

**Official Title:** A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy of SAGE-217 in the Treatment of Adult Subjects With Major Depressive Disorder

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Protocol Version 3.0: 11 October 2018  
Protocol Version 2.0: 25 September 2018  
Protocol Version 1.0: 16 July 2018

## 1. PROTOCOL AND AMENDMENTS

The original protocol (Version 1) was amended 4 times during the conduct of Part A. Links to each version of the protocol are provided below.

### Protocol Versions

[Version 1, 16 July 2018](#)

[Amendment 1, Version 2, 25 September 2018](#)

- [Summary of Changes from Amendment 1](#)

[Amendment 2, Version 3, 11 October 2018](#)

- [Summary of Changes from Amendment 2](#)

[Amendment 3, Version 4, 07 March 2019](#)

- [Summary of Changes from Amendment 3](#)

[Amendment 4, Version 5, 25 March 2019](#)

- [Summary of Changes from Amendment 4](#)

### Administrative Letters

[Administrative Letter #1, 08 November 2018](#)

[Administrative Letter #2, 15 August 2019](#)

[Administrative Letter #3, 29 August 2019](#)



**STUDY TITLE: A PHASE 3, MULTICENTER, DOUBLE-  
BLIND, RANDOMIZED, PLACEBO-CONTROLLED  
STUDY EVALUATING THE EFFICACY OF SAGE-217  
IN THE TREATMENT OF ADULT SUBJECTS WITH  
MAJOR DEPRESSIVE DISORDER**

**PROTOCOL NUMBER: 217-MDD-301**

|                           |  |
|---------------------------|--|
| Study Drug                | SAGE-217   |
| Clinical Phase            | Phase 3  |
| Sponsor                   | Sage Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 |
| Sponsor Contact           | [REDACTED]<br>Tel: [REDACTED]<br>email: [REDACTED]                 |
| Sponsor Medical Monitor   | [REDACTED] MD, MBA<br>Tel: [REDACTED]<br>email: [REDACTED]         |
| Date of Original Protocol | Version 1.0, 16 JUL 2018   |

**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.

**Protocol Number:** 217-MDD-301  
**Study Drug:** SAGE-217  
**Study Phase:** Phase 3  
**Sponsor:** Sage Therapeutics, Inc.  
**Protocol Date:** Version 1.0, 16 July 2018

**Sponsor Approval**

|                         |                    |
|-------------------------|--------------------|
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| Sage Therapeutics       |                    |

## INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-MDD-301 clinical 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.

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Printed name of Investigator

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Signature of Investigator

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Date (DD Month YYYY)



- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at Day 15 and all other time points
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at Day 15 and all other time points
- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15 and all other time points
- Change from baseline in HAM-D subscale and individual item scores at all time points
- Improvements in sleep at Day 15 and all other time points, as assessed by
  - Insomnia Severity Index (ISI)
  - Subjective sleep parameters collected with the Core Consensus Sleep Diary
- PRO measures of health-related quality of life, as assessed by responses to the 36-item Short Form survey version 2 (SF-36v2)

Safety Endpoints:

- Incidence and severity of adverse events/serious adverse events
- Changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs)
- Suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)

[REDACTED]

**Study Description:**

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD (HAM-D total score  $\geq 22$ ). Randomization will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline and carried out within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo; subjects will be treated for 14 days beginning on Day 1.

The study will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, and a 4-week Follow-up Period.

The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the HAM-D and CGI-S.

Antidepressants are permitted provided subjects are on a stable dose for at least 60 days prior to Day 1 and agree to continue on the stable dose through the follow-up period (Day 42). Initiation of new antidepressants or any other medications that may potentially have an impact on efficacy

or safety endpoints will not be allowed between screening and completion of the Day 42 assessments.

Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) and randomized within each stratum to one of 3 treatment groups (SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo) in a 1:1:1 ratio. Subjects will self-administer a single dose of study drug once daily at bedtime with food, on an outpatient basis, for 14 days. Subjects will return to the study center during the treatment and follow-up periods as outlined in [Table 1](#).

Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated. Subjects who discontinue treatment early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place every 7 days after the last dose of treatment for a total of 4 follow-up visits. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for both visits will be conducted.

**Number of Subjects (planned):**

Approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects.

**Eligibility Criteria:**

**Inclusion Criteria:**

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a HAM-D total score of  $\geq 22$  at screening and Day 1 (prior to dosing).
7. If subject presents for the study while currently receiving psychotropic medications that are used with the intent to treat depressive symptoms such as antidepressants, atypical antipsychotics, etc., the medications must have been taken at the same dose for at least 60 days prior to Day 1.
8. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, until after study completion.
9. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH]  $>40$  mIU/mL) and/or surgically sterile (hysterectomy or bilateral oophorectomy):

- 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/occlusion
  - Vasectomized partner
  - Sexual abstinence (no sexual intercourse)
10. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug. Acceptable methods of effective contraception for males includes sexual abstinence, vasectomy, or a condom with spermicide used together with highly effective female contraception methods if the female partner is of child-bearing potential (see Inclusion Criteria #9 for acceptable contraception methods).
11. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
12. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

**Exclusion Criteria:**

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
4. Subject has a history of treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants (excluding antipsychotics) from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment). Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.
5. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
6. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration.
7. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.

8. Subject has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
9. Subject has active psychosis per Investigator assessment.
10. Subject has a medical history of seizures.
11. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
12. Subject 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.
13. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
14. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
15. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to the first dose of study drug.
16. Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
17. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
18. Subject plans to undergo elective surgery during participation in the study.

**Study Drug, Dosage and Mode of Administration:**

SAGE-217 is available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose (SMCC), colloidal silicon dioxide and sodium stearyl fumarate as excipients. Colloidal silicon dioxide may be either a component of the SMCC or a standalone excipient in the formulation. SAGE-217 capsules will be orally administered as a 30-mg or 20-mg dose.

**Reference Therapy, Dosage, and Mode of Administration:**

Placebo will be provided as hard gelatin capsules for oral administration containing only the excipients listed above for the active capsule.

**Duration of Treatment:** 14 days

**Statistical methods:**

A 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 and treatment unblinding. Any deviations from or changes to the SAP following database lock will be described in detail in the Clinical Study Report.

### **General Considerations**

For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration.

Continuous endpoints will be summarized descriptively with 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 Randomized Set, defined as all subjects who are randomized, will be used for all data listings, unless otherwise specified.

The Safety Set, defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects in the Safety Set with at least 1 post-baseline HAM D evaluation, will be used for analysis of efficacy data.

### **Determination of Sample Size**

Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable subjects would provide 90% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation (SD) of 10 points. Assuming a 11% dropout rate and a 1:1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 450 total randomized subjects will be required to obtain 399 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is greater than 11%.

### **Analysis of Primary Endpoint**

The primary efficacy endpoint, the change from baseline to each assessment in HAM-D total score, 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 post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. The Toeplitz or compound symmetry covariance structure will be used if there is a convergence issue with the unstructured covariance model.

### **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, SF-36v2 score, sleep endpoints (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO), ISI score and selected individual items and/or subscale scores.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as  $\geq 50\%$  reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of  $\leq 7.0$ ). 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 the 15-day time point. 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 including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.

[REDACTED]

[REDACTED]

**Safety Analysis**

Safety and tolerability of study drug will be evaluated by incidence of adverse events/serious adverse events, concomitant medication usage, vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**Table 1: Schedule of Events**

| Visits                                       | Screening Period | Double-Blind, Placebo-Controlled Treatment Period |          |          |           |                                   | Follow-up Period |           |           |                 |
|--|------------------|---|----------|----------|-----------|-----------------------------------|------------------|-----------|-----------|-----------------|
|  | D-28 to D-1      | D1  | D3 (±1d) | D8 (+1d) | D12 (±1d) | D15 (±1d) and/or EOT <sup>a</sup> | D21 (±1d)        | D28 (±3d) | D35 (±3d) | D42 (±3d) or ET |
| Visit Days                                   | V1               | V2  | V3       | V4       | V5        | V6                                | V7               | V8        | V9        | V10             |
| Visit Number                                 | V1               | V2  | V3       | V4       | V5        | V6                                | V7               | V8        | V9        | V10             |
| <b>Study Procedure</b>                       |                  |   |          |          |           |                                   |                  |           |           |                 |
| Informed Consent                             | X                |   |          |          |           |                                   |                  |           |           |                 |
| Duplicate Subject Check <sup>b</sup>         | X                |   |          |          |           |                                   |                  |           |           |                 |
| Inclusion/Exclusion                          | X                | X   |          |          |           |                                   |                  |           |           |                 |
| Serum FSH test <sup>c</sup>                  | X                |   |          |          |           |                                   |                  |           |           |                 |
| SCID-5-CT                                    | X                |   |          |          |           |                                   |                  |           |           |                 |
| MGH ATRQ                                     | X                |   |          |          |           |                                   |                  |           |           |                 |
| Demographics                                 | X                |   |          |          |           |                                   |                  |           |           |                 |
| Medical/Family History                       | X                |   |          |          |           |                                   |                  |           |           |                 |
| Subject training <sup>d</sup>                | X                | X   |          |          |           |                                   |                  |           |           |                 |
| Randomization                                |                  | X   |          |          |           |                                   |                  |           |           |                 |
| Physical Examination <sup>e</sup>            | X                | X   |          |          |           |                                   |                  |           |           | X               |
| Body Weight/Height                           | X                |   |          |          |           | X (wt only)                       |                  |           |           | X (wt only)     |
| Clinical Laboratory Assessments <sup>f</sup> | X                | X   |          | X        |           | X                                 | X                | X         |           | X               |
| Drug & Alcohol Screen <sup>g</sup>           | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| Pregnancy Test <sup>h</sup>                  | X                | X   |          |          |           | X                                 |                  | X         |           | X               |
| Hepatitis & HIV Screen                       | X                |   |          |          |           |                                   |                  |           |           |                 |
|  |                  |   |          |          |           |                                   |                  |           |           |                 |
| Vital Signs <sup>k</sup>                     | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| 12-Lead ECG <sup>l</sup>                     | X                | X   |          |          |           | X                                 |                  |           |           | X               |
| C-SSRS <sup>m</sup>                          | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| HAM-D <sup>n, o</sup>                        | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| MADRS  |                  | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| HAM-A <sup>o</sup>                           |                  | X   |          | X        |           | X                                 |                  | X         |           | X               |
| CGI-S  | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| CGI-I  |                  |   | X        | X        | X         | X                                 | X                | X         | X         | X               |



- <sup>k</sup> Vital signs include oral temperature (°C), respiratory rate, 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 subject has been resting for 5 minutes and then after 1 minute in the standing position. Vital signs may be repeated at the discretion of the Investigator as clinically indicated.
- <sup>l</sup> Triplicate ECGs will be collected. [REDACTED]
- <sup>m</sup> The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- <sup>n</sup> The HAM-D is to be completed as early during the visit as possible.
- <sup>o</sup> The assessment timeframe for HAM-D and HAM-A scales will refer to the past 7 days (1 week) at Screening and “Since Last Visit” for all other visits.
- <sup>p</sup> Subjects are instructed to complete the Core Consensus Sleep Diary starting at least 7 days prior to Day 1 and then daily through Day 28.  
[REDACTED]
- <sup>r</sup> To be performed at the ET visit only.
- <sup>s</sup> Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject’s participation in the study.
- <sup>t</sup> Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.



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| <b>Abbreviation or specialist term</b> | <b>Explanation</b>   |
|--|--|
| MDD                                    | major depressive disorder  |
| MGH ATRQ                               | Massachusetts General Hospital Antidepressant Treatment Response Questionnaire |
| MMRM                                   | mixed effects model for repeated measures                                      |
| NCS                                    | not clinically significant   |
| PCS                                    | Potentially clinically significant   |
| PK                                     | pharmacokinetic  |
| PRO                                    | patient-reported outcome   |
| 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   |
| SF-36v2                                | 36-item Short Form version 2   |
| SUSAR                                  | suspected, unexpected, serious, adverse reactions                              |
| TEAE                                   | treatment-emergent adverse event   |
| WHO                                    | World Health Organization  |

## 5. INTRODUCTION

### 5.1. Background of Major Depressive Disorder and Unmet Medical Need

The World Health Organization (WHO) has identified depression as the leading cause of disability worldwide, and as a major contributor to the overall global burden of disease (<http://www.who.int/mediacentre/factsheets/fs369/en/>). Globally, depression has been estimated to affect over 300 million people.

In the United States, the economic burden of depression, including workplace costs, direct costs and suicide-related costs, was estimated to be \$210.5 billion in 2010 ([Greenberg 2015](#)). As per WHO statistics, over 800,000 people die due to suicide every year, and suicide is the second leading cause of death in 15- to 29-year-olds. The rate of US adults making a suicide attempt has increased (0.62% from 2004 to 2005 to 0.79% from 2012 to 2013), with a shift to more attempts among younger adults (42% to 50%, respectively) and among those with a depressive disorder (26% to 54%, respectively; [Olfson 2017](#)).

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition ([DSM-5](#)), depression refers to an overarching set of diagnoses, including major depressive disorder (MDD). Diagnostic criteria for MDD includes a set of at least 5 depressive symptoms out of 9, including depressed mood and/or loss of interest or pleasure, and other changes affecting appetite or weight, sleep, psychomotor activity, energy level, feelings of guilt, concentration ability and suicidality during the same 2-week period, that represents a change from previous functioning ([DSM-5](#)).

