# A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF SAGE-217 IN THE TREATMENT OF ADULTS WITH SEVERE POSTPARTUM DEPRESSION

## PROTOCOL NUMBER: 217-PPD-301

## EUDRACT NUMBER: 2020-001424-34

| | |
|---|---|
| Investigational Product | SAGE-217 |
| Clinical Phase | Phase 3 |
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| Date of Original Protocol | 01 April 2020 |

Confidentiality Statement

The confidential information in this document is provided to you as an investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from Sage Therapeutics, Inc.

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# SPONSOR APPROVAL

| | |
|---|---|
| **Protocol Number:** | 217-PPD-301 |
| **Study Title:** | A Randomized, Double-Blind, Placebo-controlled Study Evaluating the Efficacy and Safety of SAGE-217 in the Treatment of Adults with Severe Postpartum Depression |
| **Protocol Version and Date:** | Version 1, 01 April 2020 |

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# INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-PPD-301 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

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# CONTACT INFORMATION

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# 2. SYNOPSIS

**Name of Sponsor/Company:**
Sage Therapeutics, Inc. (hereafter referred to as Sage Therapeutics, or Sage)

**Name of Investigational Product:**
SAGE-217

**Name of Active Ingredient:**
SAGE-217

**Title of Study:**
A Randomized, Double-Blind, Placebo-controlled Study Evaluating the Efficacy and Safety of SAGE-217 in the Treatment of Adults with Severe Postpartum Depression

**Number of Sites and Study Location:** This study will take place at approximately 75 sites globally.

**Phase of Development:** Phase 3

**Planned Duration for each Study Participant:**
The duration of participation for each participant will be up to 76 days, including screening, treatment period and follow-up period.

**Objectives and Endpoints**:

**Objectives**:

Primary:

- To determine if treatment with SAGE-217 reduces depressive symptoms in adults with severe postpartum depression (PPD) compared to placebo

Secondary:

- To determine if treatment with SAGE-217 reduces anxiety symptoms compared to placebo
- To assess self-report of depressive symptoms
- To evaluate the safety and tolerability of SAGE-217

Other:

- To assess the plasma pharmacokinetics (PK) of SAGE-217

**Endpoints:**

Primary:

- Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 15

Key Secondary:

- Change from baseline in HAM-D total score at Day 3, Day 28, and Day 45
- Change from baseline in Clinical Global Impressions – Severity (CGI-S) score at Day 15

Other Secondary:

- HAM-D response at Day 15 and Day 45
- HAM-D remission at Day 15 and Day 45
- Clinical Global Impressions – Improvement (CGI-I) response at Day 15
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at Day 15

- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15
- Change from baseline in HAM-D subscale at Day 15
- Change from baseline in self-reported measures of depressive symptoms, as assessed by the Edinburgh Postnatal Depression Scale (EPDS) total score and 9-item Patient Health Questionnaire (PHQ-9)
- Incidence of treatment-emergent adverse events (TEAEs)

Other:

- Change from baseline in vital signs, electrocardiogram (ECG), clinical laboratory parameters, Columbia Severity Rating Scale (C-SSRS) responses, and 20-item Physician Withdrawal Checklist (PWC-20)
- PK parameters (eg, clearance) and exposure estimates (eg, area under the curve over a dosing interval, maximum plasma concentration) as assessed via population PK methods

**Study Description:**

This is a randomized, double-blind, placebo-controlled, parallel group study of the efficacy and safety of SAGE-217 in adults diagnosed with severe PPD. Participants, site staff, and sponsor personnel will be masked to treatment allocation.

This study will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a Follow-up Period through Day 45.

The Screening Period begins with the signing of the informed consent form (ICF); the ICF must be signed prior to beginning any screening activities. 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-5-CT). Participants will undergo preliminary screening procedures to determine eligibility. A full personal medical history will be taken including documentation of all major depression episodes, other Axis I, and any prior PPD episodes. In addition, PPD episodes experienced by immediate female family members, including siblings, parents, and grandparents will be documented.

During the study, a qualified lactation consultant will be made available upon request to participants who are breastfeeding.

Psychotropic medications are permitted provided participants are on a stable dose for at least 30 days prior to Day 1 and agree to continue on a stable dose through completion of the Day 45 assessments. Initiation of new psychotropic medications that may potentially have an impact on efficacy and/or safety endpoints will not be allowed within 30 days prior to Day 1 through completion of the Day 45 assessments. On Day 1, eligible participants will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥30 days or >5 half-lives) and randomized within each stratum to 1 of 2 treatment groups (SAGE-217 50 mg or matching placebo) in a 1:1 ratio. Participants will self-administer investigational product (IP) once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. As local regulations permit, IP administration will be monitored via a medication adherence monitoring platform used on smartphones to visually confirm IP ingestion. Participants will return to the study center during the treatment and follow-up periods as outlined in Table 2.

During the treatment period, participants will be able to receive IP as long as there are no dose limiting safety/tolerability concerns. Participants who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the investigator, participants who cannot tolerate the 40-mg dose will be discontinued from IP. Participants who discontinue IP early should

return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after IP is discontinued. Follow-up visits should take place as scheduled relative to the last dose of treatment (eg, if a participant's last dose is on Day 13, their first follow-up visit should occur 4 days later). If necessary, the EOT and early termination visits can be on the same day if a participant discontinues IP and terminates the study on the same day during a clinic visit; in this case, all EOT visit assessments should be conducted.

**Number of Participants (planned):** Approximately 192 participants, with a total of approximately 96 per treatment group (SAGE-217 or placebo)

**Eligibility Criteria:**

Inclusion Criteria:

1. Participant has signed an ICF prior to any study-specific procedures being performed.
2. Participant is an ambulatory female between 18 and 45 years of age, inclusive.
3. Participant 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. Participant agrees to adhere to the study requirements, including not participating in night shift work.
5. Participant has ceased lactating or agrees not to provide breastmilk to her infant(s) from just prior to receiving IP on Day 1 until 7 days after the last dose of IP.
6. Participant must have a negative pregnancy test at screening and Day 1 prior to the start of IP administration.
7. Participant 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 SCID-5-CT.
8. Participant has a HAM-D total score of ≥26 at screening and Day 1 (prior to randomization).
9. Participant is ≤6 months postpartum.
10. Participants taking antidepressants must have been taking these medications at the same dose for at least 30 days prior to Day 1. Participants who have stopped taking antidepressants within 30 days must have stopped for longer than 5 half-lives of the antidepressant prior to Day 1, and will be stratified into the "no antidepressant group". Participants receiving psychotherapy must have been receiving therapy on a regular schedule for at least 30 days prior to Day 1.
11. Participant is willing to delay the start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, until after completion of the Day 45 visit.
12. Participant agrees to use at least 1 method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of IP, unless she is surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence).
13. Participant agrees to refrain from drugs of abuse and alcohol for the duration of the study.

Exclusion Criteria:

1. Participant is currently at significant risk of suicide, as judged by the investigator or has attempted suicide associated with the current episode of PPD.

2. Participant has a recent history of active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eye, ears, nose, and throat disorders, or any other acute or chronic condition that, in the investigator's opinion, would limit the participant's ability to participate in or complete the clinical study. A body mass index (BMI) ≤18 or ≥45 kg/m$^2$ at screening is exclusionary; a BMI of 40 to 44.9 kg/m$^2$, inclusive, at screening is subject to a broader evaluation of medical comorbidities (eg, chronic obstructive pulmonary disease [COPD]), concomitant medications, and prior tolerability of sedating agents.
3. Participant has a clinically significant abnormal 12-lead ECG at the screening or Day 1 visit. NOTE: a mean QT interval calculated using the Fridericia method (QTcF) of >470 msec will be the basis for exclusion from the study.
4. Participant has a known allergy to SAGE-217, allopregnanolone, or related compounds.
5. Participant has active psychosis per investigator assessment.
6. Participant's index pregnancy resulted in a miscarriage, still birth, or neonatal death; or participant has terminated parental rights (eg, child has been placed for adoption).
7. Participant has a medical history of nonfebrile seizures.
8. Participant has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
9. Participant has a history of mild, moderate, or severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to screening.
10. Participant has had exposure to another investigational medication or device within 30 days prior to screening.
11. Participant has previously participated in this study or any other study employing SAGE-217 or SAGE-547 (brexanolone), ganaxolone, any other compound containing allopregnanolone, or has previously been treated with ZULRESSO™ (brexanolone).
12. Participant has a history of sleep apnea.
13. Participant has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current PPD episode.
14. Participant has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
15. Participant is taking benzodiazepines, barbiturates, or γ-aminobutyric acid $(GABA)_A$ receptor modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Day 1 or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Participant is taking any benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 30 days prior to Day 1.
16. Participant is taking non-GABA anti-insomnia medications (eg, melatonin, Benadryl [antihistamines], trazodone), or first or second generation (typical/atypical) antipsychotics within 14 days prior to Day 1.

17. Participant has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to screening.
18. Participant is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as needed, within 28 days prior to Day 1.
19. 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 IP.
20. Participant has a positive urine drug test and/or alcohol screen at screening or on Day 1 prior to dosing.
21. Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St. John's Wort within 14 days or 5 half-lives (whichever is longer) prior to the first dose of IP.
22. Participant plans to undergo elective surgery during participation in the study.
23. Participant is a dependent of the sponsor, investigator, investigator's deputy, or study site staff.
24. Participant is involuntarily confined or detained in a penal institution or other institution under court order.

**Investigational Product Dosage and Mode of Administration:**

SAGE-217 and placebo will be provided as hard gelatin capsules for oral administration. Available dose strengths of SAGE-217 are:

- 50-mg with the option to reduce to 40-mg for intolerable AEs

**Duration of Treatment:**

SAGE-217 or placebo will be administered once daily for 14 days.

**Statistical Methods:**

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock.

**General Considerations**

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to receipt of IP.

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**

The Safety Set will include all participants administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a valid baseline and at least one valid postbaseline HAM-D total score.

The Per Protocol Set is defined as all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding.

**Determination of Sample Size**

Using a 2-sided test at an alpha level of 0.05, a sample size of approximately 86 evaluable participants 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 of 8 points.

Assuming a 10% dropout and a 1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 192 randomized participants (96 per treatment group) will be required to obtain 86 evaluable participants per treatment group. Evaluable participants are defined as those randomized participants who receive IP and have a valid baseline and at least 1 postbaseline HAM-D assessment. Additional participants may be randomized if the dropout rate is higher than 10%.

**Analysis of Primary Endpoint**

The estimand for the primary efficacy analysis is the mean change from baseline in HAM-D total score at Day 15. This will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline time points will be included in the model. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

**Analysis of Secondary Endpoints**

Similar to those methods described above for the primary endpoint, an MMRM will be used for the analysis of the change from baseline in other time points in HAM-D total score, MADRS total score, HAM-A total score, EPDS total score, PHQ-9 score, and selected individual items and/or subscale scores in HAM-D.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as ≥50% reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of ≤7.0). GEE models will include terms for treatment, baseline score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 and matching placebo at Day 15. Model-based point estimates (ie, odds ratios), 95% confidence intervals, and p values will be reported.

