Study Protocol

"Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial"

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Primary Efficacy Objective:

- To determine if treatment with zuranolone reduces depressive symptoms in subjects with severe postpartum depression (PPD) compared to placebo as assessed by the change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 15.

Secondary Efficacy Objectives:

- To determine if treatment with zuranolone Capsules 30 mg QD reduces depressive symptoms in subjects with severe PPD compared to placebo as assessed by the change from baseline in the HAM-D total score at all other time points.
- To determine if treatment with zuranolone Capsules 30 mg QD reduces depressive symptoms compared to placebo as assessed by HAM-D response, HAM-D remission, change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAM-D subscales and individual item scores at Day 15 and all other time points.
- To determine if treatment with zuranolone Capsules 30 mg QD reduces anxiety symptoms compared to placebo as assessed by changes from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score Day 15 and all other time points.

Safety Objective:

- To evaluate the safety and tolerability of zuranolone compared to placebo as assessed by the incidence of adverse events, vital sign measurements, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS).

Other Objectives:

- To determine if treatment with zuranolone Capsules 30 mg QD improves maternal behaviors compared to placebo as assessed by the change from baseline in the Barkin Index of Maternal Functioning (BIMF) total and subscale scores at Day 15 and other time points.

Study Design and Methodology:

- This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and pharmacokinetics of zuranolone in adult subjects diagnosed with severe PPD.
- The study will be conducted in 2 parts. One subject was enrolled and dosed in Part A before it was closed to enrollment (see Protocol Amendment 2, Version 3.0); the current amendment describes Part B only.

Screening Period:

- The Screening Period will begin with the signature of the informed consent form (ICF). The diagnosis of depression will be determined using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) Axis I Disorders (SCID-I). Eligibility will be determined by applying the inclusion/exclusion criteria. A full medical and family history will be taken including recording of all major depression episodes, other Axis I and Axis II disorders, and postpartum depression episodes in immediate female family members.

Treatment Period:

- Once subjects are confirmed as eligible for the study, they will be randomized to active study drug or placebo on a 1:1 basis.
- Randomized subjects will receive 30 mg QD of study drug (zuranolone Capsules or placebo). Those subjects who cannot tolerate 30 mg QD will receive 20 mg QD for the remainder of the Treatment Period. Subjects who experience intolerable adverse events (AEs) at the 20 mg QD dose level may be discontinued from study treatment at the discretion of the Investigator. Subjects will be instructed to take the study drug with food. Study drug will be self-administered by subjects in the evening (8:00 pm
- ±30 min) on an outpatient basis for the entire 14-day Treatment Period. Study drug administration will be monitored via a follow-up call from the site each evening (within approximately 1 hour following the scheduled evening dose) on Days 1 to 14.
- Subjects will not be allowed to initiate psychotropic medications or other medications that may potentially have an impact on efficacy or safety endpoints within 30 days prior to informed consent until completion of the Day 15 assessments. Psychotropic medications initiated at least 30 days prior to informed consent must remain at a stable dose until completion of the Day 15 assessments.
- Efficacy and safety assessments will be performed periodically during the study, and blood samples may be collected for analysis of zuranolone and metabolites of zuranolone as outlined in the Schedule of Events. Blood samples will be collected and outcome measures will be obtained at pre-specified times over the 14-day Treatment Period. In addition, breast milk for assessment of zuranolone concentrations may be collected if consent is received from the subject.

Follow-up Period:

- The Follow-up Period assessments will be conducted on an outpatient basis on Day 21±1 day and Day 45±3 days after the initiation of study drug administration.

Number of Subjects:

- Approximately 140 subjects will be randomized in a 1:1 ratio for approximately 70 subjects per treatment group. Additional subjects may be enrolled in order to ensure there are 130 evaluable subjects. Evaluable subjects are defined as those randomized subjects receiving study drug with valid baseline and at least 1 post-baseline HAM-D assessment.

Inclusion Criteria:

The following inclusion criteria must be met for individuals to be eligible for the study.

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory female between 18 and 45 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject either must have ceased lactating at screening or, if still lactating or actively breastfeeding at screening, must agree to temporarily cease giving breast milk to her infant(s) from just prior to receiving study drug through Day 21, allowing for a 7-day washout after the last dose of study drug.
6. Subject must have a negative pregnancy test at screening and Day 1 prior to the start of study drug administration.
7. Subject has had a major depressive episode that began no earlier than the third trimester and no later than the first 4 weeks following delivery, and meets criteria for major depressive episode per DSM-5, diagnosed by Structured Clinical Interview for (DSM-5) Axis I Disorders (SCID- I).
8. Subject has a HAM-D total score of ≥26 at screening and Day 1 (prior to randomization).
9. Subject is ≤6 months postpartum.
10. Subject is willing to delay start of other antidepressant or anxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics, until after the Treatment Period ends and all Day 15 assessments have been completed.
11. Subject has no detectable hepatitis B surface antigen (HBsAg), no detectable anti-hepatitis C virus (HCV), detectable anti-HCV but negative viral load, and no detectable human immunodeficiency virus (HIV) antibody at screening.
12. Subject agrees to use 1 of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are surgically sterile:
    - Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation.
    - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
    - Intrauterine device.
    - Intrauterine hormone-releasing system.
    - Bilateral tubal occlusion.
    - Vasectomized partner.

Exclusion Criteria:

Subjects will be excluded if they meet any of the following exclusion criteria.

1. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to participate in or complete this clinical study.
2. Subject has a known allergy to zuranolone Capsule or its excipients.
3. Subject has active psychosis per Investigator assessment.
4. Subject has attempted suicide associated with the current episode of PPD.
5. Subject has a medical history of seizures.
6. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
7. Subject has a history of active alcoholism or drug addiction (including benzodiazepines) in the 12 months prior to screening.
8. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
9. Subject has prior participation in any SAGE-547 or zuranolone clinical study.
10. Subject who presents for the study while currently receiving psychotropic medications that are used with the intent to treat depressive symptoms such as antidepressants, atypical antipsychotics, etc., which have not been taken at the same dose for at least 30 days prior to Day 1. (Subjects presenting for the study who have stopped taking these medications within the 30 days prior to the start day of study drug may be eligible if they will be off of the medications for longer than 5 half-lives until the start day of study drug).
11. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 14 days or 5 half- lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug and throughout the study.
12. Use of any CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital or St John's Wort, within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study drug and throughout the study.
13. Subject has a positive urine drug test at the screening visit.
14. Subject plans to undergo elective surgery during participation in the study.

Investigational Product, Dosage, and Mode of Administration:

- Zuranolone Capsules are available in 10-mg, 20-mg, and 30-mg strengths in order to provide treatment doses of 20 mg and 30 mg. Subjects will be administered 2 capsules per dose.

Reference Therapy, Dosage, and Mode of Administration:

- Matched placebo capsules will be provided. Subjects will be administered 2 placebo capsules per day, to maintain blinding.

Duration of Participation:

- Up to 76 days (14 days of treatment)

Randomization:

- Subjects will be randomized to receive zuranolone or matching placebo in a 1:1 ratio.
- Subjects, clinicians, and the study team will be blinded to treatment allocation. Randomization will be performed centrally via an interactive response technology (IRT) system.

Dose Adjustment for Safety/Tolerability Reasons:

- During the Treatment Period, subjects will be able to receive study drug as long as there are no dose-limiting safety/tolerability concerns. Dose adjustment criteria are described in Section 9.3 of the protocol.

Criteria for Evaluation:

Primary Efficacy Endpoint

- The primary efficacy endpoint will be the change from baseline in HAM-D total score at the end of the Treatment Period (Day 15). The HAM-D total score will be calculated as the sum of the 17 individual item scores.

Secondary Efficacy Endpoints

Secondary endpoints will include:

- Change from baseline in the HAM-D total score at all time points other than Day 15;
- HAM-D response defined as a 50% or greater reduction from baseline in HAM-D total score;
- HAM-D remission defined as a HAM-D total score of ≤7;
- Change from baseline in MADRS total score at Day 15 and other time points;
- CGI-I response defined as “very much improved” or “much improved”;
- Change from baseline in HAM-A total score at Day 15 and other time points;
- Changes from baseline in HAM-D subscales and individual item scores at Day 15 and other time points

Safety Endpoints

- Safety and tolerability of study drug will be evaluated by frequency of adverse events; severity, relatedness, and seriousness of adverse events; clinical laboratory measures, vital signs, ECGs; and concomitant medication usage. Suicidality will be monitored using the C-SSRS.
- Concomitant medications: The doses of all psychotropic medications will be recorded throughout the study. No changes and/or additions to antidepressant or anxiolytic medicine will be allowed during the Treatment Period.

Other Endpoints

- Additional measures of affective symptoms and function related to the current episode of PPD severity will be collected before, during, and after the Treatment Period.
- Total and subscale scores including changes from baseline will be calculated where applicable. Changes from baseline to the end of the Treatment Period (Day 15) and other time points will be evaluated as other efficacy endpoints. In addition to the above scores, total score categories and individual item scores will be evaluated as other endpoints.

Statistical Methods:

General:

- For the purpose of all safety, efficacy, and other analyses where applicable, baseline is defined as the last measurement prior to the start of blinded study drug administration.
- Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

Analysis Sets and Methods:

- The All Randomized Set, defined as all subjects who have been randomized, will be used for subject disposition, demographics, and baseline characteristic summaries. Subjects will be classified according to randomized treatment.
- The Safety Set, defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data. Subjects will be summarized according to treatment received.
- The Efficacy Set, defined as all subjects in the All Randomized Set who complete at least 1 day of study drug and have a valid baseline and at least 1 post-baseline efficacy assessment, will be used to analyze efficacy data. Efficacy data will be analyzed using appropriate descriptive statistics and pre- specified statistical methods, as well as other data presentation methods where applicable; subject

listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment.

- The PK Set will consist of all subjects in the Safety Set with plasma concentration determinations for zuranolone, and will be used for population PK modeling.
- The change from baseline in HAM-D total score will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include center, treatment, baseline HAM-D total score, assessment time point, and time point-by-treatment as explanatory variables. All post-baseline time points will be included in the model. The primary comparison will be between zuranolone and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means), 95% confidence intervals, and p-values will be reported. An unstructured covariance structure will be used to model the within-subject errors. Continuous secondary and other variables will be analyzed using similar methods.
- Binary efficacy endpoints, including responder and remission endpoints, will be summarized and analyzed using the generalized estimating equation method.
- Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA™) Version 19.1 or higher. The overall incidence of adverse events will be displayed by System Organ Class, preferred term, and treatment. The incidence of adverse events will also be presented by maximum severity and relationship to study drug. Vital signs, clinical laboratory measures, ECG, concomitant medication usage, and C-SSRS data will be summarized by treatment, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable. Safety data will be summarized and examined for possible relationships between subject characteristics and plasma zuranolone concentrations, as appropriate. Suicidality data collected using the C-SSRS at baseline and at each visit during the active Treatment Period will be listed for all subjects. The C-SSRS listings will include behavior type and/or category for suicidal ideation and suicidal behavior of the C-SSRS.

Sample Size Calculation:

- Assuming a 2-sided test at an alpha level of 0.05, a sample size of approximately 65 subjects per treatment group would provide 90% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15 assuming standard deviation (SD) of 7 points.