Antidepressants are a mainstay of pharmacological treatment for depressive disorders. Selective serotonin uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other compounds that affect monoaminergic neurotransmission, such as mirtazapine and bupropion, represent the major classes of antidepressants. While antidepressants are widely used, large scale studies have demonstrated their limited efficacy, including low remission rates and untreated symptoms ([Trivedi 2006](#); [Conradi 2011](#); [Romera 2013](#)).

Converging preclinical and clinical evidence ([Gerner 1981](#); [Honig 1988](#); [Drugan 1989](#); [Luscher 2011](#); [Mann 2014](#)) implicates deficits in  $\gamma$ -aminobutyric acid (GABA)-ergic neurotransmission in the pathophysiology of depressive disorders including MDD. Furthermore, experimental data implicate deficiencies in the normal regulation of endogenous neuroactive steroids in depressive disorders ([Maguire 2008](#); [Maguire 2009](#)). Depressed patients show low levels of GABA in the brain and of neurosteroids in the cerebrospinal fluid (CSF) and plasma, and antidepressant therapy restores GABA levels in relevant animal models and neurosteroid concentrations in depressed patients ([Luscher 2011](#); [Schüle 2014](#)).

### 5.2. SAGE-217

SAGE-217 is a synthetic positive allosteric modulator of GABA<sub>A</sub> receptors, the major class of inhibitory neurotransmitter receptors in the brain. 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<sub>A</sub> receptors, and, consistent with the actions of other GABA<sub>A</sub> receptor potentiators ([Rudolph 2011](#)), exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo.

Data from an open-label Phase 2a study of SAGE-217 administered to subjects with moderate to severe MDD showed clinically significant improvements from baseline in depression and anxiety scale scores (Hamilton Rating Scale for Depression [HAM-D], Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Anxiety Rating Scale [HAM-A], and Clinical Global Impression – Improvement [CGI-I]) as early as Day 2 of the 14-day treatment period, with durable responses following the end of treatment. This result was further supported by the randomized, double-blind portion of this study including 89 subjects, in which a rapid and substantial decrease in HAM-D scores was observed at Day 15 (primary endpoint), starting at Day 2. This response pattern was also observed with other efficacy scales, including MADRS, CGI-I, and HAM-A.

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, and dizziness. Most adverse events (AEs) were reported as mild or moderate in intensity. Among the over 260 subjects exposed to SAGE-217 in clinical trials, there have been no deaths and only one subject with essential tremor experienced a serious adverse event (SAE) of transient confusion leading to discontinuation of study drug. No other SAEs have been reported in any study of SAGE-217.

Additional information on nonclinical and clinical data is provided in the [Investigator's Brochure](#).

### **5.3. Potential Risks and Benefits**

Nonserious events of sedation, somnolence, and dizziness were the most commonly reported AEs with SAGE-217. Given the outcome of the Phase 2a study of SAGE-217 in subjects with MDD, the current significant unmet need in the treatment of depression, and a favorable benefit-risk profile, further investigation of SAGE-217 in patients with MDD is justified.

### **5.4. Dose Justification**

There will be 2 dose levels of SAGE-217 in this study in order to study dose ranging: 30 mg per day and 20 mg per day. The higher dose level of 30 mg per day is the maximum tolerated dose in the multiple ascending dose study of SAGE-217 in healthy subjects and is also the dose level that was effective and generally well tolerated in a Phase 2 study in subjects with MDD (217-MDD-201). The lower dose of 20 mg per day will be studied in subjects with MDD for the first time in the current study and is anticipated to be well tolerated as it is lower than the maximum tolerated dose level. Due to sedation/somnolence observed in previous clinical trials when administered in the morning, and improved tolerability when given in the evening, both doses of SAGE-217 will be administered at bedtime in this study.

## **6. STUDY OBJECTIVES AND PURPOSE**

### **6.1. Study Objective**

#### **6.1.1. Primary Objective**

The primary objective is to evaluate the efficacy of SAGE-217 in the treatment of MDD compared to placebo.

#### **6.1.2. Secondary Objective(s)**

Secondary objectives are:

- To evaluate the effect of SAGE-217 on sleep
- To assess patient-reported outcome (PRO) measures as they relate to health-related quality of life

#### **6.1.3. Safety Objective**

The safety objective is to evaluate the safety and tolerability of SAGE-217.

[REDACTED]

### **6.2. Endpoints**

#### **6.2.1. Primary Endpoint**

The primary endpoint of this study is the change from baseline in the 17-item HAM-D total score at Day 15.

#### **6.2.2. Secondary Endpoint(s)**

- Change from baseline in the 17-item HAM-D total score at other time points
- HAM-D response at Day 15 and all other time points, defined as a  $\geq 50\%$  reduction in HAM-D score from baseline
- HAM-D remission at Day 15 and all other time points, defined as HAM-D total score  $\leq 7$
- CGI-I response at Day 15 and all other time points, defined as “much improved” or “very much improved”
- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at Day 15 and all other time points

- Change from baseline in HAM-A total score at Day 15 and all other time points
- Change from baseline in the MADRS total score at Day 15 and all other time points
- Change from baseline in HAM-D subscale and individual item scores at all time points
- Improvements in sleep at Day 15 and all other time points, as assessed by:
  - Insomnia Severity Index (ISI)
  - Subjective sleep parameters collected with the Core Consensus Sleep Diary
- Patient-reported outcome measures of health-related quality of life, as assessed by responses to the 36-item Short Form survey (SF-36) version 2

**6.2.3. Safety Endpoint(s)**

- Incidence and severity of adverse events/serious adverse events
- Changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs)
- Suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)

[REDACTED]

[REDACTED]

- [REDACTED]
  - [REDACTED]
  - [REDACTED]
- [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]

## **7. INVESTIGATIONAL PLAN**

### **7.1. Overall Study Design**

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD (HAM-D total score  $\geq 22$ ). The study will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, and a 4-week Follow-up Period.

The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. At the time of providing informed consent for the study, subjects will also be asked to authorize that their unique subject identifiers be entered into a registry ([www.subjectregistry.com](http://www.subjectregistry.com)) with the intent of identifying subjects who may meet exclusion criteria due to participation in another clinical study ([Section 8.2](#)).

The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and DSM-5 Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the HAM-D and CGI-S.

Antidepressants are permitted provided subjects are on a stable dose for at least 60 days prior to Day 1 and agree to continue on the stable dose through the follow-up period (Day 42). Initiation of new antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints is prohibited between screening and completion of the Day 42 assessments.

Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) and randomized within each stratum to one of 3 treatment groups (SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo) in a 1:1:1 ratio. Subjects will self-administer a single dose of study drug with food once daily at bedtime on an outpatient basis, for 14 days. Dose reductions are not permitted. Study drug administration will be monitored via a clinical monitoring service (see [Section 9.3](#)).

Subjects will return to the study center during the treatment and follow-up periods as outlined in [Table 1](#).

### **7.2. Number of Subjects**

Approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects (see [Section 13.8](#)).

### **7.3. Treatment Assignment**

Subjects will be randomly assigned to a treatment group on Day 1. Randomization will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline and performed within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo.

#### **7.4. Dose Adjustment Criteria**

Dose adjustments are not permitted in this study. Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated (see [Section 8.3](#)).

#### **7.5. Criteria for Study Termination**

Sage Therapeutics may 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 subjects, 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 ethics committee and initiate withdrawal procedures for participating subjects.

## **8. SELECTION AND WITHDRAWAL OF SUBJECTS**

### **8.1. Subject Inclusion Criteria**

Qualified subjects will meet all of the following criteria:

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a HAM-D total score of  $\geq 22$  at screening and Day 1 (prior to dosing).
7. If subject presents for the study while currently receiving psychotropic medications that are used with the intent to treat depressive symptoms such as antidepressants, atypical antipsychotics, etc., the medications must have been taken at the same dose for at least 60 days prior to Day 1.
8. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, until after study completion.
9. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH]  $>40$  mIU/mL) and/or surgically sterile (hysterectomy or bilateral oophorectomy):
  - 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/occlusion.
  - Vasectomized partner.
  - Sexual abstinence (no sexual intercourse).
10. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug. Acceptable methods of effective contraception for males includes sexual abstinence, vasectomy, or a condom with spermicide used together with highly effective female contraception methods if the female partner is of child-bearing potential (see Inclusion Criteria #9 for acceptable contraception methods).

11. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
12. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

## **8.2. Subject Exclusion Criteria**

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

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
4. Subject has a history of treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants (excluding antipsychotics) from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment). Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.
5. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
6. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration.
7. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
8. Subject has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
9. Subject has active psychosis per Investigator assessment.
10. Subject has a medical history of seizures.
11. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
12. Subject 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.
13. Subject has had exposure to another investigational medication or device within 30 days prior to screening.

14. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
15. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to the first dose of study drug.
16. Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
17. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
18. Subject plans to undergo elective surgery during participation in the study.

### **8.3. Subject Withdrawal Criteria**

Subjects may withdraw from the study drug or terminate from the study at any time for any reason. The Investigator may withdraw the subject from the study drug or from the study for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol
- The subject experiences an intolerable AE
- Other medical or safety reason, at the discretion of the Investigator and/or the Medical Monitor

The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject withdraws from study drug or terminates the study for any reason. The reason must be recorded in the subject's electronic case report form (eCRF).

If a subject is persistently noncompliant, the Investigator should discuss with the Sponsor the potential discontinuation of the subject. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the subject's eCRF, including:

- missed visits;
- interruptions in the schedule of study drug administration;
- non-permitted medications (see [Section 9.2](#)).

Subjects 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.

Subjects who discontinue study drug early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place every 7 days after the last dose of treatment for 28 days. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for the ET visit will be conducted.

A subject will be deemed lost to follow-up after attempts at contacting the subject have been unsuccessful.

**8.3.1. Replacement of Subjects**

Subjects will not be replaced. Additional subjects may be randomized if the drop-out rate is higher than anticipated ([Section 13.8](#)).

## **9. TREATMENT OF SUBJECTS**

### **9.1. Study Drug**

Subjects will self-administer SAGE-217 (20 or 30 mg) or matching placebo orally once daily at bedtime with food for 14 days.

### **9.2. Prior Medications, Concomitant Medications, and Restrictions**

#### **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 Screening and throughout the duration of the study will be recorded. In addition, psychotropic medications taken 6 months prior to Screening will be recorded.

Any medication and/or supplement determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study.

Antidepressants, atypical antipsychotics, or sleep aids that have been taken at the same dose for at least 60 days prior to Day 1 are permitted if the subject intends to continue the stable dose through the follow-up period (Day 42).

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

- 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**

The following specific classes of medications are prohibited at any time during the treatment period:

- Initiation of new psychotropic medications
- Exposure to another investigational medication or device
- Any known strong inhibitors CYP3A4
- Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort.

#### **9.2.3. Other Restrictions**

The consumption of grapefruit juice, grapefruit, or Seville oranges, or products containing these is prohibited throughout the treatment period.

Consumption of alcohol or use of drugs of abuse is discouraged throughout the duration of the study.

### **9.3. Treatment Adherence**

SAGE-217 or placebo will be self-administered by subjects once daily at bedtime with food. Sites will dispense study drug to the subjects to take at home with instructions for use (see [Section 10.4](#) and [Table 1](#)).

Administration of study drug will be monitored by a medication adherence monitoring platform used on smartphones to visually confirm medication ingestion. Subjects will receive a reminder within a predefined time window to take study drug while using the application. Subjects 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 study drug administration by dose level, as well as missed doses.

In addition, the subject will be instructed to bring their dosing kit to the site as outlined in [Table 1](#), 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 subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

The Investigator(s) will record any reasons for non-compliance in the source documents.

### **9.4. Randomization and Blinding**

This is a randomized double-blind, placebo-controlled study. Subjects who meet the entrance criteria will be randomized in a stratified manner based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline; randomization will be done within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matched placebo. Subjects, 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 (SAGE-217 20 mg, SAGE-217 30 mg, or placebo) 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.

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IRT (see [Section 12.6](#) for more details related to unblinding).

## **10. STUDY DRUG MATERIALS AND MANAGEMENT**

### **10.1. Description of Study Drug**

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 (SMCC), colloidal silicon dioxide, and sodium stearyl fumarate as excipients. Colloidal silicon dioxide may be either a component of the SMCC or a standalone excipient in the formulation. 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. Study Drug 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 study drug in appropriately labeled, subject-specific kits containing sealed unit doses. Each unit dose consists of 1 capsule. Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Study drug 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. Study Drug Storage**

SAGE-217 and matched placebo 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. Study Drug Preparation**

Not applicable.

### **10.5. Study Drug Administration**

SAGE-217 is to be administered orally once daily at bedtime with food. If a subject misses a dose at bedtime, the subject should skip that dose (ie, they should not take the dose in the morning) and take the next scheduled dose at bedtime the next day.

### **10.6. Study Drug Accountability**

Upon receipt of study drug, the Investigator(s), or the responsible pharmacist or designee, will inspect the study drug and complete and follow the instructions regarding receipt 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 subject-specific kits to subjects at the planned dispensation visit intervals outlined in [Table 1](#).

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

At the subsequent study drug-dispensing visit, the investigator or designee will access the IRT, providing the same subject ID number assigned at Screening, to obtain the medication ID number for the study drug to be dispensed at that visit. The medication ID number, the number of capsules dispensed, and the number of capsules returned by the subject 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 study drug provided is for use only as directed in this protocol. After the study is completed, all unused study drug must be returned as directed or destroyed on site per the Sponsor's instructions. The Investigator or designee must keep a record of all study drug received, dispensed and discarded.