A GEE method will also be used for the analysis of CGI-I response (defined as “much improved” or “very much improved”) including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.

**Analysis of Other Endpoints**

Descriptive summary statistics will be provided for other endpoints.

**Safety Analysis**

Safety and tolerability of SAGE-217 will be evaluated by incidence of TEAEs, changes from baseline in vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS responses. Potential withdrawal symptoms after discontinuation of SAGE-217 will be assessed using the PWC-20.

**Pharmacokinetic Analysis**

SAGE-217 concentration-time data will be evaluated using a nonlinear mixed-effects model. The model will be used to estimate population PK parameters and identify any covariates that may contribute to observed variability. PK data from this study will be analyzed and reported separately.

**Table 2: Schedule of Assessments**

| | Study Period / Visit Day | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Screening Period | Treatment Period[a] | | | | Follow-up Period | | | |
| Study Procedure | D-28 to -1 | D1 (assessments completed predose) | D3 (±1 d) | D8 (+1 d) | D15 (+1 d) and/or EOT [b] | D18 (±1 d) | D21 (±1 d) | D28 (±3 d) | D45/ET (±3 d) |
| Informed Consent | X | | | | | | | | |
| Duplicate Participant Check [c] | X | | | | | | | | |
| Inclusion/Exclusion | X | X | | | | | | | |
| SCID-5-CT | X | | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical/Family History | X | | | | | | | | |
| Participant training [d] | X | X | | | | | | | |
| Physical Examination [e] | X | | | X | X | | X | | |
| Body Weight/Height | X | | | | X (weight only) | | X (weight only) | | |
| Clinical Laboratory Assessments [f] | X | | | X | X | | X | X | X |
| Drug & Alcohol Screen [g] | X | X | X | X | X | X | X | X | X |
| Pregnancy Test [h] | X | X | | | X | | | | X |
| Hormone Sample [i] | O | | | O | O | | | | |
| Genetic Sample [j] | O | | | | | | | | |
| Vital Signs [k] | X | X | X | X | X | X | X | X | X |
| 12-Lead ECG [l] | X | X | | | X | | | | X |
| C-SSRS [m] | X | X | X | X | X | X | X | X | X |
| PWC-20 | | X | | | X | X | X | | X (ET only) |
| CGI-I | | | X | X | X | | X | X | X |
| CGI-S | X | X | X | X | X | | X | X | X |
| HAM-A [n] | | X | X | X | X | | X | X | X |
| HAM-D [n, o] | X | X | X | X | X | | X | X | X |
| MADRS | | X | | X | X | | | X | X |
| EPDS | X | X | X | X | X | | X | X | X |
| PHQ-9 | X | X | X | X | X | | X | X | X |
| Plasma PK [p] | | | X | X | X | | | | |
| Randomization | | X | | | | | | | |

| Study Procedure | Study Period / Visit Day | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Screening Period** | **Treatment Period[a]** | | | | **Follow-up Period** | | | |
| | **D-28 to -1** | **D1 (assessments completed predose)** | **D3 (±1 d)** | **D8 (+1 d)** | **D15 (+1 d) and/or EOT [b]** | **D18 (±1 d)** | **D21 (±1 d)** | **D28 (±3 d)** | **D45/ET (±3 d)** |
| Dispense IP | | X | | X | | | | | |
| IP Administration | | X (once daily in the evening through Day 14 - inclusive) | | | | | | | |
| IP Adherence [q] | | X | | | | | | | |
| IP Accountability/Return | | | | X | X | | | | |
| Adverse Events | X (from time of ICF throughout the duration of participation) | | | | | | | | |
| Prior/Concomitant Medications [r] | X | | | | | | | | |

CGI-I = Clinical Global Impressions - Improvement; CGI-S = Clinical Global Impressions - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ECG = electrocardiogram; EOT = end of treatment; EPDS = Edinburgh Postnatal Depression Scale; ET = early termination; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; IP = investigational product; MADRS = Montgomery-Åsberg Depression Rating Scale; O = optional; PHQ-9 = Patient Health Questionnaire; PK = pharmacokinetic

Note: When ECG, vital signs, and/or blood draws are scheduled to occur at the same time, the order of assessments should be as follows: vital signs, ECG, blood draw.

[a] An unscheduled visit may be needed if a dose adjustment is deemed necessary by the investigator. Any remaining current dose should be returned, and the adjusted dose should be dispensed at this visit.

[b] Participants who discontinue IP early should return to the site for an EOT visit as soon as possible, preferably the day after IP is discontinued. If necessary, the EOT and ET visits can be on the same day if a participant discontinues IP and terminates the study on the same day during a clinic visit; in this case, all EOT visit assessments should be conducted.

[c] Participants in the US only will be asked to authorize that their unique participant identifiers be entered into a registry with the intent of identifying participants who may meet exclusion criteria for participation in another clinical study.

[d] Participants will be trained on the use of software applications and devices necessary for the conduct of the study by site personnel.

[e] A full physical examination will be conducted at screening and abbreviated physical examinations will be conducted thereafter. A full physical examination includes assessment of body systems (eg; head; eye; ear, nose, and throat; heart; lungs; abdomen; and extremities). An abbreviated physical examination includes a brief medical history followed by targeted physical examination.

[f] Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis.

[g] Urine toxicology for selected drugs of abuse and breath test for alcohol

[h] Serum pregnancy test at screening and urine pregnancy test at all other visits indicated. A urine pregnancy test will also be collected as part of the ET assessments for participants who discontinue the study early.

[i] An optional blood sample for stress hormone levels, kynurenine biochemistry, and markers of inflammation, where consent is given.

[j] An optional genetic sample for biomarker testing, where consent is given.

[k] Vital signs include respiratory rate, oral body temperature, heart rate, and blood pressure (supine and standing). Heart rate and blood pressure to be collected in supine position at all scheduled time points after the participant has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Vital signs may be repeated at the discretion of the investigator as clinically indicated.

[l] Triplicate ECGs will be collected.

[m] The "Baseline/Screening" C-SSRS form will be completed at screening. The "Since Last Visit" C-SSRS form will be completed at all subsequent time points.

[n] The assessment timeframe for HAM-D scales will refer to the past 7 days (1 week) at Screening and "Since Last Visit" for all other visits. The assessment timeframe for HAM-A scales will refer to the past 7 days (1 week) at all visits.

[o] HAM-D is to be completed as early during the visit as possible.

[p] Plasma samples for PK analysis will be collected at each indicated visit. In the event of a dose adjustment at an unscheduled visit, an unscheduled PK sample should be collected, if possible, prior to the dose adjustment.

[q] As local regulations permit, IP administration will be monitored via a medication adherence monitoring platform used on smartphones to visually confirm IP ingestion. Optional consent may be required in regions with restricted regulations.

[r] Prior medications will be collected at screening and concomitant medications and/or procedures will be collected at each subsequent visit (see Section 9.2.1).

## 3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 3: Abbreviations and Specialist Terms**

| Abbreviation | Definition |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| AUC | area under the curve |
| BMI | body mass index |
| CBD | cannabidiol |
| CGI-I | Clinical Global Impressions – Improvement |
| CGI-S | Clinical Global Impressions – Severity |
| $C_{max}$ | maximum observed concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CS | clinically significant |
| CSR | clinical study report |
| CYP | cytochrome P450 |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition |
| IEC | independent ethics committee |
| IRT | interactive response technology |
| ECG | Electrocardiogram |
| eCRF | electronic case report form |
| EOT | end of treatment |
| EPDS | Edinburgh Postnatal Depression Scale |
| ET | early termination |
| FDA | Food and Drug Administration |
| GABA | γ-aminobutyric acid |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| GEE | generalized estimating equation |
| HAM-A | Hamilton Rating Scale for Anxiety |
| HAM-D | Hamilton Rating Scale for Depression |
| IB | Investigator's Brochure |
| ICF | informed consent form |

| Abbreviation | Definition |
|---|---|
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IP | investigational product |
| IRB | institutional review board |
| LDH | lactate dehydrogenase |
| LS | least squares |
| MADRS | Montgomery Åsberg Depression Rating Scale |
| MDD | major depressive disorder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed-effects model for repeated measures |
| MTD | maximum tolerated dose |
| NCS | not clinically significant |
| NOAEL | no-observed-adverse-effect level |
| OS | oral solution |
| PCS | potentially clinically significant |
| PHQ-9 | 9-item Patient Health Questionnaire |
| PK | pharmacokinetic |
| PPD | postpartum depression |
| PWC-20 | 20-item Physician Withdrawal Checklist |
| PV | pharmacovigilance |
| QTcF | QT corrected according to Fridericia's formula |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SCID-5-CT | Structured Clinical Interview for Diagnostic and DSM-5 Clinical Trial Version |
| SD | standard deviation |
| SSRI | selective serotonin reuptake inhibitors |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TSH | thyroid stimulating hormone |
| WHO | World Health Organization |

# 5. INTRODUCTION

Postpartum depression (PPD) is defined as the occurrence of major depressive episode within 4 weeks of delivery (DSM-IV 1994) or up to a year after giving birth (Okun 2013). In Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the onset specifier includes the entire pregnancy as well as 4 weeks following delivery (DSM-5 2013). There are 2 entry criteria for the diagnosis of depression (depressed mood and/or loss of interest) and 7 associated symptoms of depression (appetite problems, sleep problems, motor problems, lack of concentration, loss of energy, poor self-esteem, and suicidality). To be diagnosed with severe PPD, women must present at least 5 symptoms of depression (DSM-5 2013). The estimated prevalence of PPD in the US is 11.5% (Ko 2017). Based on data from several studies, approximately 25% of PPD cases are considered severe (McCabe 2016; PACT Consortium 2015). If untreated, PPD can have devastating consequences for the woman and her family (Fihrer 2009; Verbeek 2012).

PPD is characterized by significant functional impairment for the mother due to sadness and depressed mood, loss of interest in daily activities, changes in eating and sleeping habits, fatigue and decreased energy, inability to concentrate, and feelings of worthlessness, shame, or guilt. Postpartum depression also carries an increased risk for suicide (Savitz 2011; American Psychiatric Association 2013), which is the leading cause of maternal death following childbirth (Oates 2003) in developed countries.

Current standard of care for severe PPD comprises cautious use of pharmacological therapies combined with a number of counseling, behavioral, and nonpharmacological therapy approaches (Altshuler 2001). Use of tricyclic antidepressants and/or selective serotonin reuptake inhibitors (SSRIs) is based on use in the general depressed population rather than any extensive studies in PPD (Austin 2013) Data to support the efficacy of MDD antidepressants in PPD are mixed (refer to Investigator's Brochure for more information). SSRIs tend to be preferred due to better data on safety while breastfeeding (Altshuler 2001). Based on the level of evidence for antidepressants in MDD (Kirsch 2008; Fournier 2010), there is a considerable need for improved pharmacological therapy for PPD.

