our views as to the opportunity represented by Sage's portfolio and business. 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 FDA may decide not to approve our NDA for brexanolone IV in PPD; the clinical and non-clinical data we have generated with our proprietary formulation of brexanolone to date may be determined by the FDA and other regulatory authorities, despite prior advice, to be insufficient to gain regulatory approval to launch and commercialize our product in PPD and regulatory authorities may determine that additional trials or data are necessary in order to obtain approval; regulatory authorities may find fault with the data generated at particular clinical site or sites or with the activities of our trial monitor or may disagree with our analyses of the results of our trials or identify issues with our manufacturing or quality systems, and any such findings or issues could require additional data or analyses or changes to our systems that could delay or prevent us from gaining approval of brexanolone IV; even if brexanolone IV is approved in PPD, regulatory authorities may impose significant restrictions or conditions on use or on administration, including on sites of care; the number of women with PPD, and the actual market for brexanolone IV, may be smaller than our current estimates; we may encounter unexpected safety or tolerability issues with respect to brexanolone IV or any of our other product candidates; we may not be successful in our development of any of our product candidates in any indication we are currently pursuing or may in the future pursue; success in early stage clinical trials may not be repeated or observed in ongoing or future studies of our product candidates; ongoing and future clinical results 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; and we may encounter new data or technical and other unexpected hurdles in the development, manufacture and potential future commercialization 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, and 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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