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

### **10.7. Study Drug Handling and Disposal**

At the end of the study, all used and unused study drug will be reconciled and returned to Sage Therapeutics for destruction or destroyed locally; disposition of study drug will be documented.

A copy of the inventory record and a record of any clinical supplies that have been received, dispensed or destroyed must be documented by the site as directed. This documentation must include at least the information below:

- the number of dispensed units;
- the number of unused units;
- the number of units destroyed at the end of the study;
- the date, method and location of destruction.

## 11. ASSESSMENT OF EFFICACY [REDACTED]

All assessments will be conducted according to the schedule of assessments (Table 1). Study assessments that involve subject 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. Efficacy Assessments

#### 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 subject. An assessment timeframe of 7 days 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 subjects 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 of  $\leq 7$ .

#### 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 subjects 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 Impression (CGI)**

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 subject'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 subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject 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 subject's condition posttreatment. The Investigator will rate the subject'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. Short Form-36 Version 2 (SF-36v2)**

The Medical Outcomes Study SF-36v2 is a 36-item measure of health status that has undergone validation in many different disease states (Ware 2007). The SF-36v2 covers eight health dimensions including four physical health status domains (physical functioning, role participation with physical health problems [role-physical], bodily pain, and general health) and four mental health status domains (vitality, social functioning, role participation with emotional health problems [role-emotional], and mental health). In addition, two summary scores, physical component summary and mental component summary, are produced by taking a weighted linear combination of the eight individual domains. The SF-36v2 is available with two recall periods: the standard recall period is 4 weeks and the acute recall period is 1 week. This study will use the acute version, which asks patients to respond to questions as they pertain to the past week. Higher SF-36v2 scores indicate a better state of health.

#### **11.1.6. Insomnia Severity Index (ISI)**

The ISI is a validated questionnaire designed to assess the nature, severity, and impact of insomnia (Morin 2011). The ISI uses a 5-point Likert Scale to measure various aspects of insomnia severity (0 = none, 1 = mild, 2 = moderate; 3 = severe; 4 = very severe), satisfaction with current sleep pattern (0 = very satisfied, 1 = satisfied, 2 = moderately satisfied, 3 = dissatisfied, 4 = very dissatisfied), and various aspects of the impact of insomnia on daily functioning (0 = not at all, 1 = a little, 2 = somewhat, 3 = much, 4 = very much). A total score of 0 to 7 = "no clinically significant insomnia," 8 to 14 = subthreshold insomnia," 15 to 21 = "clinical insomnia (moderate severity)," and 22 to 28 = "clinical insomnia (severe)."

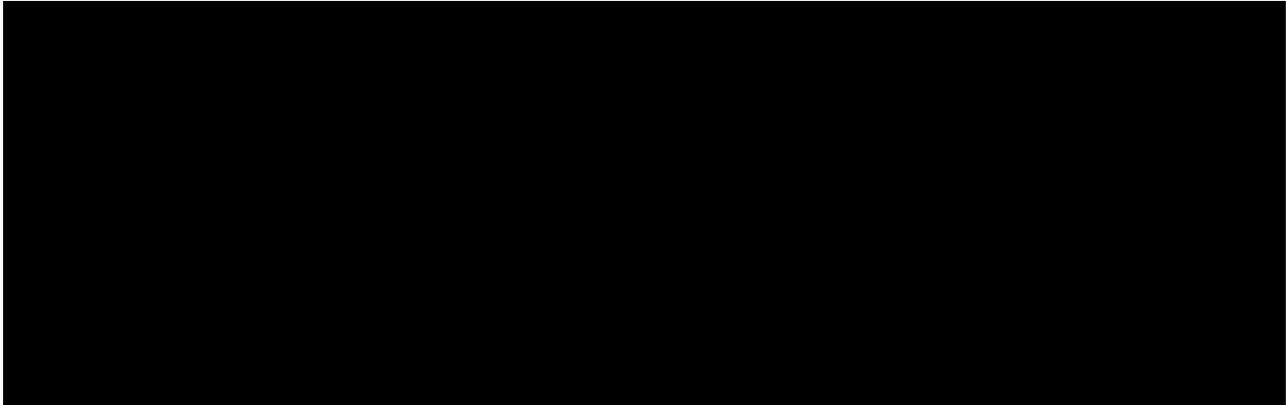
**11.1.7. Core Consensus Sleep Diary**

The Core Consensus Sleep Diary collects subjective sleep parameters, including sleep onset latency, total sleep time, and wake after sleep onset, number of awakenings, and sleep quality. The take-home subject sleep diary assessment will be administered using an eDiary solution. The eDiary will be captured using either a provisioned smartphone device or bring-your-own-device (BYOD) solution, depending on the subject's preference.

[REDACTED]

[REDACTED]

[REDACTED]



## **12. ASSESSMENT OF SAFETY**

### **12.1. Safety Parameters**

All assessments will be conducted according to the schedule of assessments ([Table 1](#)).

#### **12.1.1. Demographic/Medical History**

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including family psychiatric history, will be documented. The diagnosis of MDD will be determined using the SCID-5-CT. If available, the disease code associated with the diagnosis of MDD based on the 10<sup>th</sup> revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used to determine whether the subject has a history of treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment).

#### **12.1.2. Weight and Height**

Height (Screening only) and weight will be measured and documented.

#### **12.1.3. Physical Examination**

Physical examinations assessing body systems (eg, head, eyes, ears, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Whenever possible, the same individual is to perform all physical examinations for a given subject. Unscheduled brief, symptom-driven physical examinations may also be conducted per the Investigator's discretion.

Any abnormality in physical examinations will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to [Section 12.2.1.1](#).

#### **12.1.4. Vital Signs**

Vital signs comprise both supine and standing for systolic and diastolic blood pressure and heart rate measurements. Heart rate and blood pressure are to be collected in supine position after the subject has been resting for 5 minutes and then after 1 minute in the standing position.

Respiratory rate, pulse oximetry and temperature are collected once, in either position. Vital signs will be documented. When vital signs are scheduled at the same time as blood draws, vital signs will be obtained first.

Any abnormality in vital signs will be interpreted by the Investigator as abnormal, NCS or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to [Section 12.2.1.1](#).

### 12.1.5. Electrocardiogram (ECG)

Supine 12-lead ECGs 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. [REDACTED]

### 12.1.6. Laboratory Assessments

Samples will be collected in accordance with acceptable laboratory procedures detailed in the laboratory manual.

The clinical laboratory tests to be performed are listed in Table 3.

**Table 3: Clinical Laboratory Tests**

| Hematology                                   | Serum Chemistry  | Urinalysis          | Coagulation                           |
|--|--|---------------------|---------------------------------------|
| Red blood cell count                         | Alanine aminotransferase   | pH                  | Activated partial thromboplastin time |
| Hemoglobin                                   | Albumin  | Specific gravity    | Prothrombin time                      |
| Hematocrit                                   | Alkaline phosphatase   | Protein             | International normalized ratio        |
| White blood cell count with differential     | Aspartate aminotransferase   | Glucose             |                                       |
| Reticulocytes                                | Total bilirubin  | Red blood cell      |                                       |
| Platelet count                               | Direct bilirubin   | Nitrite             |                                       |
| Red blood cell morphology                    | Indirect bilirubin   | Leukocyte esterase  |                                       |
|  | Total protein  | Ketones             |                                       |
|  | Creatinine   | Bilirubin           |                                       |
|  | Blood urea nitrogen  | Urobilinogen        |                                       |
|  | Creatine kinase  |                     |                                       |
|  | Gamma-glutamyl transferase   |                     |                                       |
|  | Potassium  |                     |                                       |
|  | Sodium   |                     |                                       |
|  | Lactate dehydrogenase  |                     |                                       |
|  | Glucose  |                     |                                       |
|  | Chloride   |                     |                                       |
|  | Bicarbonate  |                     |                                       |
|  | Calcium  |                     |                                       |
|  | Phosphorus   |                     |                                       |
|  | Triglycerides  |                     |                                       |
|  | Thyroid stimulating hormone  |                     |                                       |
| <b>Diagnostic</b>                            |  |                     |                                       |
| <b>Serum</b>                                 | <b>Urine</b>   | <b>Breathalyzer</b> |                                       |
| Hepatitis B<br>Hepatitis C<br>Reflex HCV RNA | Drug screen including:<br>amphetamines,<br>barbiturates,<br>benzodiazepines, | Alcohol             |                                       |

|   |   |  |  |
|---|---|--|--|
| <p>HIV-1 and -2<br/>Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: serum hCG<br/>Female subjects, if menopause is suspected and not surgically sterile: FSH</p> | <p>cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene<br/>Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: urine hCG</p> |  |  |
|---|---|--|--|

Abbreviations: FSH = follicle stimulating hormone; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus

The central laboratory will perform laboratory tests for hematology, serum chemistry, urinalysis, and coagulation. The results of laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to Sage Therapeutics or designee in the format requested by Sage Therapeutics.

Laboratory reports must be signed and dated by the Investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will require clear and complete documentation in the source documents as to the investigator’s assessment of not clinically significant before proceeding with randomization.

All clinical laboratory test results outside the central laboratory’s reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to [Section 12.2.1.1](#). A clinically significant laboratory abnormality following subject randomization will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

A serum follicle stimulating hormone test will be conducted at Screening to confirm whether a female subject with  $\geq 12$  months of spontaneous amenorrhea meets the protocol-defined criteria for being post-menopausal ([Section 8.1](#)).

[REDACTED]

### **12.1.6.1. Drugs of Abuse and Alcohol**

Urine toxicology tests will be performed for selected drugs of abuse (see [Table 3](#)). A breath test for alcohol will be performed.

### **12.1.6.2. Pregnancy Screen**

For female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at all other scheduled timepoints thereafter, including the ET visit for subjects who prematurely discontinue.

### **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 subject with suicidal ideation and behavior, and a post-baseline 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, as outlined in [Table 1](#).

## **12.2. Adverse and Serious Adverse Events**

### **12.2.1. Definition of Adverse Events**

#### **12.2.1.1. Adverse Event (AE)**

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 an AE that occurs after the first administration of any study drug. The term study drug includes any Sage investigational product, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) and/or if the Investigator considers them to be clinically significant. Laboratory values and vital signs that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations 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 subject 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.

#### **12.2.1.2. Serious Adverse Event (SAE)**

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 subject or may require medical intervention to prevent one 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 subject 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 form provided by Sage Therapeutics. Serious adverse events occurring after a subject's final visit (including the last follow-up visit) should be reported to Sage or designee only if the Investigator considers the SAE to be related to study treatment.

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject 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 subject'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 the Investigator, between the subject's consent to participate in the study and at the time of the procedure or treatment.

### **12.3. Relationship to Study Drug**

The Investigator must make the determination of relationship to the study drug for each adverse event (not related, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as "not related." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational

product and the occurrence of the adverse event, then the adverse event should be considered at least “possibly related.”

**Table 4: Relationship to Study Drug**

| <b>Relationship</b> | <b>Definition</b>  |
|---------------------|--|
| Not Related:        | No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject’s clinical state.  |
| Possibly Related:   | A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.<br>The reaction might have been produced by the subject’s clinical state or other modes of therapy administered to the subject, but this is not known for sure.    |
| Probably Related:   | A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.<br>The reaction cannot be reasonably explained by the known characteristics of the subject’s clinical state or other modes of therapy administered to the subject. |

If the relationship between the adverse event/serious adverse event and the investigational product is determined to be “possible” or “probable”, the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

## 12.4. Recording Adverse Events

Adverse events spontaneously reported by the subject 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, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study drug or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

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 12.2.1.2](#). An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on the Sage Therapeutics pregnancy notification form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented on the Sage Therapeutics pregnancy outcome form, even if the subject was discontinued from the study. All reports of

congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs.

## **12.5. Reporting Serious Adverse Events**

All SAEs must be reported to Sage, or designee, immediately. A written account of the SAE must be sent to Sage, or designee, within 24 hours of the first awareness of the event by the investigator and/or his staff. The Investigator must complete, sign and date the SAE form, verify the accuracy of the information recorded on the SAE pages 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 Therapeutics, 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 case report form (CRF) and/or study file.

Any SAEs discovered by the Investigator after the designated follow up time for the study, should be promptly reported to Sage, or designee, according to the timelines noted above.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the ethics committee 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. Ethics Committee (EC)/Institutional Review Boards (IRBs) will be notified of SAEs and/or SUSARs as required by local law. In addition, appropriate Sponsor Drug Safety and Pharmacovigilance personnel, or designee, will unblind SUSARs for the purpose of regulatory reporting. The Sponsor, or designee, will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. The Sponsor, or designee, will submit SUSARs to investigators in a blinded fashion.

## **12.6. Emergency Identification of Study Drug**

During the study, the blind is to be broken by the Investigator only when the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. Unless a subject is at immediate risk, the Investigator must make diligent attempts to contact Sage prior to unblinding the study treatment administered to a subject. Any request from the Investigator about the treatment administered to study subjects must be discussed with Sage. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented in the source records. Unless a subject is at immediate risk, any request for the unblinding of individual subjects must be made in writing to Sage and approved by the appropriate Sage personnel, according to standard operating procedures.

In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the eCRF. If the subject or study center personnel have been unblinded, the subject will be permanently discontinued from the study.

### **13. STATISTICS**

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the clinical study report.

#### **13.1. Data Analysis Sets**

The Randomized set, defined as all subjects who are randomized, will be used for all data listings, unless otherwise specified.

The Safety Set, defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects in the Safety Set with at least 1 post-baseline HAM-D evaluation, will be used for analysis of efficacy data.