In 2019, brexanolone, a positive allosteric modulator of γ-aminobutyric acid $(GABA)_A$ receptors, the major class of inhibitory neurotransmitter receptors in the brain, was approved by the FDA as a treatment for PPD. In clinical studies, intravenous infusion of brexanolone over 60 hours was more effective than placebo in improving depressive symptom scores in women with moderate to severe PPD (Kanes 2017; Meltzer-Brody 2018). These data suggest that augmenting extrasynaptic $GABA_A$ receptor function provides a therapeutic benefit in PPD.

## 5.1. SAGE-217

SAGE-217 is a synthetic positive allosteric modulator of $GABA_A$ receptors. In pharmacokinetic (PK) studies in mice and rats, SAGE-217 demonstrated rapid penetration and equilibrium across the blood brain barrier and is generally expected to have good extravascular exposure. In exploratory in vitro receptor and ion channel assays and in vivo safety pharmacology studies, SAGE-217 was highly selective for $GABA_A$ receptors, and, consistent with the actions of other $GABA_A$ receptor potentiators (Rudolph 2011), exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo.

Unlike other neurotropic medications that target $GABA_A$ receptors, SAGE-217 is an allosteric modulator of both synaptic as well as extrasynaptic $GABA_A$ receptors (Martinez Botella 2017). As such, SAGE-217 may represent a therapeutic advantage in the treatment of depressive disorders, including PPD, by resetting the GABAergic imbalance in depression by affecting both phasic and tonic inhibition.

In a Phase 3 study of adults with severe PPD, rapid and significant improvements of depressive symptoms were observed over 14 days of treatment. The SAGE-217 treatment group began to show statistically significant improvement over the placebo group as early as Day 3. The odds ratios associated with response and remission were 2.6 and 2.5, respectively, favoring SAGE-217. This improvement over the placebo group was overall consistent across assessments (ie, HAM-D, MADRS, HAM-A, CGI-I) and was sustained after the treatment period was completed.

## 5.2. Potential Risks and Benefits

The apparent risks of SAGE-217 are based on both nonclinical and clinical data in completed and ongoing studies and the known pharmacology of the drug. SAGE-217 has been generally well-tolerated in clinical studies. Sedation, somnolence, and dizziness were identified as adverse drug reactions. Most AEs were reported as mild or moderate in intensity and reversible. The proposed 50-mg or 40-mg doses have not been studied in participants with PPD, but the benefit-risk profile is expected to be acceptable (see Section 5.3). Refer to the Investigator's Brochure for a detailed description of the chemistry, pharmacology, efficacy, and safety of SAGE-217. SAGE-217 may present a treatment option for PPD that has more rapid onset of action (days instead of weeks) when compared to current standard of care.

Based on nonclinical findings, embryo-fetal toxicity and withdrawal effects are considered important potential risks for SAGE-217. Risk mitigation measures in this study include monitoring for adverse effects, monitoring for potential withdrawal effects, requiring highly effective contraceptive measures for study participants, and inclusion of dose adjustment criteria. Finally, due to the sedation/somnolence observed, SAGE-217 is administered in the evening in this study.

Given the outcome of the completed studies of SAGE-217 in adults with MDD and PPD, the current significant unmet need in the treatment of depression, and a favorable benefit-risk profile, further investigation of SAGE-217 in adults with PPD is justified.

## 5.3. Dose Justification

To date, the current capsule utilized in clinical studies is not associated with a maximum tolerated dose (MTD). Initial MTD assessments were performed using SAGE-217 in an oral solution (OS) at steady-state in healthy participants, which provided an MTD with a $C_{max}$ of 125 ng/mL at 30 mg OS. While reidentification of the MTD using the capsule formulations was not conducted, steady-state 30-mg capsules provide a model-derived $C_{max}$ approximately 50% lower (64 ng/mL) than the concentration associated with the MTD of 30 mg OS (125 ng/mL).

Studies 217-MDD-201 and 217-PPD-201, employing 30-mg capsules administered each evening for 14 days, demonstrated significant reduction in symptoms of depression, anxiety and insomnia. The safety profile in these studies is consistent with the $GABA_A$ neurosteroid

mechanism, including adverse drug reactions (ADRs) of somnolence, sedation, and dizziness at rates of 4% to 15%; the majority with mild intensity. Phase 3 studies in a broader patient population demonstrate activity of SAGE-217 associated with improvement in depressive symptoms, however, both the efficacy and safety findings support investigation of a higher dose, with predictable ADRs expected to be within an acceptable range.

Study 217-MDD-301, a randomized, multicenter, 3-arm study examining SAGE-217 20 -and 30-mg capsules compared to placebo, found significant antidepressant effects compared to placebo at Days 3, 8, and 12 but not Day 15 (primary endpoint) for the 30-mg dose. The 20-mg dose did not separate from placebo at any time point. The rates of expected ADRs of somnolence, sedation and dizziness in the 30-mg arm were each less than 10%; rates of discontinuation for adverse events were lower with SAGE-217 30 mg (2.1%) than with placebo (3.2%). No clinically relevant changes in vital signs, laboratory results, electrocardiogram measures, or suicidal thinking were observed in either 217-MDD-301 or across the full SAGE-217 program, now with over 2000 participants exposed to treatment. Relevant results from 217-MDD-301 are available in the Investigator's Brochure.

Direct and modeled data from completed studies to date (including efficacy studies 217-MDD-201 and 217-PPD-201) in addition to 217-MDD-301 (through Day 42 of the double-blind period), have been used to assess and predict the efficacy and safety outcomes at SAGE-217 concentrations expected with higher doses of SAGE-217 capsules (eg, 40 and 50 mg).

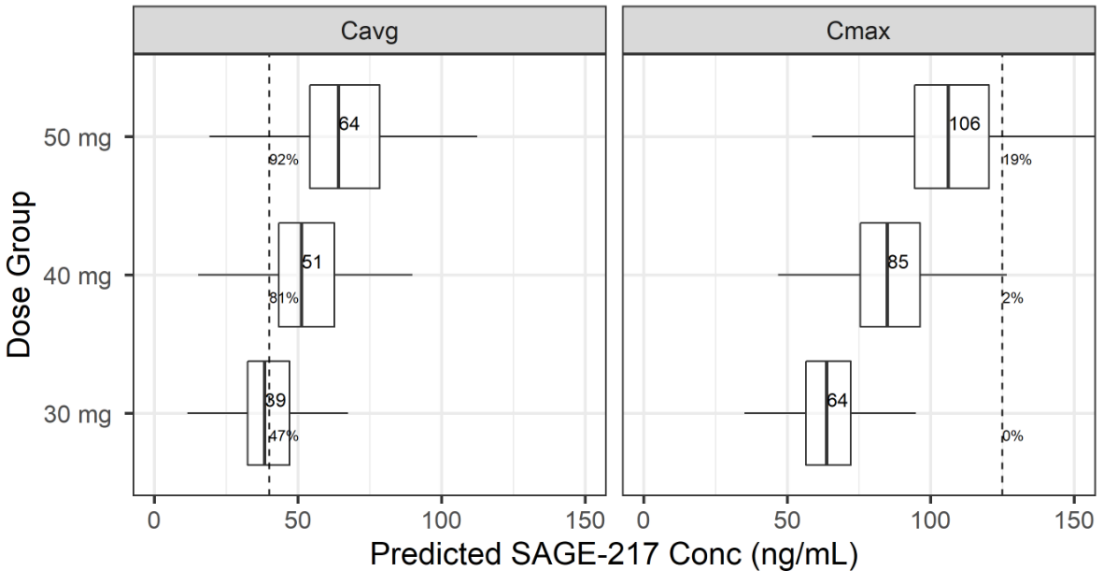
Direct safety data come from more than 140 participants exposed to concentrations of SAGE-217 that are higher than those achieved with a 30-mg capsule daily dose, primarily in the clinical pharmacology program. No serious adverse events (SAEs) were reported in association with any of these higher exposures. Consistent with the pharmacological action of SAGE-217 at the $GABA_A$ receptor, reports of somnolence, dizziness and sedation were increased at increased plasma concentrations. Results from a clinically complete study that evaluated the effects of SAGE-217 on driving performance (217-CLP-113), in which participants (n = 59) were exposed to 4 days of 30 mg capsules, followed by a single dose of 60-mg capsules administered the evening prior to a driving simulation test, are illustrative. During treatment with 30-mg capsules daily (Days 1 to 4), the rates of somnolence and dizziness were 8.5% and 13.6%, respectively. After a single dose of 60 mg on Day 5, the rates of somnolence and dizziness increased to 13.8% and 22.4%, respectively. For these ADRs, the events were mild or moderate in intensity, and no discontinuations due to the adverse events occurred. No events of sedation were reported but could be reflected as events of fatigue, which were reported at a rate of 3.4% with 30 mg (Day 1 to 4) and 13.8% after a dose of 60 mg on Day 5. In addition, in this study, while there was an increase in incidence of somnolence, dizziness and fatigue at 60 mg, there was not an increase in the severity of events. Additional data from Study 217-CLP-113 are provided in the Investigator's Brochure.

Direct evidence related to efficacy and safety outcomes following administration of SAGE-217 capsules at doses above 30 mg is further provided by results from a Phase 1, placebo-controlled study in healthy participants using a 5-hour phase advance model of insomnia (Study 217-EXM-101). Administration of single doses of SAGE-217 up to 45 mg improved sleep efficiency, duration, maintenance, and sleep quality compared with placebo. Evening administration of SAGE-217 was generally well tolerated, with an acceptable safety and

tolerability profile. All reported TEAEs were mild and all resolved. Additional data from Study 217-EXM-101 are provided in the Investigator's Brochure.

Using exposure-response models developed for both efficacy and safety outcomes, the benefit-risk profile of SAGE-217 at doses of 40- or 50-mg capsules is expected to be acceptable. In Figure 1, the predicted concentrations of SAGE-217 following doses of 30-, 40- or 50-mg capsules once daily are shown relative to 2 important concentration markers: $C_{avg}$ as a marker for efficacy, identified based on pharmacodynamic biomarker modeling and clinical effectiveness (40 ng/mL) and $C_{max}$ as a marker for safety, associated with the maximally tolerated dose of the oral solution (125 ng/mL).

**Figure 1: Predicted SAGE-217 concentrations ($C_{avg}$ and $C_{max}$) following dosing of 30 to 50 mg daily**

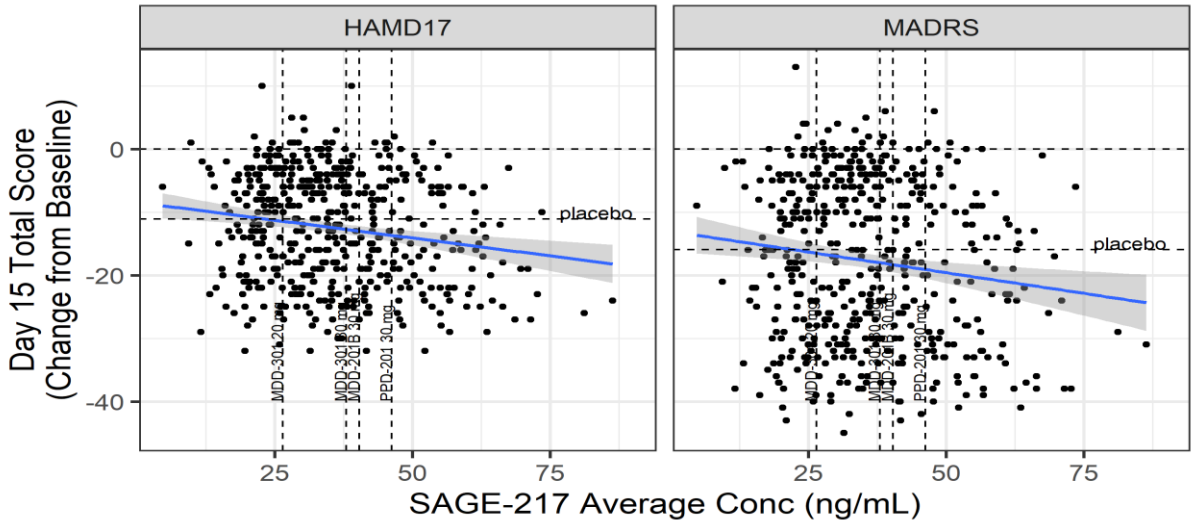



Dashed vertical lines represent target concentrations for efficacy ($C_{avg}$ > 40 ng/mL) and safety ($C_{max}$ < 125 ng/mL). Percentage next to dashed lines indicate the percentages with $C_{avg}$ > 40 ng/mL or with $C_{max}$ > 124 ng.

The selection of 50 mg dosed daily was based first on efficacy, enabling the largest number of participants to achieve a steady-state $C_{avg}$ over 40 ng/mL. Figure 1 shows a dose of 50 mg will allow >90% participants to maintain the target $C_{avg}$ yet remain within the range of acceptable tolerability. With respect to $C_{max}$, less than 1 in 5 (19%) participants at the 50-mg dose level are expected to exceed a $C_{max}$ over 125 ng/mL, a level observed in Phase 1 studies which utilized oral solution and which was associated with a greater rate of sedation events.

Increased granularity of the exposure-efficacy relationship is provided in Figure 2. Across Studies 217-MDD-201B, 217-MDD-301, and 217-PPD-201, increased concentrations of SAGE-217 were associated with a larger reduction in depressive symptoms (Figure 2). Based on linear regression modeling, effect sizes for HAM-D were dose dependent, with a 50-mg dose administered once daily for 14 days predicted to provide greater therapeutic benefit compared to daily doses of 40 and 30 mg. Based on the 217-MDD-301 results, a dose of 30 mg may be considered the minimally effective dose.

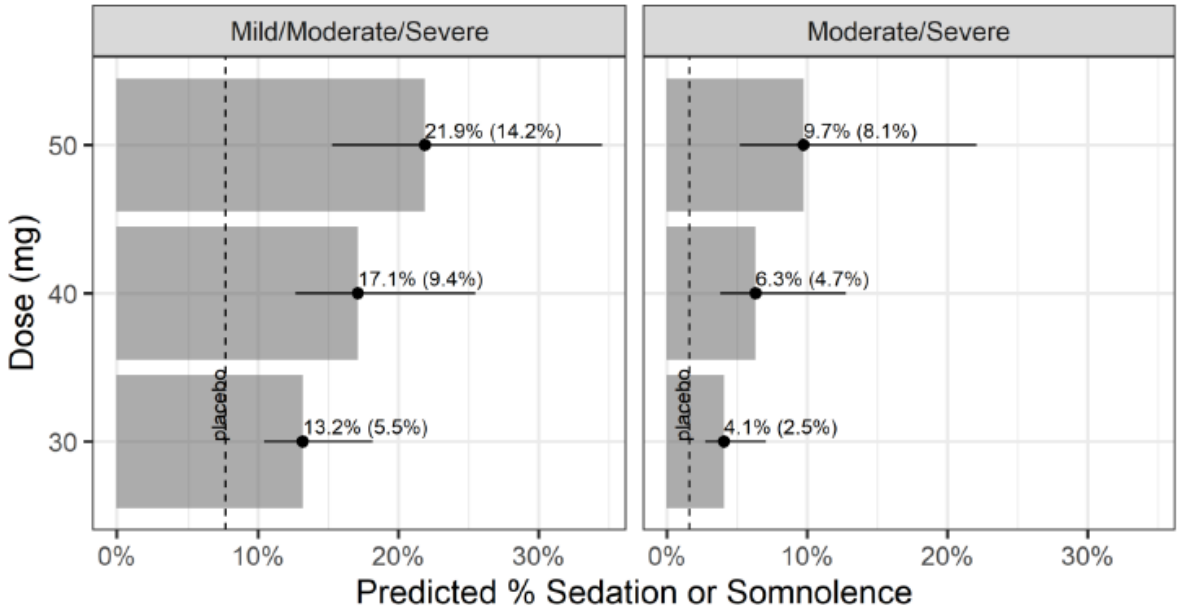
**Figure 2: Total score change on Day 15 (Studies 217-MDD-201B, 217-MDD-301, 217-PPD-201)**




Solid blue line = linear regression line; shaded area = 95% CI around the regression; horizontal dashed line = mean placebo response; Vertical dashed lines from left to right are average concentrations for 20-mg capsules 217-MDD-301, 30-mg capsules MDD-301, 30-mg capsules 217-MDD-201B; 30-mg capsules 217-PPD-201

Exposure-response modeling for safety quantified the relationship between maximum plasma concentration ($C_{max}$) and safety from studies 217-MDD-301, 217-MDD-201, and 217-PPD-201. The safety endpoint for modeling was selected as the incidence of sedation or somnolence during SAGE-217 treatment, as they represent on-target effects at the $GABA_A$ receptor and are the most commonly occurring adverse events with SAGE-217 when considering all doses and formulations. Logistic regression modeling indicated higher $C_{max}$ values were associated with an increased incidence of sedation or somnolence across mild, moderate and severe intensities. Based on this observed relationship, the predicted incidence rates of sedation or somnolence were simulated at SAGE-217 doses of 30, 40 or 50 mg administered once daily (Figure 3).

**Figure 3: Predicted incidence of sedation or somnolence by dose**




Circle and solid line = point estimate and 95% prediction interval. Percentage on the right of the bar = absolute percentage of patients with sedation or somnolence during treatment with SAGE-217; percentage in parentheses = difference in percentage from placebo.

While Figure 3 indicates an increasing incidence of sedation or somnolence with a higher dose the rates of such events across all levels of severity are expected to be approximately 20% to 25%, consistent with safety outcomes associated with some currently available antidepressants. As with usual clinical practice, participants will have the option to dose reduce to 40 mg at any time should a lack of tolerability develop. As a reflection of the model accuracy, the cohort in Study 217-CLP-113 exposed to 30 mg daily for 4 days, followed by a single dose of 60 mg achieved a mean plasma concentration of 97 ng/mL at 8.5 hours after dosing, suggesting the $C_{max}$ experienced by these participants approached or exceeded 125 ng/mL and was higher than the predicted $C_{max}$ of 106 ng/mL for a 50-mg dose (data on file).

Safety margins have been calculated using the NOAELs from the 6-month rat and 9-month dog general toxicology studies (most conservative approach) and predicted steady-state exposures in humans following daily administration of 30-, 40-, or 50-mg SAGE-217 capsules. At present, mean steady-state exposures in humans following daily administration of 30 mg SAGE-217 capsules following a high-fat meal (most conservative; $C_{max}$ = 64 ng/mL; area under the curve [AUC] = 936 ng·h/mL) maintain safety margins of approximately 5x to 8x in rat ($C_{max}$ or AUC) and 6x in dog ($C_{max}$ or AUC) relative to the NOAEL in the respective species. While these margins are expectedly reduced with higher SAGE-217 concentrations, they remain approximately 3x to 5x in rat and 4x in dog ($C_{max}$ or AUC) to predicted plasma exposures for a 50-mg capsule administered once daily.

Sedation, an extension of the pharmacologic mechanism of SAGE-217, was the primary dose-limiting effect in toxicity studies in rats and dogs. In dogs, the toxicologic ‘effect dose’ levels of 2.5 mg/kg/day (9-month study, episodic dosing study) or 2 mg/kg/day (3-month study) associated with a low incidence of convulsion and/or early mortality during or following the

dosing phase, were associated with exposures 7- to 11-fold above clinically relevant $C_{max}$ following administration of 30-mg capsules. Similar margin calculations for adverse effect levels in dogs to potential higher SAGE-217 dose levels (40 or 50 mg/day) remain at or above 4.5x for both $C_{max}$ and AUC. All nonclinical findings are provided in the Investigator's Brochure. The totality of the nonclinical safety data supports the use of SAGE-217 for the treatment of patients at the higher clinical dose regimen, particularly in the context of the current safety database of over 2000 participants exposed to SAGE-217 treatment.

In summary, preliminary results through Day 42 of the double-blind period in Part A of Study 217-MDD-301 in adults with MDD support the need for higher steady-state concentrations of SAGE-217 to allow participants to experience maximum anti-depressant, antianxiety, and anti-insomnia benefits. Doses of SAGE-217 40 and 50 mg will be utilized in this trial, as well as all other ongoing trials with SAGE-217, under the 14-day regimen of an initial evening dose of 50 mg with reduction to 40 mg as needed based on tolerability. These higher doses of SAGE-217 are expected to exhibit a favorable benefit-risk profile in the context of 30 mg now being identified as a minimally effective dose. While higher rates of ADRs may be anticipated, SAGE-217 is expected to maintain an acceptable tolerability profile, based on a current safety database of greater than 2000 participants exposed to SAGE-217 treatment across different doses/concentrations. In addition, higher doses offer the potential for improved therapeutic benefit over the short 14-day treatment course.

# 6. STUDY OBJECTIVES AND ENDPOINTS

## 6.1. Study Objective

### 6.1.1. Primary Objective

The primary objective is to determine if treatment with SAGE-217 reduces depressive symptoms in adults with severe postpartum depression (PPD) compared to placebo.