#### **13.2. Handling of Missing Data**

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data. A sensitivity analysis will be used to investigate the impact of missing data if  $\geq 5\%$  of subjects in any treatment group have missing data.

#### **13.3. General Considerations**

For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), 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 ([Section 12.1.1](#)) and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized using the Safety Set.

Hepatitis, HIV, drug and alcohol, and pregnancy screening results will be listed, but not summarized as they are considered part of the inclusion/exclusion criteria.

Medical/family history will be listed by subject.

### **13.5. Efficacy Analyses**

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment.

The primary efficacy endpoint, the change from baseline to each assessment in HAM-D total score, 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 post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. The Toeplitz or compound symmetry covariance structure will be used if there is a convergence issue with the unstructured covariance model.

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, SF-36v2 score, sleep endpoints (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO), ISI score and selected individual items and/or subscale scores.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as  $\geq 50\%$  reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of  $\leq 7.0$ ). 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 the 15-day time point. 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 including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.

### **13.6. Safety Analyses**

Safety and tolerability of study drug will be evaluated by incidence of adverse events/serious adverse events, concomitant medication usage, vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Safety data will be listed by subject and summarized by treatment group. All safety summaries will be performed on the Safety Set. Where applicable, ranges of potentially clinically significant (PCS) values are provided in the SAP.

#### **13.6.1. Adverse Events**

The analysis of adverse events will be based on the concept of TEAEs. The incidence of TEAEs will be summarized overall and by Medical Dictionary for Regulatory Activities (MedDRA)

Version 18.1 or higher, System Organ Class (SOC), and preferred term. Incidences will be presented in order of decreasing frequency. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to study drug (see [Section 12.3](#)).

Any TEAEs leading to discontinuation and SAEs with onset after the start of study drug will also be summarized.

All AEs and SAEs (including those with onset or worsening before the start of study drug) 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 range of each parameter is provided by the laboratory; shift from baseline to post-baseline values in abnormality of results will be provided. Potentially clinically significant values will be summarized by treatment. Any abnormal values deemed clinically significant by the investigator will be reported as an AE (see [Section 12.2](#)). Clinical laboratory results will be listed by subject and timing of collection.

### **13.6.3. Physical Examinations**

The occurrence of a physical examination (Y/N) and the date performed will be listed by subject. Any clinically significant observation in physical examination will be reported as an AE (see [Section 12.2](#)).

### **13.6.4. Vital Signs**

Results from each visit and mean changes from baseline in vital signs will be summarized by scheduled visit. Any abnormality deemed clinically significant by the investigator will be reported as an AE (see [Section 12.2](#)). Potentially clinically significant values will be summarized by treatment. Vital sign results will be listed by subject 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 subject: 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 subject 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 signing the ICF through the duration of the study will be recorded. In addition, all psychotropic medications taken 6 months prior to Screening will be recorded. Those medications taken prior to the initiation of the start of study drug will be denoted "Prior". Those medications taken prior to the initiation of the study drug and continuing beyond the initiation of the study drug or those medications started at the same time or after the

initiation of the study drug will be denoted “Concomitant” (ie, those with a start date on or after the first dose of study drug, or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug).

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 subject, 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 summarized by treatment. Listings will include all data, including behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

[REDACTED]

### **13.8. Determination of Sample Size**

Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable subjects 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 SD of 10 points. Assuming an 11% dropout rate and a 1:1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 450 total randomized subjects will be required to obtain 399 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is greater than 11%.

## **14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **14.1. Study Monitoring**

Before an investigational site can enter a subject into the study, a representative of Sage Therapeutics (or designee) 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 investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject'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 subject (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.

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

### **14.2. Audits and Inspections**

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics audit or 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, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

### **14.3. Institutional Review Board (IRB) or Ethics Committee (EC)**

The Principal Investigator must obtain IRB (or EC) approval for the investigation. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the subject 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 Practices and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit. Please see [Section 14.2](#) for more details regarding the audit process.

## **16. ETHICS**

### **16.1. Ethics Review**

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or EC as appropriate. The investigator must submit written approval to Sage Therapeutics before he or she can enroll any subject into the study.

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

The Principal Investigator is also responsible for providing the IRB 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 EC according to local regulations and guidelines.

### **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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines, as well as all applicable regulatory requirements.

### **16.3. Written Informed Consent**

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

## **17. DATA HANDLING AND RECORDKEEPING**

### **17.1. Inspection of Records**

Sage Therapeutics will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **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, whichever is longer. If not approved, documentation must be maintained for 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

## **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.

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**STUDY TITLE: A PHASE 3, MULTICENTER, DOUBLE-  
BLIND, RANDOMIZED, PLACEBO-CONTROLLED  
STUDY EVALUATING THE EFFICACY OF SAGE-217  
IN THE TREATMENT OF ADULT SUBJECTS WITH  
MAJOR DEPRESSIVE DISORDER**

**PROTOCOL NUMBER: 217-MDD-301**

|                           |  |
|---------------------------|--|
| Study Drug                | SAGE-217   |
| Clinical Phase            | Phase 3  |
| Sponsor                   | Sage Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 |
| Sponsor Contact           | [REDACTED]<br>Tel: [REDACTED]<br>email: [REDACTED]                 |
| Sponsor Medical Monitor   | [REDACTED] MD, MBA<br>Tel: [REDACTED]<br>email: [REDACTED]         |
| Date of Original Protocol | Version 1.0, 16 JUL 2018   |
| Date of Amendment 1       | Version 2.0, 25 SEP 2018   |

**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.

**Protocol Number:** 217-MDD-301  
**Study Drug:** SAGE-217  
**Study Phase:** Phase 3  
**Sponsor:** Sage Therapeutics, Inc.  
**Protocol Date:** Version 2.0, 25 SEP 2018

**Sponsor Approval**

[Redacted Signature] \_\_\_\_\_  
[Redacted Name], MD, MBA Date (DD MMM YYYY)

Sage Therapeutics

[Redacted Signature] \_\_\_\_\_  
[Redacted Name] DVM, MS, MPH Date (DD MMM YYYY)

Sage Therapeutics

[Redacted Signature] \_\_\_\_\_  
[Redacted Name] R Date (DD MMM YYYY)

Sage Therapeutics

[Redacted Signature] \_\_\_\_\_  
[Redacted Name] Date (DD MMM YYYY)

Sage Therapeutics

[Redacted Signature] \_\_\_\_\_  
[Redacted Name] PhD Date (DD MMM YYYY)

Sage Therapeutics

[Redacted Signature] \_\_\_\_\_  
[Redacted Name] Date (DD MMM YYYY)

Sage Therapeutics

## INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-MDD-301 clinical 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.

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Printed name of Investigator

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Signature of Investigator

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Date (DD Month YYYY)



- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at Day 15 and all other time points
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at Day 15 and all other time points
- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15 and all other time points
- Change from baseline in HAM-D subscale and individual item scores at all time points
- Improvements in sleep at Day 15 and all other time points, as assessed by
  - Insomnia Severity Index (ISI)
  - Subjective sleep parameters collected with the Core Consensus Sleep Diary
- PRO measures of health-related quality of life, as assessed by responses to the 36-item Short Form survey version 2 (SF-36v2)

Safety Endpoints:

- Incidence and severity of adverse events/serious adverse events
- Changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs)
- Suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)

**Study Description:**

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD (HAM-D total score  $\geq 22$ ). Randomization will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline and carried out within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo; subjects will be treated for 14 days beginning on Day 1.

The study will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, and a 4-week Follow-up Period.

The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the HAM-D and CGI-S.

Antidepressants are permitted provided subjects are on a stable dose for at least 60 days prior to Day 1 and agree to continue on the stable dose through the follow-up period (Day 42). Initiation of new antidepressants or any other medications that may potentially have an impact on efficacy

or safety endpoints will not be allowed between screening and completion of the Day 42 assessments.

Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) and randomized within each stratum to one of 3 treatment groups (SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo) in a 1:1:1 ratio. Subjects will self-administer a single dose of study drug once daily in the evening with food, on an outpatient basis, for 14 days. Subjects will return to the study center during the treatment and follow-up periods as outlined in [Table 1](#).

Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated. Subjects who discontinue treatment early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place every 7 days after the last dose of treatment for a total of 4 follow-up visits. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for both visits will be conducted.

**Number of Subjects (planned):**

Approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects.

**Eligibility Criteria:**

**Inclusion Criteria:**

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a HAM-D total score of  $\geq 22$  at screening and Day 1 (prior to dosing).
7. Subjects taking psychotropic medications used to treat major depressive disorder (eg, antidepressants, atypical antipsychotics) must have been taking these medications at the same dose for at least 60 days prior to Day 1.
8. Subjects taking benzodiazepines or GABA<sub>A</sub> modulators for insomnia (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) have had these medications discontinued by Day -14.
9. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, until after study completion.
10. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative

medical cause and confirmed by follicle stimulating hormone [FSH] >40 mIU/mL) and/or surgically sterile (hysterectomy or bilateral oophorectomy):

- 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/occlusion
  - Vasectomized partner
  - Sexual abstinence (no sexual intercourse)
11. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug. Acceptable methods of effective contraception for males includes sexual abstinence, vasectomy, or a condom with spermicide used together with highly effective female contraception methods if the female partner is of child-bearing potential (see Inclusion Criteria #9 for acceptable contraception methods).
12. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
13. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

**Exclusion Criteria:**

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from two different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.
5. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
6. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk

to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.

7. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
8. Subject has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
9. Subject has active psychosis per Investigator assessment.
10. Subject has a medical history of seizures.
11. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
12. Subject 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.
13. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
14. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
15. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to the first dose of study drug.
16. Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
17. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
18. Subject plans to undergo elective surgery during participation in the study.
19. Subject is taking benzodiazepines or GABA<sub>A</sub> modulators at Day -14.

**Study Drug, Dosage and Mode of Administration:**

SAGE-217 is available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose (SMCC), colloidal silicon dioxide and sodium stearyl fumarate as excipients. Colloidal silicon dioxide may be either a component of the SMCC or a standalone excipient in the formulation. SAGE-217 capsules will be orally administered as a 30-mg or 20-mg dose.

**Reference Therapy, Dosage, and Mode of Administration:**

Placebo will be provided as hard gelatin capsules for oral administration containing only the excipients listed above for the active capsule.

**Duration of Treatment:** 14 days

**Statistical methods:**

A 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 and treatment unblinding. Any deviations from or changes to the SAP following database lock will be described in detail in the Clinical Study Report.

**General Considerations**

For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration.

Continuous endpoints will be summarized descriptively with 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 Randomized Set, defined as all subjects who are randomized, will be used for all data listings, unless otherwise specified.

The Safety Set, defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects in the Safety Set with at least 1 post-baseline HAM D evaluation, will be used for analysis of efficacy data.

**Determination of Sample Size**

Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable subjects would provide 90% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation (SD) of 10 points. Assuming a 11% dropout rate and a 1:1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 450 total randomized subjects will be required to obtain 399 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is greater than 11%.

**Analysis of Primary Endpoint**

The primary efficacy endpoint, the change from baseline to each assessment in HAM-D total score, 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 post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. The Toeplitz or compound symmetry covariance structure will be used if there is a convergence issue with the unstructured covariance model.

**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, SF-36v2 score, sleep endpoints (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO), ISI score and selected individual items and/or subscale scores.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as  $\geq 50\%$  reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of  $\leq 7.0$ ). 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 the 15-day time point. 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 including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.

[REDACTED]

### **Safety Analysis**

Safety and tolerability of study drug will be evaluated by incidence of adverse events/serious adverse events, concomitant medication usage, vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS.

[REDACTED]