### 6.1.2. Secondary Objectives

Secondary objectives are:

- To determine if treatment with SAGE-217 reduces anxiety symptoms compared to placebo
- To assess self-report of depressive symptoms
- To evaluate the safety and tolerability of SAGE-217

### 6.1.3. Other Objectives

Other objectives are:

- To assess the plasma pharmacokinetics (PK) of SAGE-217

## 6.2. Endpoints

### 6.2.1. Primary Endpoint

- Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 15

### 6.2.2. Key Secondary Endpoints

- Change from baseline in HAM-D total score at Day 3, Day 28, and Day 45
- Change from baseline in Clinical Global Impressions – Severity (CGI-S) score at Day 15

### 6.2.3. Other Secondary Endpoints

- HAM-D response at Day 15 and Day 45
- HAM-D remission at Day 15 and Day 45
- Clinical Global Impressions – Improvement (CGI-I) response at Day 15
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at Day 15
- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15
- Change from baseline in HAM-D subscale at Day 15

- Change from baseline in self-reported measures of depressive symptoms, as assessed by the Edinburgh Postnatal Depression Scale (EPDS) total score and 9-item Patient Health Questionnaire (PHQ-9)
- Incidence of treatment-emergent adverse events (TEAEs)

### 6.2.4. Other Endpoints

- Change from baseline in vital signs, electrocardiogram (ECG), clinical laboratory parameters, Columbia Severity Rating Scale (C-SSRS) responses, and 20-item Physician Withdrawal Checklist (PWC-20)
- PK parameters (eg, clearance) and exposure estimates (eg, AUC over a dosing interval, maximum plasma concentration) as assessed via population PK methods

# 7. INVESTIGATIONAL PLAN

## 7.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel group study of the efficacy and safety of SAGE-217 in adults diagnosed with severe PPD. Participants, site staff, and sponsor personnel will be masked to treatment allocation.

This study will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period and a Follow-up Period through Day 45.

The Screening Period begins with the signing of the informed consent form (ICF); the ICF must be signed prior to beginning any screening activities. 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-5-CT). Participants will undergo preliminary screening procedures to determine eligibility. A full personal medical history will be taken including documentation of all major depression episodes, other Axis I disorders, and any prior PPD episodes. In addition, PPD episodes experienced by immediate female family members, including siblings, parents, and grandparents will be documented.

During the study, a qualified lactation consultant will be made available upon request to participants who are breastfeeding.

Psychotropic medications are permitted provided participants are on a stable dose for at least 30 days prior to Day 1 and agree to continue on a stable dose through completion of the Day 45 assessments. Initiation of new psychotropic medications that may potentially have an impact on efficacy and/or safety endpoints will not be allowed within 30 days prior to Day 1 through completion of the Day 45 assessments. On Day 1, eligible participants will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥30 days or >5 half-lives) and randomized within each stratum to one of 2 treatment groups (SAGE-217 50 mg or matching placebo) in a 1:1 ratio. Participants will self-administer investigational product (IP) once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. See Section 10.5 for examples of fat-containing snacks. As local regulations permit, IP administration will be monitored via a medication adherence monitoring platform used on smartphones to visually confirm IP ingestion. Participants will return to the study center during the treatment and follow-up periods as outlined in Table 2.

During the treatment period, participants will be able to receive IP as long as there are no dose limiting safety/tolerability concerns. Participants who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the investigator, participants who cannot tolerate the 40-mg dose will be discontinued from IP.

Participants who discontinue IP early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after IP is discontinued. Follow-up visits should take place as scheduled relative to the last dose of treatment (eg, if a participant's last dose is on Day 13, their first follow-up visit should occur 4 days later). If necessary, the EOT and early termination (ET) visits can be on the same day if a participant discontinues IP and terminates the

study on the same day during a clinic visit; in this case, all EOT visit assessments should be conducted.

## 7.2. Number of Participants

Approximately 192 participants, with a total of approximately 96 per treatment group (SAGE-217 or placebo) will be randomized and dosed to obtain approximately 86 evaluable participants per treatment group. Additional participants may be randomized if the dropout rate is higher than anticipated (see Section 13.8).

## 7.3. Treatment Assignment

Participants will be randomly assigned to a treatment group on Day 1 and will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥30 days or >5 half-lives) at baseline. Randomization will be performed within each stratum in a 1:1 ratio to receive SAGE-217 50 mg or matching placebo. Additional details on randomization and blinding are provided in Section 9.5.

## 7.4. Dose Adjustment Criteria

During the treatment period, participants will be able to receive IP as long as there are no dose limiting safety/tolerability concerns. Participants who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period.

If dose adjustment is deemed necessary by the investigator at any time during the treatment period, the participant will return to the site to return any remaining IP and for the adjusted dose to be dispensed.

At the discretion of the investigator, participants who cannot tolerate the 40-mg dose will be discontinued from IP (refer to Section 8.4.1 for procedures for early IP discontinuation). Participants are encouraged to continue to come in for assessments following IP discontinuation.

## 7.5. Criteria for Study Termination

Sage Therapeutics will terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to participants, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the investigator. Investigational sites must promptly notify their institutional review board (IRB)/independent ethics committee (IEC), where required, and initiate withdrawal procedures for participating participants.

# 8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

## 8.1. Participant Inclusion Criteria

Participants must meet all of the following criteria to qualify for participation in this study:

1. Participant has signed an ICF prior to any study-specific procedures being performed.
2. Participant is an ambulatory female between 18 and 45 years of age, inclusive.
3. Participant 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. Participant agrees to adhere to the study requirements, including not participating in night shift work.
5. Participant has ceased lactating or agrees not to provide breastmilk to her infant(s) from just prior to receiving IP on Day 1 until 7 days after the last dose of IP.
6. Participant must have a negative pregnancy test at screening and Day 1 prior to the start of IP administration.
7. Participant 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 SCID-5-CT.
8. Participant has a HAM-D total score of ≥26 at screening and Day 1 (prior to randomization).
9. Participant is ≤6 months postpartum.
10. Participants taking antidepressants must have been taking these medications at the same dose for at least 30 days prior to Day 1. Participants who have stopped taking antidepressants within 30 days must have stopped for longer than 5 half-lives of the antidepressant prior to Day 1, and will be stratified into the “no antidepressant group”. Participants receiving psychotherapy must have been receiving therapy on a regular schedule for at least 30 days prior to Day 1.
11. Participant is willing to delay the start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, until after completion of the Day 45 visit.
12. Participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of IP, unless she is surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence).
13. Participant agrees to refrain from drugs of abuse and alcohol for the duration of the study.

## 8.2. Participant Exclusion Criteria

Participants who meet any of the following criteria are disqualified from participation in this study:

1. Participant is currently at significant risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of PPD.
2. Participant has a recent history of 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 participant's ability to participate in or complete the clinical study. A body mass index (BMI) ≤18 or ≥45 kg/m$^2$ at screening is exclusionary; a BMI of 40 to 44.9 kg/m$^2$, inclusive, at screening is subject to a broader evaluation of medical comorbidities (eg, chronic obstructive pulmonary disease [COPD]), concomitant medications, and prior tolerability of sedating agents.
3. Participant has a clinically significant abnormal 12-lead ECG at the screening or Day 1 visit. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >470 msec will be the basis for exclusion from the study.
4. Participant has a known allergy to SAGE-217, allopregnanolone, or related compounds.
5. Participant has active psychosis per investigator assessment.
6. Participant's index pregnancy resulted in a miscarriage, still birth, or neonatal death; or participant has terminated parental rights (eg, child has been placed for adoption).
7. Participant has a medical history of nonfebrile seizures.
8. Participant has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
9. Participant has a history of mild, moderate, or severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to screening.
10. Participant has had exposure to another investigational medication or device within 30 days prior to screening.
11. Participant has previously participated in this study or any other study employing SAGE-217 or SAGE-547 (brexanolone), ganaxolone, any other compound containing allopregnanolone, or has previously been treated with ZULRESSO™ (brexanolone).
12. Participant has a history of sleep apnea.
13. Participant has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current PPD episode.
14. Participant has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
15. Participant is taking benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Day 1, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Participant is taking any benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 30 days prior to Day 1.

16. Participant is taking non-GABA anti-insomnia medications (eg, melatonin, Benadryl [antihistamines], trazodone), or first or second generation (typical/atypical) antipsychotics within 14 days prior to Day 1.
17. Participant has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to screening.
18. Participant is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as needed, within 28 days prior to Day 1.
19. 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 IP.
20. Participant has a positive urine drug test and/or alcohol screen at screening or on Day 1 prior to dosing.
21. Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St. John's Wort within 14 days or 5 half-lives (whichever is longer) prior to the first dose of IP.
22. Participant plans to undergo elective surgery during participation in the study.
23. Participant is a dependent of the sponsor, investigator, investigator's deputy, or study site staff.
24. Participant is involuntarily confined or detained in a penal institution or other institution under court order.

## 8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number.

## 8.4. Investigational Product Discontinuation and Early Termination from the Study

A participant may withdraw from the study at any time at his/her own request for any reason. The investigator may discontinue a participant from the study and/or from IP for safety, behavioral, compliance, or administrative reasons. The investigator must discontinue a participant from the study and/or from IP for any of the following reasons:

- The participant is unwilling or unable to adhere to the protocol
- The participant loses the capacity to grant consent
- Other medical or safety reason, including suicidality, based on clinical judgment
- The participant becomes pregnant during the treatment period

The reason for IP discontinuation and/or the reason for early termination from the study must be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF).

The investigator must notify the sponsor and/or the medical monitor when a participant discontinues IP and/or stops participation in the study for any reason.

### 8.4.1. Investigational Product Discontinuation

Participants who discontinue IP early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after IP is discontinued. Follow-up visits should take place as scheduled relative to the last dose of IP (eg, if a participant's last dose is on Day 13, their first follow-up visit should occur 4 days later). If at any time after the EOT visit, a participant decides to terminate the study, the participant should return for an ET visit. If necessary, the EOT and ET visits can be on the same day if a participant discontinues IP and terminates the study on the same day during a clinic visit; in this case, all EOT visit assessments should be conducted.

### 8.4.2. Early Termination from the Study

At the time of study withdrawal/stopping study participation, if possible, an EOT and/or ET visit should be conducted. The participant will be permanently discontinued both from the IP (if applicable) and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor will retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Participants who discontinue the study due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant.

#### 8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after 3 attempts at contacting the participant have been made and it has been at least 1 month since the last participant contact. All attempts at contact and the reason for discontinuation will be documented. If the investigator becomes aware of a change in the participant's status or receives more information about a participant's disposition, this information will be documented.

#### 8.4.4. Replacement of Participants

Participants will not be replaced. Additional participants may be randomized if the dropout rate is higher than anticipated (Section 13.8).

# 9. TREATMENT OF PARTICIPANTS

## 9.1. Description of Investigational Product

Participants will self-administer SAGE-217 (50 mg or 40 mg [for dose adjustments only as permitted as described in Section 7.4]) or matching placebo orally once daily at approximately 8 PM with food for 14 days. The 50-mg and 40-mg doses will be administered as 2 capsules per dose (50 mg, administered as one 30-mg capsule and one 20-mg capsule, and 40 mg, administered as two 20-mg capsules). Placebo will also be administered as 2 capsules to maintain the blind.

## 9.2. Prior Medications, Concomitant Medications, Restrictions, and Contraception Requirements

### 9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route, dose/units, frequency, and indication for all medications and/or supplements taken within 30 days prior to signing the ICF through the first dose of IP will be recorded. In addition, psychotropic medications taken 6 months prior to Screening will be recorded.

All medications and/or supplements taken from the first dose of IP through the final study visit (including start and end dates route, dose/units, frequency, and indication) will be recorded on the eCRF. Any concomitant medication determined necessary for the welfare of the participant may be given at the discretion of the investigator at any time during the study.

Antidepressants that have been taken at the same dose for at least 30 days prior to Day 1 are permitted if the participant intends to continue the stable dose for the duration of the study.

The following medications intended for contraception are permitted for female participants:

- 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

### 9.2.2. Prohibited Medications

Restrictions on specific classes of medications include the following and any use of these medications during the specified time periods must be documented as protocol deviations:

- Initiation of new psychotropic medications, including antidepressant or antianxiety medications, and any new pharmacotherapy regimens that may potentially have an impact on efficacy and/or safety endpoints within 30 days prior to Day 1 through completion of the Day 45 visit

- Use of any benzodiazepines, barbiturates, $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Day 1 through completion of the Day 45 visit (within 30 days prior to Day 1 through completion of the Day 45 visit for benzodiazepine or GABA modulators with a half-life of ≥48 hours [eg, diazepam)
- First generation (typical) antipsychotics (eg, haloperidol, perphenazine) and second generation (atypical) antipsychotics (eg, aripiprazole, quetiapine) within 14 days prior to Day 1 through completion of the Day 45 visit
- Use of any non-GABA anti-insomnia medications (eg, melatonin, Benadryl [antihistamines], trazodone) within 14 days prior to Day 1 through completion of the Day 45 visit
- Exposure to another investigational medication or device from 30 days prior to screening through completion of the Day 45 visit
- Any known strong inhibitors of cytochrome P450 (CYP)3A4 within 14 days or 5 half-lives (whichever is longer) within 14 days prior to receiving the first dose of IP through the 14-day treatment period
- Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort within 14 days or 5 half-lives (whichever is longer) prior to receiving the first dose of IP through the 14-day treatment period

### 9.2.3. Other Restrictions

The consumption of grapefruit juice, grapefruit, or Seville oranges, or products containing these is prohibited within 14 days prior to receiving the first dose of IP and throughout the 14-day treatment period.

Consumption of alcohol, use of drugs of abuse, or use of products containing cannabidiol (CBD) is discouraged throughout the duration of the study.

Female participants who are lactating or actively breastfeeding must stop giving breast milk to the baby(ies) starting on Day 1 until 7 days after the last dose of IP. During the study, a qualified lactation consultant will be made available to participants upon request.

Elective surgeries or procedures are prohibited through completion of the Day 45 visit.

Vagus nerve stimulation and electroconvulsive therapy are prohibited through completion of the Day 45 visit.

Participants must not participate in night shift work.

Participants who are feeling sedated, somnolent, and/or dizzy are to refrain from driving or engaging in any activity requiring alertness.

Participants receiving psychotherapy on a regular schedule for at least 30 days prior to Day 1 are permitted if the participant intends to continue the regular schedule through the follow-up period (Day 45).

#### 9.2.4. Acceptable Forms of Contraception

Acceptable forms of highly effective contraception for participants who are not surgically sterile include:

- 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 ligation or bilateral tubal occlusion (performed at least 3 months prior to screening)
- Vasectomized partner (performed at least 3 months prior to screening)

## 9.3. Intervention after the End of the Study

No intervention following the end of the study is planned.

## 9.4. Treatment Adherence

SAGE-217 or placebo will be self-administered by participants once daily in the evening with food. Sites will dispense a weekly supply of IP to the participants to take at home with instructions for use (see Section 10.5 and Table 2).

As local regulations permit, administration of IP will be monitored by a medication adherence monitoring platform used on smartphones to visually confirm medication ingestion. Participants will receive a reminder within a predefined time window to take IP while using the application. Participants will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application will record the date and time of IP administration by dose level, as well as missed doses.

In addition, the participant will be instructed to bring their dosing kit to the site as outlined in Table 2, at which time the investigator or designee will be responsible for ensuring the kit contains sufficient doses for the duration of the treatment period.

All participants should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the participant source records.

The investigator(s) will record any reasons for noncompliance in the source documents.

## 9.5. Randomization and Blinding

This is a randomized double-blind, placebo-controlled study. Participants who meet the entrance criteria will be randomized in a stratified manner based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥30 days) at baseline.

Randomization will be done within each stratum in a 1:1 ratio to receive SAGE-217 50 mg or matched placebo.

Participants, clinicians, and the study team will be blinded to treatment allocation. Randomization will be performed centrally via an interactive response technology (IRT) system. Randomization schedules will be generated by an independent statistician. The allocation to treatment group will be based on the randomization schedule. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

### 9.5.1. Emergency Unblinding

During the study, the blind is to be broken only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate risk, the investigator should make attempts to contact Sage prior to unblinding the study treatment administered to a participant. Requests from the investigator about the treatment administered to study participants should be discussed with the Sage medical monitor. If the unblinding occurs without Sage's knowledge, the investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the IP allocation for a participant is unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's records and on the eCRF. At the time of withdrawal from the study/stopping participation, if possible, an EOT and/or ET visit should be conducted.

# 10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

## 10.1. Investigational Product

SAGE-217 is available as hard gelatin capsules containing a white to off-white powder. In addition to the specified amount of SAGE-217 Drug Substance, active SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, colloidal silicon dioxide, and sodium stearyl fumarate as excipients. Capsules will be available in 20-mg and 30-mg dose strengths.

Matching placebo capsules are hard gelatin capsules containing only the excipients listed for the active capsule.

## 10.2. Investigational Product Packaging and Labeling

SAGE-217 capsules and matched placebo capsules will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the IP in appropriately labeled, participant-specific kits containing sealed unit doses. Each unit dose consists of 2 capsules (see Section 9.1). Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Investigational product labels with all required information and conforming to all applicable FDA Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices guidelines will be prepared by the sponsor.

## 10.3. Investigational Product Storage

SAGE-217 and matching placebo capsules are to be stored at room temperature (59°F to 86°F; 15°C to 30°C), safely and separately from other drugs.

## 10.4. Investigational Product Preparation

Not applicable.

## 10.5. Investigational Product Administration

SAGE-217 is to be administered orally once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack). Examples of fat-containing snacks include nuts, peanut butter, avocado, eggs, and cheese.

If a participant misses a dose, the participant should skip that dose (ie, they should not take the dose in the morning) and take the next scheduled dose in the evening the next day.

## 10.6. Investigational Product Accountability, Handling, and Disposal

Upon receipt of IP, the investigator(s), or the responsible pharmacist or designee, will inspect the IP and complete and follow the instructions regarding receipt and storage in the Investigator's Brochure and (where applicable) in the pharmacy manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the supplied participant-specific kits to participants at the planned dispensation visit intervals outlined in Table 2.

Site staff will access the IRT at the Screening Visit to obtain a participant identification (ID) number for each participant that has signed an ICF. On Day 1, site staff will access the IRT and provide the necessary participant-identifying information, including the participant ID number assigned at screening, to randomize the eligible participant into the study and obtain the medication ID number for the IP to be dispensed to that participant. The medication ID number and the number of capsules dispensed must be recorded.

At the subsequent IP-dispensing visit, the investigator or designee will access the IRT, providing the same participant ID number assigned at Screening, to obtain the medication ID number for the IP to be dispensed at that visit. The medication ID number, the number of capsules dispensed, and the number of capsules returned by the participant at this visit must be recorded.

If dispensing errors or discrepancies are discovered by site staff or sponsor's designee, the sponsor must be notified immediately.

The IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all IP received, used and returned/discarded. It must be clear from the records which participant received which dose of active or placebo treatment.

Sage Therapeutics will be permitted access to the study supplies at any time with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

The investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

At the end of the study, any unused IP will be returned to Sage Therapeutics for destruction or destroyed locally per the site's procedures; disposition of IP will be documented.

## 10.7. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness or performance (applicable for approved marketed products) of a drug product after it is released for distribution.

In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in Table 1. Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

# 11. EFFICACY AND CLINICAL PHARMACOLOGY ASSESSMENTS

## 11.1. Efficacy Assessments

All assessments will be conducted according to the Schedule of Assessments (Table 2). Study assessments that involve participant interviews, including the HAM-D and SCID-5-CT, may be audiotaped for independent quality control purposes. All assessments must be conducted by raters that have been trained and certified to conduct assessments in this study.

### 11.1.1. Hamilton Rating Scale for Depression (HAM-D)

The primary outcome measure is the change from baseline in 17-item HAM-D total score at the end of the Treatment Period (Day 15). Every effort should be made for the same rater to perform all HAM-D assessments for an individual participant. An assessment timeframe of past 7 days (1 week) will be used at Screening and 'Since Last Visit' will be used for all other visits.

The 17-item HAM-D will be used to rate the severity of depression in participants who are already diagnosed as depressed (Williams 2013a; Williams 2013b). The 17-item HAM-D comprises individual ratings related to the following symptoms: depressed mood (sadness, hopeless, helpless, worthless), feelings of guilt, suicide, insomnia (early, middle, late), work and activities, retardation (slowness of thought and speech; impaired ability to concentrate; decreased motor activity), agitation, anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis, loss of weight, and insight.

The HAM-D total score will be calculated as the sum of the 17 individual item scores.

In addition to the primary efficacy endpoint of change from baseline in HAM-D total score, several secondary efficacy endpoints will be derived for the HAM-D. Hamilton Rating Scale for Depression subscale scores will be calculated as the sum of the items comprising each subscale. Hamilton Rating Scale for Depression response will be defined as having a 50% or greater reduction from baseline in HAM-D total score. Hamilton Rating Scale for Depression remission will be defined as having a HAM-D total score $\leq$7.

### 11.1.2. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in participants with mood disorders. It was designed as an adjunct to the HAM-D that would be more sensitive to the changes brought on by antidepressants and other forms of treatment than the Hamilton Scale.

Higher MADRS scores indicate more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60 (Williams 2008).

The MADRS total score will be calculated as the sum of the 10 individual item scores.

### 11.1.3. Hamilton Anxiety Rating Scale (HAM-A)

The 14-item HAM-A will be used to rate the severity of symptoms of anxiety (Williams 2013c; Williams 2013d). Each of the 14 items is defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Scoring for HAM-A is calculated by assigning scores of 0 (not

present) to 4 (very severe), with a total score range of 0 to 56, where <17 indicates mild severity, 18 to 24, mild to moderate severity, and 25 to 30, moderate to severe severity. The HAM-A total score will be calculated as the sum of the 14 individual item scores.