**Table 1: Schedule of Events**

| Visits                                       | Screening Period | Double-Blind, Placebo-Controlled Treatment Period |          |          |           |                                   | Follow-up Period |           |           |                 |
|--|------------------|---|----------|----------|-----------|-----------------------------------|------------------|-----------|-----------|-----------------|
|  | D-28 to D-1      | D1  | D3 (±1d) | D8 (+1d) | D12 (±1d) | D15 (±1d) and/or EOT <sup>a</sup> | D21 (±1d)        | D28 (±3d) | D35 (±3d) | D42 (±3d) or ET |
| Visit Days                                   | V1               | V2  | V3       | V4       | V5        | V6                                | V7               | V8        | V9        | V10             |
| Visit Number                                 | V1               | V2  | V3       | V4       | V5        | V6                                | V7               | V8        | V9        | V10             |
| <b>Study Procedure</b>                       |                  |   |          |          |           |                                   |                  |           |           |                 |
| Informed Consent                             | X                |   |          |          |           |                                   |                  |           |           |                 |
| Duplicate Subject Check <sup>b</sup>         | X                |   |          |          |           |                                   |                  |           |           |                 |
| Inclusion/Exclusion                          | X                | X   |          |          |           |                                   |                  |           |           |                 |
| Serum FSH test <sup>c</sup>                  | X                |   |          |          |           |                                   |                  |           |           |                 |
| SCID-5-CT                                    | X                |   |          |          |           |                                   |                  |           |           |                 |
| MGH ATRQ                                     | X                |   |          |          |           |                                   |                  |           |           |                 |
| Demographics                                 | X                |   |          |          |           |                                   |                  |           |           |                 |
| Medical/Family History                       | X                |   |          |          |           |                                   |                  |           |           |                 |
| Subject training <sup>d</sup>                | X                | X   |          |          |           |                                   |                  |           |           |                 |
| Randomization                                |                  | X   |          |          |           |                                   |                  |           |           |                 |
| Physical Examination <sup>e</sup>            | X                | X   |          |          |           |                                   |                  |           |           | X               |
| Body Weight/Height                           | X                |   |          |          |           | X (wt only)                       |                  |           |           | X (wt only)     |
| Clinical Laboratory Assessments <sup>f</sup> | X                | X   |          | X        |           | X                                 | X                | X         |           | X               |
| Drug & Alcohol Screen <sup>g</sup>           | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| Pregnancy Test <sup>h</sup>                  | X                | X   |          |          |           | X                                 |                  | X         |           | X               |
| Hepatitis & HIV Screen                       | X                |   |          |          |           |                                   |                  |           |           |                 |
|  |                  |   |          |          |           |                                   |                  |           |           |                 |
| Vital Signs <sup>k</sup>                     | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| 12-Lead ECG <sup>l</sup>                     | X                | X   |          |          |           | X                                 |                  |           |           | X               |
| C-SSRS <sup>m</sup>                          | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| HAM-D <sup>n, o</sup>                        | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| MADRS  |                  | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| HAM-A <sup>o</sup>                           |                  | X   |          | X        |           | X                                 |                  | X         |           | X               |
| CGI-S  | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X               |
| CGI-I  |                  |   | X        | X        | X         | X                                 | X                | X         | X         | X               |

| Visits  | Screening Period | Double-Blind, Placebo-Controlled Treatment Period |          |          |           |                                   | Follow-up Period |           |           |                 |                |  |
|---|------------------|---|----------|----------|-----------|-----------------------------------|------------------|-----------|-----------|-----------------|----------------|--|
|   |                  | D1  | D3 (±1d) | D8 (+1d) | D12 (±1d) | D15 (±1d) and/or EOT <sup>a</sup> | D21 (±1d)        | D28 (±3d) | D35 (±3d) | D42 (±3d) or ET |                |  |
| Visit Days  | D-28 to D-1      | V1  | V2       | V3       | V4        | V5                                | V6               | V7        | V8        | V9              | V10            |  |
| Visit Number  | V1               | V2  | V3       | V4       | V5        | V6                                | V7               | V8        | V9        | V10             |                |  |
| Study Procedure                                       |                  |   |          |          |           |                                   |                  |           |           |                 |                |  |
| SF-36v2   | X                | X   |          | X        |           | X                                 |                  | X         |           | X               |                |  |
| ISI   |                  | X   |          | X        |           | X                                 | X                | X         |           |                 | X              |  |
| Sleep diary <sup>p</sup>                              | X                | X   |          |          |           |                                   |                  |           |           |                 |                |  |
| Study Drug Dispensation                               |                  | X   |          | X        |           |                                   |                  |           |           |                 |                |  |
| Study Drug Administration                             |                  | X (Day 1 through Day 14)                          |          |          |           |                                   |                  |           |           |                 |                |  |
| Study Drug Accountability/Return                      |                  |   |          | X        |           | X                                 |                  |           |           |                 | X <sup>r</sup> |  |
| Adverse Events/SAEs <sup>s</sup>                      |                  | X   |          |          |           |                                   |                  |           |           |                 |                |  |
| Prior/Concomitant Medications/Procedures <sup>t</sup> |                  | X   |          |          |           |                                   |                  |           |           |                 |                |  |

CGI-I = Clinical Global Impression – Improvement; CGI-S – Clinical Global Impression – Severity; [REDACTED] Short Form; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; EOT = end of treatment; ET = early termination; ECG = electrocardiogram; [REDACTED]; FSH = follicle stimulating hormone; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; ISI = Insomnia Severity Index; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; O = Optional; [REDACTED]; SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Clinical Trials Version; SF-36v2 = 36-item Short Form survey version 2; V = visit; wt = weight

- <sup>a</sup> Subjects who discontinue treatment early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place every 7 days after the last dose of treatment for a total of 4 follow-up visits. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for both visits will be conducted.
- <sup>b</sup> Subjects will be asked to authorize that their unique subject identifiers be entered into a registry (www.subjectregistry.com) with the intent of identifying subjects who may meet exclusion criteria for participation in another clinical study.
- <sup>c</sup> A serum follicle stimulating hormone test will be conducted at Screening for female subjects that are not surgically sterile to confirm whether a female subject with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being post-menopausal.
- <sup>d</sup> Subjects will be trained on use of software applications and devices necessary for the conduct of the study by site personnel.
- <sup>e</sup> 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).
- <sup>f</sup> Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis.
- <sup>g</sup> Urine toxicology for selected drugs of abuse (as per the lab manual) and breath test for alcohol.
- <sup>h</sup> Serum pregnancy test at screening and urine pregnancy test thereafter for female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal.

[REDACTED]

- <sup>k</sup> Vital signs include oral temperature (°C), respiratory rate, 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 subject has been resting for 5 minutes and then after 1 minute in the standing position. Vital signs may be repeated at the discretion of the Investigator as clinically indicated.
- <sup>l</sup> Triplicate ECGs will be collected. [REDACTED]
- <sup>m</sup> The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- <sup>n</sup> The HAM-D is to be completed as early during the visit as possible.
- <sup>o</sup> 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 scale will refer to the past 7 days (1 week) at all visits.
- <sup>p</sup> Subjects are instructed to complete the Core Consensus Sleep Diary starting at least 7 days prior to Day 1 and then daily through Day 28.  
[REDACTED]
- <sup>r</sup> To be performed at the ET visit only.
- <sup>s</sup> Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject’s participation in the study.
- <sup>t</sup> Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.

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**Table 2: Abbreviations and specialist terms (Continued)**

| <b>Abbreviation or specialist term</b> | <b>Explanation</b>   |
|--|--|
| MDD                                    | major depressive disorder  |
| MGH ATRQ                               | Massachusetts General Hospital Antidepressant Treatment Response Questionnaire |
| MMRM                                   | mixed effects model for repeated measures                                      |
| NCS                                    | not clinically significant   |
| PCS                                    | Potentially clinically significant   |
| PK                                     | pharmacokinetic  |
| PRO                                    | patient-reported outcome   |
| 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   |
| SF-36v2                                | 36-item Short Form version 2   |
| SUSAR                                  | suspected, unexpected, serious, adverse reactions                              |
| TEAE                                   | treatment-emergent adverse event   |
| WHO                                    | World Health Organization  |

## 5. INTRODUCTION

### 5.1. Background of Major Depressive Disorder and Unmet Medical Need

The World Health Organization (WHO) has identified depression as the leading cause of disability worldwide, and as a major contributor to the overall global burden of disease (<http://www.who.int/mediacentre/factsheets/fs369/en/>). Globally, depression has been estimated to affect over 300 million people.

In the United States, the economic burden of depression, including workplace costs, direct costs and suicide-related costs, was estimated to be \$210.5 billion in 2010 ([Greenberg 2015](#)). As per WHO statistics, over 800,000 people die due to suicide every year, and suicide is the second leading cause of death in 15- to 29-year-olds. The rate of US adults making a suicide attempt has increased (0.62% from 2004 to 2005 to 0.79% from 2012 to 2013), with a shift to more attempts among younger adults (42% to 50%, respectively) and among those with a depressive disorder (26% to 54%, respectively; [Olfson 2017](#)).

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition ([DSM-5](#)), depression refers to an overarching set of diagnoses, including major depressive disorder (MDD). Diagnostic criteria for MDD includes a set of at least 5 depressive symptoms out of 9, including depressed mood and/or loss of interest or pleasure, and other changes affecting appetite or weight, sleep, psychomotor activity, energy level, feelings of guilt, concentration ability and suicidality during the same 2-week period, that represents a change from previous functioning ([DSM-5](#)).

Antidepressants are a mainstay of pharmacological treatment for depressive disorders. Selective serotonin uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other compounds that affect monoaminergic neurotransmission, such as mirtazapine and bupropion, represent the major classes of antidepressants. While antidepressants are widely used, large scale studies have demonstrated their limited efficacy, including low remission rates and untreated symptoms ([Trivedi 2006](#); [Conradi 2011](#); [Romera 2013](#)).

Converging preclinical and clinical evidence ([Gerner 1981](#); [Honig 1988](#); [Drugan 1989](#); [Luscher 2011](#); [Mann 2014](#)) implicates deficits in  $\gamma$ -aminobutyric acid (GABA)-ergic neurotransmission in the pathophysiology of depressive disorders including MDD. Furthermore, experimental data implicate deficiencies in the normal regulation of endogenous neuroactive steroids in depressive disorders ([Maguire 2008](#); [Maguire 2009](#)). Depressed patients show low levels of GABA in the brain and of neurosteroids in the cerebrospinal fluid (CSF) and plasma, and antidepressant therapy restores GABA levels in relevant animal models and neurosteroid concentrations in depressed patients ([Luscher 2011](#); [Schüle 2014](#)).

### 5.2. SAGE-217

SAGE-217 is a synthetic positive allosteric modulator of GABA<sub>A</sub> receptors, the major class of inhibitory neurotransmitter receptors in the brain. 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<sub>A</sub> receptors, and, consistent with the actions of other GABA<sub>A</sub> receptor potentiators ([Rudolph 2011](#)), exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo.

Data from an open-label Phase 2a study of SAGE-217 administered to subjects with moderate to severe MDD showed clinically significant improvements from baseline in depression and anxiety scale scores (Hamilton Rating Scale for Depression [HAM-D], Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Anxiety Rating Scale [HAM-A], and Clinical Global Impression – Improvement [CGI-I]) as early as Day 2 of the 14-day treatment period, with durable responses following the end of treatment. This result was further supported by the randomized, double-blind portion of this study including 89 subjects, in which a rapid and substantial decrease in HAM-D scores was observed at Day 15 (primary endpoint), starting at Day 2. This response pattern was also observed with other efficacy scales, including MADRS, CGI-I, and HAM-A.

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, and dizziness. Most adverse events (AEs) were reported as mild or moderate in intensity. Among the over 260 subjects exposed to SAGE-217 in clinical trials, there have been no deaths and only one subject with essential tremor experienced a serious adverse event (SAE) of transient confusion leading to discontinuation of study drug. No other SAEs have been reported in any study of SAGE-217.

Additional information on nonclinical and clinical data is provided in the [Investigator's Brochure](#).

### **5.3. Potential Risks and Benefits**

Nonserious events of sedation, somnolence, and dizziness were the most commonly reported AEs with SAGE-217. Given the outcome of the Phase 2a study of SAGE-217 in subjects with MDD, the current significant unmet need in the treatment of depression, and a favorable benefit-risk profile, further investigation of SAGE-217 in patients with MDD is justified.

### **5.4. Dose Justification**

There will be 2 dose levels of SAGE-217 in this study in order to study dose ranging: 30 mg per day and 20 mg per day. The higher dose level of 30 mg per day is the maximum tolerated dose in the multiple ascending dose study of SAGE-217 in healthy subjects and is also the dose level that was effective and generally well tolerated in a Phase 2 study in subjects with MDD (217-MDD-201). The lower dose of 20 mg per day will be studied in subjects with MDD for the first time in the current study and is anticipated to be well tolerated as it is lower than the maximum tolerated dose level. Due to sedation/somnolence observed in previous clinical trials when administered in the morning, and improved tolerability when given in the evening, both doses of SAGE-217 will be administered in the evening in this study.

## **6. STUDY OBJECTIVES AND PURPOSE**

### **6.1. Study Objective**

#### **6.1.1. Primary Objective**

The primary objective is to evaluate the efficacy of SAGE-217 in the treatment of MDD compared to placebo.

#### **6.1.2. Secondary Objective(s)**

Secondary objectives are:

- To evaluate the effect of SAGE-217 on sleep
- To assess patient-reported outcome (PRO) measures as they relate to health-related quality of life

#### **6.1.3. Safety Objective**

The safety objective is to evaluate the safety and tolerability of SAGE-217.

[REDACTED]

### **6.2. Endpoints**

#### **6.2.1. Primary Endpoint**

The primary endpoint of this study is the change from baseline in the 17-item HAM-D total score at Day 15.

#### **6.2.2. Secondary Endpoint(s)**

- Change from baseline in the 17-item HAM-D total score at other time points
- HAM-D response at Day 15 and all other time points, defined as a  $\geq 50\%$  reduction in HAM-D score from baseline
- HAM-D remission at Day 15 and all other time points, defined as HAM-D total score  $\leq 7$
- CGI-I response at Day 15 and all other time points, defined as “much improved” or “very much improved”
- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at Day 15 and all other time points



## **7. INVESTIGATIONAL PLAN**

### **7.1. Overall Study Design**

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD (HAM-D total score  $\geq 22$ ). The study will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, and a 4-week Follow-up Period.

The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. At the time of providing informed consent for the study, subjects will also be asked to authorize that their unique subject identifiers be entered into a registry ([www.subjectregistry.com](http://www.subjectregistry.com)) with the intent of identifying subjects who may meet exclusion criteria due to participation in another clinical study (Section 8.2).

The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and DSM-5 Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the HAM-D and CGI-S.

Antidepressants are permitted provided subjects are on a stable dose for at least 60 days prior to Day 1 and agree to continue on the stable dose through the follow-up period (Day 42). Initiation of new antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints is prohibited between screening and completion of the Day 42 assessments.

Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) and randomized within each stratum to one of 3 treatment groups (SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo) in a 1:1:1 ratio. Subjects will self-administer a single dose of study drug with food once daily in the evening on an outpatient basis, for 14 days. Dose reductions are not permitted. Study drug administration will be monitored via a clinical monitoring service (see Section 9.3).

Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 1.

### **7.2. Number of Subjects**

Approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects (see Section 13.8).

### **7.3. Treatment Assignment**

Subjects will be randomly assigned to a treatment group on Day 1. Randomization will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline and performed within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo.