### 11.1.4. Clinical Global Impressions

The CGI is a validated measure often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the participant's condition. The CGI scale consists of 3 items. Only the first 2 items are being used in this study.

The CGI-S uses a 7-point Likert scale to rate the severity of the participant's illness at the time of assessment, relative to the clinician's past experience with participants who have the same diagnosis. Considering total clinical experience, a participant is assessed on severity of mental illness at the time of rating as 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = extremely ill (Busner 2007a).

The CGI-I employs a 7-point Likert scale to measure the overall improvement in the participant's condition posttreatment. The investigator will rate the participant's total improvement whether or not it is due entirely to drug treatment. Response choices include: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse (Busner 2007b). The CGI-I is only rated at posttreatment assessments. By definition, all CGI-I assessments are evaluated against baseline conditions. CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved."

### 11.1.5. Edinburgh Postnatal Depression Scale

The EPDS is a self-rated depressive symptom severity scale specific to the perinatal period (Cox 1987). The EPDS total score will be calculated as the sum of the 10 individual item scores.

### 11.1.6. Patient Health Questionnaire

The PHQ-9 is a self-rated depressive symptom severity scale. To monitor severity over time for newly diagnosed participants or participants in current treatment for depression, participants may complete questionnaires at baseline and at regular intervals thereafter. Scoring is based on responses to specific questions, as follows: 0 = not at all; 1 = several days; 2 = more than half the days; and 3 = nearly every day.

The PHQ-9 total score will be calculated as the sum of the 9 individual item scores. The PHQ-9 total score will be categorized as follows: 1 to 4 = minimal depression, 5 to 9 = mild depression, 10 to 14 = moderate depression, 15 to 19 = moderately severe depression; and 20 to 27 = severe depression.

## 11.2. Clinical Pharmacology Assessments

Pharmacokinetic parameters (eg, clearance) and exposure estimates (eg, AUC over a dosing interval, maximum plasma concentration) will be assessed via population PK methods.

### 11.2.1. Pharmacokinetic Assessments

Pharmacokinetic blood samples will be collected and processed for analysis for concentrations of SAGE-217.

The plasma samples must be kept frozen at approximately -70 to -80°C until analyzed. They should be packed as directed in the laboratory manual. A specimen-identification form or equivalent must be completed and sent to the laboratory with each set of samples. The clinical site will arrange to have the plasma samples transported as directed for bioanalysis as detailed in the PK instructions.

### 11.2.2. Blood Sample Collection

Plasma samples for PK analysis will be collected according to the sampling schedule outlined in Table 2. The investigator or designee will arrange to have the plasma samples transported as directed for bioanalysis.

An additional PK sample may be collected at any time if clinically indicated and at the discretion of the investigator (eg, for unusual or severe AEs). In the event of a dose adjustment, an unscheduled PK sample should be collected, if possible, just prior to the dose adjustment.

Each sample will be marked with unique identifiers with at least the study number, participant number, and visit day. The date and actual time that the blood sample was taken will be recorded on the case report form.

### 11.2.3. Sample Analysis

Bioanalysis of plasma samples for the determination of SAGE-217 will be performed using a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.

### 11.2.4. Optional Blood Sample Collection for Hormones and Exploratory Biochemistry

Where consent is given, optional blood samples will be collected at the time points indicated in Table 2 and may be analyzed for stress hormone levels, kynurenine biochemistry, and markers of inflammation. Future research may suggest other biochemical pathways as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the exploratory biochemistry may involve study of additional unnamed molecular pathways, but only as related to disease susceptibility and drug action.

#### 11.2.4.1. Optional Genetic Testing

Where consent is given, optional genetic samples (blood) for exploratory biomarker research will be collected at the time points indicated in Table 2. Genetic samples may be stored and analyzed to assess genetic factors involved in the metabolism or response to SAGE-217 and/or to evaluate their association with observed clinical responses. Additional analyses may be conducted if it is hypothesized that the analyses may help further understand the clinical data. The samples and the results of the analyses may also be used to help design future clinical trials, develop compounds, or develop assays and diagnostic or other tests.

The sponsor will store the deidentified samples in a secure storage space with adequate measures to protect participant confidentiality. Only the sponsor and those persons or entities working with the sponsor will have access to the samples and associated data.

# 12. SAFETY ASSESSMENTS

## 12.1. Safety Parameters

All assessments will be conducted according to the Schedule of Assessments (Table 2).

### 12.1.1. Demography and Medical History

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full personal medical history, including: generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder; bipolar disorder, persistent depressive disorder, postpartum depression, substance use disorder, alcohol use disorder, major depressive disorder with seasonal pattern, major depressive disorder with psychotic features, premenstrual dysphoric disorder, major depressive disorder with atypical features, schizophrenia, or schizoaffective disorder will be documented. The delivery date of the index pregnancy and any other prior pregnancies with associated postpartum depressive episodes will also be recorded. In addition, postpartum depression episodes experienced by immediate female family members, including siblings, parents, and grandparents will be documented.

The diagnosis of PPD will be determined using the SCID-5-CT. If available, the disease code associated with the diagnosis of PPD based on the 10$^{th}$ revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

### 12.1.2. Weight and Height

Height (screening only) and weight will be measured and documented. BMI will be calculated and documented.

### 12.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations. Physical examinations will include assessment of body systems (eg, head, eye, ear, nose and throat; heart; lungs; abdomen; and extremities) as well as cognitive and neurological examination and mental status examination. An abbreviated physical examination includes a brief medical history followed by a targeted physical examination. Unscheduled physical examinations may also be conducted per the investigator's discretion.

Any abnormality in physical examinations will be interpreted by an Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

### 12.1.4. Vital Signs

Vital signs comprise heart rate, respiratory rate, temperature, and blood pressure. Heart rate and systolic and diastolic blood pressure are to be collected after the participant has been supine for at least 5 minutes prior to the measurement. Measurements should be repeated approximately 3 minutes after standing. Respiratory rate and temperature are collected once, in either position.

Any abnormality in vital signs will be interpreted by an Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

### 12.1.5. Electrocardiogram (ECG)

A 12-lead ECG will be performed in triplicate at all scheduled time points.

The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded.

Electrocardiograms will be performed after the participant has been resting in a supine position for at least 5 minutes. When ECG measurements coincide with safety assessments, vital signs assessment or blood draws, procedures should be carried out in the following order: vital signs, ECG, blood draw.

All abnormal ECGs will be interpreted by an investigator as abnormal NCS, or abnormal CS in source documents.

### 12.1.6. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected. Analytes to be evaluated are summarized in Table 4.

**Table 4: Summary of Clinical Laboratory Analytes**

| | |
|---|---|
| **Biochemistry** | *Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, creatine kinase, sodium, potassium, chloride, bicarbonate<br>*Hepatic Panel*: albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, direct bilirubin, indirect bilirubin, total protein, lactate dehydrogenase, gamma glutamyl transferase<br>*Other*: triglycerides, creatine phosphokinase, thyroid stimulating hormone (TSH) and reflex to free T3/T4 if TSH is abnormal |
| **Coagulation** | Activated partial thromboplastin time, prothrombin time, and international normalized ratio |
| **Hematology** | red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, red blood cell indices (MCV, MCH, MCHC) and if RBC indices are abnormal, and reflex to red blood cell morphology if indices are abnormal |
| **Urinalysis** | protein, glucose, pH, specific gravity, red blood cell, leukocyte esterase, urobilinogen, bilirubin, ketones, nitrite |

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

#### 12.1.6.1. Drugs of Abuse and Alcohol

Separate urine samples for assessment of selected drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine will be collected and a breath test for alcohol will be administered according to the time points in Table 2.

#### 12.1.6.2. Pregnancy Screen

A serum pregnancy test will be conducted for all participants at screening; a urine pregnancy test will be conducted for all participants at all other scheduled time points.

### 12.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the study using the C-SSRS (Posner 2011). This scale consists of a baseline evaluation that assesses the lifetime experience of the participant with suicidal ideation and behavior, and a postbaseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes 'yes' or 'no' responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

The "Baseline/Screening" C-SSRS form will be completed at screening (lifetime history and past 24 months). The "Since Last Visit" C-SSRS form will be completed at all subsequent time points outlined in Table 2.

### 12.1.8. Physician Withdrawal Checklist

The PWC is based on the 35-item Penn Physician Withdrawal Checklist that was developed in the 1960s to measure benzodiazepine and benzodiazepine-like discontinuation symptoms. The PWC-20 is a shorter version of the Penn Physician Withdrawal Checklist based on the 20 items that provided the best differentiation from placebo in previous studies. The PWC-20 is made up of a list of 20 symptoms (eg, loss of appetite, nausea-vomiting, diarrhea, anxiety-nervousness, irritability, etc) that are rated on a scale of 0 (not present) to 3 (severe) (Rickels 2008). The PWC-20 will be used to monitor for the presence of potential withdrawal symptoms following discontinuation of SAGE-217.

## 12.2. Adverse and Serious Adverse Events

### 12.2.1. Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

A TEAE is defined as an adverse event with onset after the start of IP, or any worsening of a preexisting medical condition/adverse event with onset after the start of IP and throughout the study. The term IP includes any Sage IP, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities and changes from baseline in vital signs, and ECGs are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for a SAE should be reported in

an expedited manner. Laboratory abnormalities and changes from baseline in vital signs and ECGs that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

All AEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be reported to Sage Therapeutics.

Subjects who discontinue the IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant. Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The sponsor or its representative retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

### 12.2.2. Serious Adverse Event Definition

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

An SAE may also be any other medically important event that, in the opinion of the investigator may jeopardize the participant or may require medical intervention to prevent 1 of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

All SAEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE report form provided by Sage Therapeutics. Any SAE that is ongoing when the participant completes their final study visit, will be followed by the investigator until the event has resolved, stabilized, returned to baseline status, or until the participant dies or is lost to follow up.

A prescheduled or elective procedure or routinely scheduled treatment will not be considered an SAE, even if the participant is hospitalized. The site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or on a waiting list to be scheduled) prior to obtaining the participant's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress, in the opinion of an

investigator, between the participant's consent to participate in the study and at the time of the procedure or treatment.

### 12.2.3. Relationship to Investigational Product

The investigator must make the determination of relationship to the IP for each adverse event (not related, related). The following definitions should be considered when evaluating the relationship of AEs and SAEs to the IP.

| | |
|---|---|
| Not Related | An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the IP. Factors pointing towards this assessment include but are not limited to: the lack of temporal relationship between administration of the IP and the event, the presence of biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE |
| Related | An AE will be considered "related" to the use of the IP if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point towards this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of alternative explanation for the AE |

### 12.2.4. Recording Adverse Events

Adverse events spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, outcome, and seriousness (if applicable), and whether or not it caused the participant to discontinue the IP or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild: symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s)
- Moderate: symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed
- Severe: symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with IP; treatment for symptom(s) may be given and/or participant hospitalized

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.2. An AE of severe intensity may not necessarily be considered serious.