#### **7.4. Dose Adjustment Criteria**

Dose adjustments are not permitted in this study. Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated (see Section 8.3).

#### **7.5. Criteria for Study Termination**

Sage Therapeutics may 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 subjects, 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 ethics committee and initiate withdrawal procedures for participating subjects.

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

### 8.1. Subject Inclusion Criteria

Qualified subjects will meet all of the following criteria:

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a HAM-D total score of  $\geq 22$  at screening and Day 1 (prior to dosing).
7. Subjects taking psychotropic medications used to treat major depressive disorder (eg, antidepressants, atypical antipsychotics) must have been taking these medications at the same dose for at least 60 days prior to Day 1.
8. Subjects taking benzodiazepines or GABA<sub>A</sub> modulators for insomnia (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) have had these medications discontinued by Day -14.
9. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, until after study completion.
10. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH]  $>40$  mIU/mL) and/or surgically sterile (hysterectomy or bilateral oophorectomy):
  - 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/occlusion.
  - Vasectomized partner.
  - Sexual abstinence (no sexual intercourse).
11. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug. Acceptable methods of effective contraception for males includes sexual abstinence, vasectomy, or a condom with spermicide used together with highly effective female

contraception methods if the female partner is of child-bearing potential (see Inclusion Criteria #9 for acceptable contraception methods).

12. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
13. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

## **8.2. Subject Exclusion Criteria**

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

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from two different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.
5. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
6. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.
7. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
8. Subject has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
9. Subject has active psychosis per Investigator assessment.
10. Subject has a medical history of seizures.
11. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.

12. Subject 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.
13. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
14. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
15. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to the first dose of study drug.
16. Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
17. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
18. Subject plans to undergo elective surgery during participation in the study.
19. Subject is taking benzodiazepines or GABA<sub>A</sub> modulators at Day -14.

### **8.3. Subject Withdrawal Criteria**

Subjects may withdraw from the study drug or terminate from the study at any time for any reason. The Investigator may withdraw the subject from the study drug or from the study for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol
- The subject experiences an intolerable AE
- Other medical or safety reason, at the discretion of the Investigator and/or the Medical Monitor

The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject withdraws from study drug or terminates the study for any reason. The reason must be recorded in the subject's electronic case report form (eCRF).

If a subject is persistently noncompliant, the Investigator should discuss with the Sponsor the potential discontinuation of the subject. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the subject's eCRF, including:

- missed visits;
- interruptions in the schedule of study drug administration;
- non-permitted medications (see Section 9.2).

Subjects 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.

Subjects who discontinue study drug early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place every 7 days after the last dose of treatment for 28 days. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for the ET visit will be conducted.

A subject will be deemed lost to follow-up after attempts at contacting the subject have been unsuccessful.

### **8.3.1. Replacement of Subjects**

Subjects will not be replaced. Additional subjects may be randomized if the drop-out rate is higher than anticipated (Section [13.8](#)).

## **9. TREATMENT OF SUBJECTS**

### **9.1. Study Drug**

Subjects will self-administer SAGE-217 (20 or 30 mg) or matching placebo orally once daily in the evening with food for 14 days.

### **9.2. Prior Medications, Concomitant Medications, and Restrictions**

#### **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 Screening and throughout the duration of the study will be recorded. In addition, psychotropic medications taken 6 months prior to Screening will be recorded.

Any medication and/or supplement determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study.

Antidepressants or atypical antipsychotics that have been taken at the same dose for at least 60 days prior to Day 1 are permitted if the subject intends to continue the stable dose through the follow-up period (Day 42).

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

- 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**

The following specific classes of medications are prohibited at any time during the treatment period:

- Initiation of new psychotropic medications
- Use of any benzodiazepines, GABA<sub>A</sub> modulators, or GABA<sub>A</sub>-like acting drugs
- Exposure to another investigational medication or device
- Any known strong inhibitors CYP3A4
- Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort.

### **9.2.3. Other Restrictions**

The consumption of grapefruit juice, grapefruit, or Seville oranges, or products containing these is prohibited throughout the treatment period.

Consumption of alcohol or use of drugs of abuse is discouraged throughout the duration of the study.

Female subjects 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 study drug.

### **9.3. Treatment Adherence**

SAGE-217 or placebo will be self-administered by subjects once daily in the evening with food. Sites will dispense study drug to the subjects to take at home with instructions for use (see Section 10.4 and Table 1).

Administration of study drug will be monitored by a medication adherence monitoring platform used on smartphones to visually confirm medication ingestion. Subjects will receive a reminder within a predefined time window to take study drug while using the application. Subjects 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 study drug administration by dose level, as well as missed doses.

In addition, the subject will be instructed to bring their dosing kit to the site as outlined in Table 1, 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 subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

The Investigator(s) will record any reasons for non-compliance in the source documents.

### **9.4. Randomization and Blinding**

This is a randomized double-blind, placebo-controlled study. Subjects who meet the entrance criteria will be randomized in a stratified manner based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline; randomization will be done within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matched placebo. Subjects, 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 (SAGE-217 20 mg, SAGE-217 30 mg, or placebo) 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.

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IRT (see Section 12.6 for more details related to unblinding).

## **10. STUDY DRUG MATERIALS AND MANAGEMENT**

### **10.1. Description of Study Drug**

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 (SMCC), colloidal silicon dioxide, and sodium stearyl fumarate as excipients. Colloidal silicon dioxide may be either a component of the SMCC or a standalone excipient in the formulation. 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. Study Drug 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 study drug in appropriately labeled, subject-specific kits containing sealed unit doses. Each unit dose consists of 1 capsule. Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Study drug 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. Study Drug Storage**

SAGE-217 and matched placebo 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. Study Drug Preparation**

Not applicable.

### **10.5. Study Drug Administration**

SAGE-217 is to be administered orally once daily in the evening with food. If a subject misses a dose, the subject 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. Study Drug Accountability**

Upon receipt of study drug, the Investigator(s), or the responsible pharmacist or designee, will inspect the study drug and complete and follow the instructions regarding receipt 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 subject-specific kits to subjects at the planned dispensation visit intervals outlined in [Table 1](#).

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

At the subsequent study drug-dispensing visit, the investigator or designee will access the IRT, providing the same subject ID number assigned at Screening, to obtain the medication ID number for the study drug to be dispensed at that visit. The medication ID number, the number of capsules dispensed, and the number of capsules returned by the subject 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 study drug provided is for use only as directed in this protocol. After the study is completed, all unused study drug must be returned as directed or destroyed on site per the Sponsor's instructions. The Investigator or designee must keep a record of all study drug received, dispensed and discarded.

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

### **10.7. Study Drug Handling and Disposal**

At the end of the study, all used and unused study drug will be reconciled and returned to Sage Therapeutics for destruction or destroyed locally; disposition of study drug will be documented.

A copy of the inventory record and a record of any clinical supplies that have been received, dispensed or destroyed must be documented by the site as directed. This documentation must include at least the information below:

- the number of dispensed units;
- the number of unused units;
- the number of units destroyed at the end of the study;
- the date, method and location of destruction.

## 11. ASSESSMENT OF EFFICACY [REDACTED]

All assessments will be conducted according to the schedule of assessments (Table 1). Study assessments that involve subject 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. Efficacy Assessments

#### 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 subject. An assessment timeframe of 7 days 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 subjects 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 of  $\leq 7$ .

#### 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 subjects 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 Impression (CGI)**

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 subject'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 subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject 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 subject's condition posttreatment. The Investigator will rate the subject'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. Short Form-36 Version 2 (SF-36v2)**

The Medical Outcomes Study SF-36v2 is a 36-item measure of health status that has undergone validation in many different disease states (Ware 2007). The SF-36v2 covers eight health dimensions including four physical health status domains (physical functioning, role participation with physical health problems [role-physical], bodily pain, and general health) and four mental health status domains (vitality, social functioning, role participation with emotional health problems [role-emotional], and mental health). In addition, two summary scores, physical component summary and mental component summary, are produced by taking a weighted linear combination of the eight individual domains. The SF-36v2 is available with two recall periods: the standard recall period is 4 weeks and the acute recall period is 1 week. This study will use the acute version, which asks patients to respond to questions as they pertain to the past week. Higher SF-36v2 scores indicate a better state of health.

#### **11.1.6. Insomnia Severity Index (ISI)**

The ISI is a validated questionnaire designed to assess the nature, severity, and impact of insomnia (Morin 2011). The ISI uses a 5-point Likert Scale to measure various aspects of insomnia severity (0 = none, 1 = mild, 2 = moderate; 3 = severe; 4 = very severe), satisfaction with current sleep pattern (0 = very satisfied, 1 = satisfied, 2 = neutral, 3 = dissatisfied, 4 = very dissatisfied), and various aspects of the impact of insomnia on daily functioning (0 = not at all, 1 = a little, 2 = somewhat, 3 = much, 4 = very much). A total score of 0 to 7 = "no clinically significant insomnia," 8 to 14 = "subthreshold insomnia," 15 to 21 = "clinical insomnia (moderate severity)," and 22 to 28 = "clinical insomnia (severe)."

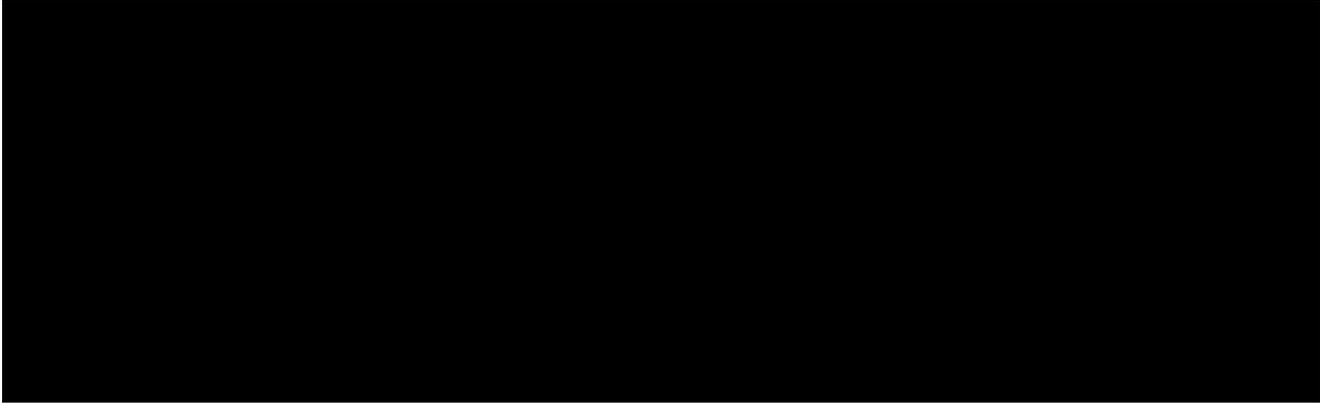
**11.1.7. Core Consensus Sleep Diary**

The Core Consensus Sleep Diary collects subjective sleep parameters, including sleep onset latency, total sleep time, and wake after sleep onset, number of awakenings, and sleep quality. The take-home subject sleep diary assessment will be administered using an eDiary solution. The eDiary will be captured using either a provisioned smartphone device or bring-your-own-device (BYOD) solution, depending on the subject's preference.

[REDACTED]

[REDACTED]

[REDACTED]



## **12. ASSESSMENT OF SAFETY**

### **12.1. Safety Parameters**

All assessments will be conducted according to the schedule of assessments ([Table 1](#)).

#### **12.1.1. Demographic/Medical History**

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including family psychiatric history, will be documented. The diagnosis of MDD will be determined using the SCID-5-CT. If available, the disease code associated with the diagnosis of MDD based on the 10<sup>th</sup> revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used to determine whether the subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment during the current major depressive episode with adequate doses of antidepressants from two different classes for at least 4 weeks of treatment.

#### **12.1.2. Weight and Height**

Height (Screening only) and weight will be measured and documented.

#### **12.1.3. Physical Examination**

Physical examinations assessing body systems (eg, head, eyes, ears, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Whenever possible, the same individual is to perform all physical examinations for a given subject. Unscheduled brief, symptom-driven physical examinations may also be conducted per the Investigator's discretion.

Any abnormality in physical examinations will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section [12.2.1.1](#).

#### **12.1.4. Vital Signs**

Vital signs comprise both supine and standing for systolic and diastolic blood pressure and heart rate measurements. Heart rate and blood pressure are to be collected in supine position after the subject has been resting for 5 minutes and then after 1 minute in the standing position.

Respiratory rate, pulse oximetry and temperature are collected once, in either position. Vital signs will be documented. When vital signs are scheduled at the same time as blood draws, vital signs will be obtained first.

Any abnormality in vital signs will be interpreted by the Investigator as abnormal, NCS or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section [12.2.1.1](#).

### 12.1.5. Electrocardiogram (ECG)

Supine 12-lead ECGs 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.

### 12.1.6. Laboratory Assessments

Samples will be collected in accordance with acceptable laboratory procedures detailed in the laboratory manual.

The clinical laboratory tests to be performed are listed in [Table 3](#).

**Table 3: Clinical Laboratory Tests**

| Hematology                               | Serum Chemistry             | Urinalysis         | Coagulation                           |
|--|-----------------------------|--------------------|---------------------------------------|
| Red blood cell count                     | Alanine aminotransferase    | pH                 | Activated partial thromboplastin time |
| Hemoglobin                               | Albumin                     | Specific gravity   |                                       |
| Hematocrit                               | Alkaline phosphatase        | Protein            | Prothrombin time                      |
| White blood cell count with differential | Aspartate aminotransferase  | Glucose            |                                       |
| Platelet count                           | Total bilirubin             | Red blood cell     | International normalized ratio        |
| Red blood cell morphology                | Direct bilirubin            | Nitrite            |                                       |
|  | Indirect bilirubin          | Leukocyte esterase |                                       |
|  | Total protein               | Ketones            |                                       |
|  | Creatinine                  | Bilirubin          |                                       |
|  | Blood urea nitrogen         | Urobilinogen       |                                       |
|  | Creatine kinase             |                    |                                       |
|  | Gamma-glutamyl transferase  |                    |                                       |
|  | Potassium                   |                    |                                       |
|  | Sodium                      |                    |                                       |
|  | Lactate dehydrogenase       |                    |                                       |
|  | Glucose                     |                    |                                       |
|  | Chloride                    |                    |                                       |
|  | Bicarbonate                 |                    |                                       |
|  | Calcium                     |                    |                                       |
|  | Phosphorus                  |                    |                                       |
|  | Triglycerides               |                    |                                       |
|  | Thyroid stimulating hormone |                    |                                       |

**Table 3: Clinical Laboratory Tests (Continued)**

| Hematology   | Serum Chemistry  | Urinalysis          | Coagulation |
|--|--|---------------------|-------------|
| <b>Diagnostic</b>  |  |                     |             |
| <b>Serum</b>   | <b>Urine</b>   | <b>Breathalyzer</b> |             |
| Hepatitis B<br>Hepatitis C<br>Reflex HCV RNA<br>HIV-1 and -2<br>Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: serum hCG<br>Female subjects, if menopause is suspected and not surgically sterile: FSH | Drug screen including:<br>amphetamines,<br>barbiturates,<br>benzodiazepines,<br>cannabinoids, cocaine,<br>opiates, phencyclidine, and propoxyphene<br><br>Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: urine hCG | Alcohol             |             |

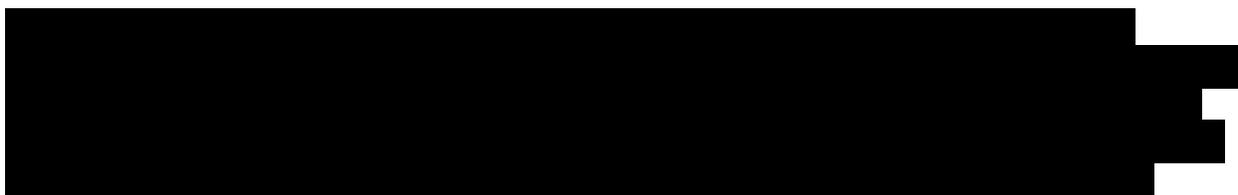
Abbreviations: FSH = follicle stimulating hormone; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus

The central laboratory will perform laboratory tests for hematology, serum chemistry, urinalysis, and coagulation. The results of laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to Sage Therapeutics or designee in the format requested by Sage Therapeutics.

Laboratory reports must be signed and dated by the Investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will require clear and complete documentation in the source documents as to the investigator’s assessment of not clinically significant before proceeding with randomization.

All clinical laboratory test results outside the central laboratory’s reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.1. A clinically significant laboratory abnormality following subject randomization will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

A serum follicle stimulating hormone test will be conducted at Screening to confirm whether a female subject with  $\geq 12$  months of spontaneous amenorrhea meets the protocol-defined criteria for being post-menopausal (Section 8.1).





#### **12.1.6.1. Drugs of Abuse and Alcohol**

Urine toxicology tests will be performed for selected drugs of abuse (see [Table 3](#)). A breath test for alcohol will be performed.

#### **12.1.6.2. Pregnancy Screen**

For female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at all other scheduled timepoints thereafter, including the ET visit for subjects who prematurely discontinue.

#### **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 subject with suicidal ideation and behavior, and a post-baseline 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, as outlined in [Table 1](#).

### **12.2. Adverse and Serious Adverse Events**

#### **12.2.1. Definition of Adverse Events**

##### **12.2.1.1. Adverse Event (AE)**

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 an AE that occurs after the first administration of any study drug. The term study drug includes any Sage investigational product, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) and/or if the Investigator considers them to be clinically significant. Laboratory values and vital signs that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations 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 subject 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.

#### **12.2.1.2. Serious Adverse Event (SAE)**

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 subject or may require medical intervention to prevent one 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 subject 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 within 24 hours of first awareness (Section 12.5). All SAEs should be followed until the event resolved, the condition stabilized, was no longer considered clinically significant or the subject was lost to follow-up. Serious adverse events occurring after a subject's final visit (including the last follow-up visit) should be reported to Sage or designee only if the Investigator considers the SAE to be related to study treatment.

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject 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 subject'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 the

Investigator, between the subject’s consent to participate in the study and at the time of the procedure or treatment.

### 12.3. Relationship to Study Drug

The Investigator must make the determination of relationship to the study drug for each adverse event (not related, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as “not related.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered at least “possibly related.”

**Table 4: Relationship to Study Drug**

| <b>Relationship</b> | <b>Definition</b>  |
|---------------------|--|
| Not Related:        | No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject’s clinical state.  |
| Possibly Related:   | A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.<br>The reaction might have been produced by the subject’s clinical state or other modes of therapy administered to the subject, but this is not known for sure.    |
| Probably Related:   | A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.<br>The reaction cannot be reasonably explained by the known characteristics of the subject’s clinical state or other modes of therapy administered to the subject. |

If the relationship between the adverse event/serious adverse event and the investigational product is determined to be “possible” or “probable”, the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

### 12.4. Recording Adverse Events

Adverse events spontaneously reported by the subject 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, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study drug or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

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 12.2.1.2. An AE of severe intensity may not be considered serious.

If a female subject becomes pregnant during this study, pregnancy information must be collected and recorded on the Sage Therapeutics pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. The Investigator will also attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is participating in study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant female subjects.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication or a complication relating to the pregnancy occurs (e.g., spontaneous abortion). If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly/birth defects), the investigator should follow the procedures for reporting an SAE.

## 12.5. Reporting Serious Adverse Events

All SAEs must be reported to Sage, or designee, immediately. A written account of the SAE must be sent to Sage, or designee, within 24 hours of the first awareness of the event by the investigator and/or his staff. 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 Therapeutics, 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 case report form (CRF) and/or study file.

Any SAEs discovered by the Investigator after the designated follow up time for the study, should be promptly reported to Sage, or designee, according to the timelines noted above.

The contact information for reporting SAEs and/or pregnancies is located in the study reference manual.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the ethics committee 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. Ethics Committee (EC)/Institutional Review Boards (IRBs) will be notified of SAEs and/or SUSARs as required by local law. In addition, appropriate Sponsor Drug Safety and Pharmacovigilance personnel, or designee, will unblind SUSARs for the purpose of regulatory reporting. The Sponsor, or

designee, will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. The Sponsor, or designee, will submit SUSARs to investigators in a blinded fashion.

## **12.6. Emergency Identification of Study Drug**

During the study, the blind is to be broken by the Investigator only when the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. Unless a subject is at immediate risk, the Investigator must make diligent attempts to contact Sage prior to unblinding the study treatment administered to a subject. Any request from the Investigator about the treatment administered to study subjects must be discussed with Sage. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented in the source records. Unless a subject is at immediate risk, any request for the unblinding of individual subjects must be made in writing to Sage and approved by the appropriate Sage personnel, according to standard operating procedures.

In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the eCRF. If the subject or study center personnel have been unblinded, the subject will be permanently discontinued from the study.

### **13. STATISTICS**

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the clinical study report.

#### **13.1. Data Analysis Sets**

The Randomized set, defined as all subjects who are randomized, will be used for all data listings, unless otherwise specified.

The Safety Set, defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects in the Safety Set with at least 1 post-baseline HAM-D evaluation, will be used for analysis of efficacy data.



#### **13.2. Handling of Missing Data**

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data. A sensitivity analysis will be used to investigate the impact of missing data if  $\geq 5\%$  of subjects in any treatment group have missing data.

#### **13.3. General Considerations**

For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), 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 (Section 12.1.1) and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized using the Safety Set.

Hepatitis, HIV, drug and alcohol, and pregnancy screening results will be listed, but not summarized as they are considered part of the inclusion/exclusion criteria.

Medical/family history will be listed by subject.

### **13.5. Efficacy Analyses**

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment.

The primary efficacy endpoint, the change from baseline to each assessment in HAM-D total score, 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 post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. The Toeplitz or compound symmetry covariance structure will be used if there is a convergence issue with the unstructured covariance model.

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, SF-36v2 score, sleep endpoints (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO), ISI score and selected individual items and/or subscale scores.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as  $\geq 50\%$  reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of  $\leq 7.0$ ). 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 the 15-day time point. 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 including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.



### **13.6. Safety Analyses**

Safety and tolerability of study drug will be evaluated by incidence of adverse events/serious adverse events, concomitant medication usage, vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Safety data will be listed by subject and summarized by treatment group. All safety summaries will be performed on the Safety Set. Where applicable, ranges of potentially clinically significant (PCS) values are provided in the SAP.

#### **13.6.1. Adverse Events**

The analysis of adverse events will be based on the concept of TEAEs. The incidence of TEAEs will be summarized overall and by Medical Dictionary for Regulatory Activities (MedDRA)

Version 18.1 or higher, System Organ Class (SOC), and preferred term. Incidences will be presented in order of decreasing frequency. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 12.3).

Any TEAEs leading to discontinuation and SAEs with onset after the start of study drug will also be summarized.

All AEs and SAEs (including those with onset or worsening before the start of study drug) 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 range of each parameter is provided by the laboratory; shift from baseline to post-baseline values in abnormality of results will be provided. Potentially clinically significant values will be summarized by treatment. Any abnormal values deemed clinically significant by the investigator will be reported as an AE (see Section 12.2). Clinical laboratory results will be listed by subject and timing of collection.

### **13.6.3. Physical Examinations**

The occurrence of a physical examination (Y/N) and the date performed will be listed by subject. Any clinically significant observation in physical examination will be reported as an AE (see Section 12.2).

### **13.6.4. Vital Signs**

Results from each visit and mean changes from baseline in vital signs will be summarized by scheduled visit. Any abnormality deemed clinically significant by the investigator will be reported as an AE (see Section 12.2). Potentially clinically significant values will be summarized by treatment. Vital sign results will be listed by subject 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 subject: 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 subject 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 signing the ICF through the duration of the study will be recorded. In addition, all psychotropic medications taken 6 months prior to Screening will be recorded. Those medications taken prior to the initiation of the start of study drug will be denoted "Prior". Those medications taken prior to the initiation of the study drug and continuing beyond the initiation of the study drug or those medications started at the same time or after the

initiation of the study drug will be denoted “Concomitant” (ie, those with a start date on or after the first dose of study drug, or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug).

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 subject, 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 summarized by treatment. Listings will include all data, including behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

[REDACTED]

### **13.8. Determination of Sample Size**

Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable subjects 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 SD of 10 points. Assuming an 11% dropout rate and a 1:1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 450 total randomized subjects will be required to obtain 399 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is greater than 11%.

## **14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **14.1. Study Monitoring**

Before an investigational site can enter a subject into the study, a representative of Sage Therapeutics (or designee) 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 investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject'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 subject (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.

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

### **14.2. Audits and Inspections**

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics audit or 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, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

### **14.3. Institutional Review Board (IRB) or Ethics Committee (EC)**

The Principal Investigator must obtain IRB (or EC) approval for the investigation. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the subject 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 Practices and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit. Please see Section [14.2](#) for more details regarding the audit process.

## **16. ETHICS**

### **16.1. Ethics Review**

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or EC as appropriate. The investigator must submit written approval to Sage Therapeutics before he or she can enroll any subject into the study.

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

The Principal Investigator is also responsible for providing the IRB 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 EC according to local regulations and guidelines.

### **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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines, as well as all applicable regulatory requirements.

### **16.3. Written Informed Consent**

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

## **17. DATA HANDLING AND RECORDKEEPING**

### **17.1. Inspection of Records**

Sage Therapeutics will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **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, whichever is longer. If not approved, documentation must be maintained for 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

## **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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## **Protocol 217-MDD-301 Amendment 1**

**Date of Amendment: 25 September 2018**

### **A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy of SAGE-217 in the Treatment of Adult Subjects with Major Depressive Disorder**

#### **Rationale for Protocol Amendment**

The primary purpose for this protocol amendment is to prohibit the concomitant use of benzodiazepines, GABA<sub>A</sub> modulators, or GABA<sub>A</sub>-like acting drugs with SAGE-217 treatment. Additional changes are being implemented as outlined below.

- Update terminology regarding timing of dosing ('bedtime' changed to 'evening')
- Clarify exclusion criteria regarding treatment-resistant depression
- Remove reticulocytes and propoxyphene from clinical laboratory assessments
- Update language for reporting SAEs
- Update language for reporting pregnancies, including partner pregnancies
- Correct an error regarding version of HAM-A scale to be used
- Prohibit breastfeeding during SAGE-217 treatment
- Correct a response category for the Insomnia Severity Index

A detailed summary of changes is provided in [Table 1](#). Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed individually, nor are administrative updates such as revising the document date, updating the document header and version number, and updating the table of contents.