### 12.2.5. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the study site must notify Sage or designee within 24 hours of the study site staff becoming aware of the SAE(s). The investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Sage or designee.

Additional follow-up information, if required or available, should all be sent to Sage or designee within 24 hours of receipt on a follow-up SAE report form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

Serious adverse events occurring after the designated follow-up time for the study, should be reported to Sage or designee according to the timelines noted above only if the investigator considers the SAE related to IP.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the principal investigator's responsibility to notify the IRB/IEC of all SAEs that occur at his or her site. Investigators will also be notified of all suspected unexpected serious adverse reactions (SUSARs) that occur during the clinical study. IRBs/IECs will be notified of SAEs and/or SUSARs as required by local law.

In addition, appropriate personnel in Sage Drug Safety and Pharmacovigilance or designee will unblind SUSARs for the purpose of regulatory reporting. Sage or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Sage, or designee, will submit SUSARS to investigators in a blinded fashion.

## 12.3. Pregnancy

If a participant becomes pregnant after the first administration of IP, pregnancy information must be collected and recorded on the Pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. Details will be collected for all pregnancies for which conception was likely to have occurred after the start of IP administration until 5 terminal half-lives following the last administration of IP or until the completion of the study whichever is longer. Any pregnancy occurring in that time frame will be followed until delivery or termination of the pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The outcome of all pregnancies (eg, spontaneous abortion, elective abortion, normal birth) must be followed and documented even if the participant was discontinued from the study. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to Sage or designee. Generally, follow up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. Any complication during pregnancy (eg, anemia, infections, preeclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death), the investigator should follow the procedures for reporting an SAE.

## 12.4. Overdose

An overdose is defined as more than 2 capsules of IP taken by a participant in an 18-hour period or more than 4 capsules taken by a participant in a 36-hour period. Overdoses, regardless of presence of associated clinical manifestation(s) (eg, headache, abnormal laboratory value) will be considered an AE and recorded as such on the eCRF. Any clinical manifestation(s) of overdose must also be recorded as an AE on the eCRF. In addition, all overdoses must be recorded on an Overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose.

# 13. STATISTICS

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock. Any changes/additions to the SAP following database lock will be described in detail in the clinical study report.

## 13.1. Data Analysis Sets

The Safety Set will include all participants administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a valid baseline and at least one valid postbaseline HAM-D total score.

The Per Protocol Set is defined as all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding.

## 13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all nonmissing data available. No imputation process will be used to estimate missing data.

## 13.3. General Considerations

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to receipt of IP.

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.

## 13.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized using the Safety Population.

Pregnancy test results and drug screen results will be listed but not summarized.

Medical history will be listed by participant.

### 13.5. Efficacy Analysis

The estimand for the primary efficacy analysis is the mean change from baseline in HAM-D total score at Day 15. This will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline time points will be included in the model. Model-based point estimates (ie, least squares means, 95% confidence intervals, and

p values) will be reported where applicable. An unstructured covariance structure will be used to model the within-participant errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Similar to those methods described above for the primary endpoint, an MMRM will be used for the analysis of the change from baseline in other time points in HAM-D total score, MADRS total score, HAM-A total score, EPDS total score, PHQ-9 score, and selected individual items and/or subscale scores in HAM-D.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as ≥50% reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of ≤7.0). GEE models will include terms for treatment, baseline score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 and matching placebo at Day 15. Model-based point estimates (ie, odds ratios), 95% confidence intervals, and p values will be reported.

A GEE method will also be used for the analysis of CGI-I response (defined as “much improved” or “very much improved”) including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.

Descriptive summary statistics will be provided for other endpoints.

## 13.6. Safety Analyses

Safety and tolerability of SAGE-217 will be evaluated by incidence of TEAEs, changes from baseline in vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Potential withdrawal symptoms after discontinuation of SAGE-217 will be assessed using the PWC-20. Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set using treatment received. Where applicable, ranges of potentially clinically significant (PCS) values are provided in the SAP.

### 13.6.1. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or higher. A treatment-emergent adverse event (TEAE) is defined as an AE with onset after the first dose of IP. The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized by System Organ Class and preferred term. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to IP (see Section 12.2).

Any TEAEs leading to discontinuation of treatment or withdrawal from the study and any treatment-emergent SAEs will be summarized.

All AEs and SAEs (including those with onset or worsening before the start of IP) through the end of the study will be listed.

### 13.6.2. Clinical Laboratory Evaluations

Results of clinical laboratory parameters in each scheduled visit and mean changes from baseline will be summarized in standard units. Normal ranges for each parameter will be provided by the laboratory; shift from baseline to postbaseline values in abnormality of results will be provided. Potentially clinically significant values will be summarized by treatment. Clinical laboratory results will be listed by participant and timing of collection.

### 13.6.3. Physical Examinations

The occurrence of a physical examination (yes/no) and the date performed will be listed by participant.

### 13.6.4. Vital Signs

Vital sign results at each visit and mean changes from baseline will be summarized by scheduled visit. Potentially clinically significant values will be summarized by treatment. Vital sign results will be listed by participant and timing of collection.

### 13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each of the triplicate ECGs for each participant: heart rate, PR, QRS, QT, and QTcF; the derived mean of each parameter will also be listed. Any clinically significant abnormalities or changes in mean ECGs should be reported as an AE (see Section 12.2). Mean ECG data will be summarized by visit. Potentially clinically significant values of QTcF will be summarized by treatment. Electrocardiogram findings will be listed by participant and visit.

### 13.6.6. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization-Drug dictionary (WHO-DD) September 2015, or later.

All medications taken within 30 days prior to informed consent through the duration of the study will be recorded. In addition, all psychotropic medications taken in the previous 6 months prior to screening will be recorded on the eCRF. Those medications taken prior to the initiation of the start of IP will be denoted “Prior”. Those medications taken prior to the initiation of the IP and continuing beyond the initiation of the IP or those medications started at the same time or after the initiation of the IP will be denoted “Concomitant”.

Medications will be presented according to whether they are “Prior” or “Concomitant” as defined above. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Details of prior and concomitant medications will be listed by participant, start date, and verbatim term.

### 13.6.7. Columbia Suicide Severity Rating Scale

Suicidality data collected on the C-SSRS at baseline and by visit during the treatment period will be listed and summarized by treatment. Listings will include all data, including behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

### 13.6.8. Physician Withdrawal Checklist

Potential withdrawal symptoms collected on the PWC-20 will be summarized by visit and treatment. Listings will include all data by participant.

## 13.7. Clinical Pharmacology Analyses

Details regarding the PK analysis will be provided in a separate PK Analysis Plan and will be reported separately.

## 13.8. Sample Size and Power

Using a 2-sided test at an alpha level of 0.05, a sample size of approximately 86 evaluable participants 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 of 8 points.

Assuming a 10% dropout and a 1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 192 randomized participants (96 per treatment group) will be required to obtain 86 evaluable participants per treatment group. Evaluable participants are defined as those randomized participants who receive IP and have a valid baseline and at least 1 postbaseline HAM-D assessment. Additional participants may be randomized if the dropout rate is higher than 10%.

# 14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

## 14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage standard operating procedures to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sage Therapeutics or its representatives. This will be documented in a Clinical Trial Agreement between Sage Therapeutics and the investigator.

During the study, a monitor from Sage Therapeutics or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or IEC.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

## 14.2. Audits and Inspections

Sage Therapeutics or authorized representatives of Sage Therapeutics, a regulatory authority, or an IEC or an IRB may visit the site to perform an audit(s) or inspection(s), including source data verification. The purpose of a Sage Therapeutics audit or a regulatory authority inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP/ICH GCP guidelines, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency or IRB/IEC about an inspection.

## 14.3. Institutional Review Board or Independent Ethics Committee

The principal investigator must obtain IRB (or IEC) approval for the clinical study prior to enrolling a participant. Initial IRB (or IEC) approval, and all materials approved by the IRB (or IEC) for this study including the participant consent form and recruitment materials must be maintained by the investigator and made available for inspection.

# 15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practice and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit(s) at the clinical site. Please see Section 14.2 for more details regarding the audit process.

The investigator must have adequate quality control practices to ensure that the study is performed in a manner consistent with the protocol, GCP/ICH GCP guidelines, and applicable regulatory requirements. The investigator is responsible for reviewing all identified protocol deviations. Significant protocol deviations should be reported to the IRB/IEC per the IRB/IEC's written procedures.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. When the investigator retains the services of any individual or party to perform trial-related duties and functions, the investigator must ensure the individual or party is qualified to perform trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed, and any data generated.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained, if necessary to provide clarification.

# 16. ETHICS

## 16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be given a written and dated approval or favorable opinion by an IRB or IEC as appropriate. The investigator must obtain and document approval before he or she can enroll any participant into the study. The IRB or IEC must supply to the sponsor a list of the IRB/IEC membership and a statement to confirm that the IRB/IEC is organized and operates according to GCP and applicable laws and regulations.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The principal investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sage Therapeutics will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines. In addition, the principal investigator must inform the IRB/IEC and sponsor of any changes significantly affecting the conduct of the trial and/or increasing the risk to participants (eg, violations to the protocol or urgent safety measures taken for participant safety).

## 16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH and GCP guidelines, as well as all applicable regional or national regulatory requirements.

## 16.3. Written Informed Consent

Prior to enrolling a trial participant, the investigator(s) will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

When the participant decides to participate in the trial, the participant (or the participant's, parent or legally authorized representative) must provide signed and dated informed consent. The written consent must be obtained before conducting any study procedures. The investigator must document the consent process in the participant's source records. The investigator must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the participant or to the participant's parent or legally authorized representative.

Throughout the trial participants should be informed of any changes made to the study and as new safety and or risk information becomes known. The provision of this information will be

documented in the participant's source records, and when applicable, an updated ICF will be provided.

# 17. DATA HANDLING AND RECORDKEEPING

## 17.1. Inspection of Records

Sage Therapeutics or its representative(s) will be allowed to conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the facility, drug storage area, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

Inspection of the study by a Regulatory Authority may occur at any time. The investigator must agree to the inspection of study-related records and source documents by the Regulatory Authority representative(s).

## 17.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for the period outlined in the site contract, or for a period of 2 years after the last marketing application approval, and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Sage is responsible to inform the investigator/institution as to when study documents no longer need to be retained.

# 18. PUBLICATION POLICY

All information concerning SAGE-217 is considered confidential and shall remain the sole property of Sage Therapeutics. The investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the investigator.

# 19. LIST OF REFERENCES

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