**Table 1: Protocol Amendment 1 Detailed Summary of Changes**

The primary section of the protocol affected by the changes in Protocol Amendment 1 is indicated. The corresponding related text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

---

**Purpose:** Prohibit the concomitant use of benzodiazepines, GABA<sub>A</sub> modulators, or GABA<sub>A</sub>-like acting drugs with SAGE-217 treatment

---

The primary change occurs in 9.2.2. Prohibited Medications

Changed text:           The following specific classes of medications are prohibited at any time during the treatment period:

- Initiation of new psychotropic medications
- **Use of any benzodiazepines, GABA<sub>A</sub> modulators, or GABA<sub>A</sub>-like acting drugs**
- Exposure to another investigational medication or device
- Any known strong inhibitors CYP3A4
- Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort.

Sections also affected by this change:

- Synopsis, 8.1. Subject Inclusion Criteria (updated #7, added new #8), 8.2. Subject Exclusion Criteria (added #19), 9.2.1 Prior and Concomitant Medications and/or Supplements

---

**Purpose:** Update terminology regarding timing of dosing

The primary change occurs in Section 9.1 Study Drug

Changed text:           Subjects will self-administer SAGE-217 (20 or 30 mg) or matching placebo orally once daily **in the evening** ~~at bedtime~~ with food for 14 days.

Sections also affected by this change:

- Synopsis, 5.4.Dose Justification, 7.1. Overall Study Design, 9.3. Treatment Adherence, 10.5. Study Drug Administration
-

**Purpose:** Clarify exclusion criteria regarding treatment-resistant depression

The primary change occurs in Section 8.2. Subject Exclusion Criteria #4

Changed text:           4. Subject has ~~a history of~~ treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants **within the current major depressive episode** (excluding antipsychotics) from two different classes for ~~an adequate amount of time (ie, at least 4 weeks of treatment)~~. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.

Sections also affected by this change:

- Synopsis, Section 12.1.1. Demographic/Medical History
- 

**Purpose:** Remove reticulocytes from clinical laboratory assessments

The primary change occurs in Table 3 ‘Clinical Laboratory Tests’

---

Changed text:           Hematology  
Red blood cell count  
Hemoglobin  
Hematocrit  
White blood cell count with differential  
~~Reticulocytes~~  
Platelet count  
Red blood cell morphology

Sections also affected by this change:

- Not applicable
-

Purpose: Update language for reporting SAEs to be consistent with current program standards

---

The primary change occurs in 12.2.1.2. Serious Adverse Event (SAE)

---

Changed text: All SAEs that occur after any subject 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 **within 24 hours of first awareness (Section 12.5). All SAEs should to be followed until the event resolved, the condition stabilized, was no longer considered clinically significant or the subject was lost to follow-up.** Serious adverse events occurring after a subject's final visit (including the last follow-up visit) should be reported to Sage or designee only if the Investigator considers the SAE to be related to study treatment.

Sections also affected by this change:

- Not applicable
- 

Purpose: Update language for reporting pregnancies, including partner pregnancies to be consistent with current program standards

---

The primary change occurs in Section 12.4. Recording Adverse Events

---

Formerly read: **If a female subject becomes pregnant during this study, pregnancy information must be collected and recorded on the Sage Therapeutics pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. The Investigator will also attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is participating in study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant female subjects.** ~~Should a pregnancy occur, it must be reported and recorded on the Sage Therapeutics pregnancy notification form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.~~  
The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented ~~on the Sage Therapeutics pregnancy outcome form,~~ even if the subject was discontinued from the study. **If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs.**  
**Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication or a complication relating to the pregnancy occurs (e.g., spontaneous abortion). If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly/birth defects), the investigator should follow the procedures for reporting an SAE.**

Now reads: If a female subject becomes pregnant during this study, pregnancy information must be collected and recorded on the Sage Therapeutics pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. The Investigator will also attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is participating in study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant female subjects.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication or a complication relating to the pregnancy occurs (e.g., spontaneous abortion). If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly/birth defects), the investigator should follow the procedures for reporting an SAE.

Sections also affected by this change:

- Not applicable

---

Purpose: Correct an error regarding version of HAM-A scale to be used

---

The primary change occurs in footnote 'o' in Table 1 'Schedule of Events'

---

Changed text: The assessment timeframe for HAM-D and ~~HAM-A~~ 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 scale will refer to the past 7 days (1 week) at all visits.**

Sections also affected by this change:

- Not applicable
-

Purpose: Prohibit breastfeeding during SAGE-217 treatment

---

The primary change occurs in Section 9.2.3. Other Restrictions

---

Added text: **Female subjects 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 study drug.**

Sections also affected by this change:

- Synopsis, 8.2. Subject Exclusion Criteria
- 

Purpose: Correct a response category for the Insomnia Severity Index

---

The primary change occurs in Section 11.1.6. Insomnia Severity Index (ISI)

---

Changed text: The ISI is a validated questionnaire designed to assess the nature, severity, and impact of insomnia (Morin 2011). The ISI uses a 5-point Likert Scale to measure various aspects of insomnia severity (0 = none, 1 = mild, 2 = moderate; 3 = severe; 4 = very severe), satisfaction with current sleep pattern (0 = very satisfied, 1 = satisfied, 2 = ~~moderately satisfied~~**neutral**, 3 = dissatisfied, 4 = very dissatisfied), and various aspects of the impact of insomnia on daily functioning (0 = not at all, 1 = a little, 2 = somewhat, 3 = much, 4 = very much). A total score of 0 to 7 = “no clinically significant insomnia,” 8 to 14 = subthreshold insomnia,” 15 to 21 = “clinical insomnia (moderate severity),” and 22 to 28 = “clinical insomnia (severe).”

Sections also affected by this change:

- Not applicable
-



**STUDY TITLE: A PHASE 3, MULTICENTER, DOUBLE-  
BLIND, RANDOMIZED, PLACEBO-CONTROLLED  
STUDY EVALUATING THE EFFICACY OF SAGE-217  
IN THE TREATMENT OF ADULT SUBJECTS WITH  
MAJOR DEPRESSIVE DISORDER**

**PROTOCOL NUMBER: 217-MDD-301**

|                           |  |
|---------------------------|--|
| Study Drug                | SAGE-217   |
| Clinical Phase            | Phase 3  |
| Sponsor                   | Sage Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 |
| Sponsor Contact           | [REDACTED]<br>Tel: [REDACTED]<br>email: [REDACTED]                 |
| Sponsor Medical Monitor   | [REDACTED] MD, MBA<br>Tel: [REDACTED]<br>emai [REDACTED]           |
| Date of Original Protocol | Version 1.0, 16 JUL 2018   |
| Date of Amendment 1       | Version 2.0, 25 SEP 2018   |
| Date of Amendment 2       | Version 3.0, 11 OCT 2018   |

**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.

**Protocol Number:** 217-MDD-301  
**Study Drug:** SAGE-217  
**Study Phase:** Phase 3  
**Sponsor:** Sage Therapeutics, Inc.  
**Protocol Date:** Version 3.0, 11 OCT 2018

**Sponsor Approval**

|                         |                    |
|-------------------------|--------------------|
| [Redacted]              | [Redacted]         |
| [Redacted] MD, MBA      | Date (DD MMM YYYY) |
| Sage Therapeutics       |                    |
| [Redacted]              | [Redacted]         |
| [Redacted] DVM, MS, MPH | Date (DD MMM YYYY) |
| Sage Therapeutics       |                    |
| [Redacted] RAC          | Date (DD MMM YYYY) |
| Sage Therapeutics       |                    |
| [Redacted]              | [Redacted]         |
| [Redacted]              | Date (DD MMM YYYY) |
| Sage Therapeutics       |                    |
| [Redacted] PhD          | Date (DD MMM YYYY) |
| Sage Therapeutics       |                    |
| [Redacted]              | [Redacted]         |
| [Redacted]              | Date (DD MMM YYYY) |
| Sage Therapeutics       |                    |

## INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-MDD-301 clinical 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

---

Date (DD Month YYYY)



- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at Day 15 and all other time points
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at Day 15 and all other time points
- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15 and all other time points
- Change from baseline in HAM-D subscale and individual item scores at all time points
- Change in sleep at Day 15 and all other time points, as assessed by
  - Insomnia Severity Index (ISI)
  - Subjective sleep parameters collected with the Core Consensus Sleep Diary
- Change from baseline in PRO measures of health-related quality of life, as assessed by responses to the 36-item Short Form survey version 2 (SF-36v2), and of depressive symptoms, as assessed by the 9-item Patient Health Questionnaire

**Safety Endpoints:**

- Incidence and severity of adverse events/serious adverse events
- Changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs)
- Suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Potential withdrawal symptoms using the 20-item Physician Withdrawal Checklist (PWC-20)

**Study Description:**

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD (MADRS total score  $\geq 30$ ). Randomization will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline and carried out within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo; subjects will be treated for 14 days beginning on Day 1.

The study will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, and a 4-week Follow-up Period.

The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the MADRS and CGI-S.

Antidepressants are permitted provided subjects are on a stable dose for at least 60 days prior to Day 1 and agree to continue on the stable dose through the follow-up period (Day 42). Initiation of new antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of the Day 42 assessments.

Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) and randomized within each stratum to one of 3 treatment groups (SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo) in a 1:1:1 ratio. Subjects will self-administer a single dose of study drug once daily in the evening with food, on an outpatient basis, for 14 days. Practical options include taking SAGE-217 within 1 hour of dinner or taking SAGE-217 later in the evening with solid food. Subjects will return to the study center during the treatment and follow-up periods as outlined in [Table 1](#).

Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated. Subjects who discontinue treatment early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place every 7 days after the last dose of treatment for a total of 4 follow-up visits. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for both visits will be conducted.

**Number of Subjects (planned):**

Approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects.

**Eligibility Criteria:**

**Inclusion Criteria:**

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is a male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a MADRS total score of  $\geq 30$  at screening and Day 1 (prior to dosing).
7. Subjects taking psychotropic medications used to treat major depressive disorder (eg, antidepressants, atypical antipsychotics) must have been taking these medications at the same dose for at least 60 days prior to Day 1.
8. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, until after study completion.
9. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative

medical cause and confirmed by follicle stimulating hormone [FSH] >40 mIU/mL), surgically sterile (hysterectomy or bilateral oophorectomy), or in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s)):

- 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/occlusion
  - Vasectomized partner
  - Sexual abstinence (no sexual intercourse)
10. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, unless the subject is in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s)). Acceptable methods of effective contraception for males includes sexual abstinence, vasectomy, or a condom with spermicide used together with highly effective female contraception methods if the female partner(s) is of child-bearing potential (see Inclusion Criteria #9 for acceptable contraception methods).
11. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
12. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

**Exclusion Criteria:**

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from two different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.
5. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.

7. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.
8. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
9. Subject has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
10. Subject has active psychosis per Investigator assessment.
11. Subject has a medical history of seizures.
12. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
13. Subject 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.
14. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
15. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
16. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to the first dose of study drug.
17. Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
18. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
19. Subject plans to undergo elective surgery during participation in the study.
20. Subject is taking benzodiazepines or GABA<sub>A</sub> modulators/GABA-containing agents (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28.
21. Subject is taking non-GABA anti-insomnia medications (eg melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) at Day -14.
22. Subject has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) within the past year prior to Screening.

23. Subject has a history of sleep apnea.

24. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.

**Study Drug, Dosage and Mode of Administration:**

SAGE-217 is available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose (SMCC), colloidal silicon dioxide and sodium stearyl fumarate as excipients. Colloidal silicon dioxide may be either a component of the SMCC or a standalone excipient in the formulation. SAGE-217 capsules will be orally administered as a 30-mg or 20-mg dose.

**Reference Therapy, Dosage, and Mode of Administration:**

Placebo will be provided as hard gelatin capsules for oral administration containing only the excipients listed above for the active capsule.

**Duration of Treatment:** 14 days

**Statistical methods:**

A 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 and treatment unblinding. Any deviations from or changes to the SAP following database lock will be described in detail in the Clinical Study Report.

**General Considerations**

For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration.

Continuous endpoints will be summarized descriptively with 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 Randomized Set, defined as all subjects who are randomized, will be used for all data listings, unless otherwise specified.

The Safety Set, defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects in the Safety Set with at least 1 post-baseline HAM D evaluation, will be used for analysis of efficacy data.

**Determination of Sample Size**

Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable subjects would provide 90% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation (SD) of 10 points. Assuming a 11% dropout rate and a 1:1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 450 total randomized subjects will be required to obtain 399 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have valid baseline and at

least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is greater than 11%.

#### **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 post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported 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, SF-36v2 score, PHQ-9 score, sleep endpoints (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score and selected individual items and/or subscale scores in HAM-D for change from baseline.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as  $\geq 50\%$  reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of  $\leq 7.0$ ). 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 the 15-day time point. 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 including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.

[REDACTED]

#### **Safety Analysis**

Safety and tolerability of study drug will be evaluated by incidence of adverse events/serious adverse events, concomitant medication usage, 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.

[REDACTED]

**Table 1: Schedule of Events**

| Visits                                       | Screening Period | Double-Blind, Placebo-Controlled Treatment Period |          |          |           |                                   | Follow-up Period |           |           |           |                 |
|--|------------------|---|----------|----------|-----------|-----------------------------------|------------------|-----------|-----------|-----------|-----------------|
|  |                  | D1  | D3 (±1d) | D8 (+1d) | D12 (±1d) | D15 (±1d) and/or EOT <sup>a</sup> | D18 (±1d)        | D21 (±1d) | D28 (±3d) | D35 (±3d) | D42 (±3d) or ET |
| Visit Days                                   | D-28 to D-1      | D1  | D3 (±1d) | D8 (+1d) | D12 (±1d) | D15 (±1d) and/or EOT <sup>a</sup> | D18 (±1d)        | D21 (±1d) | D28 (±3d) | D35 (±3d) | D42 (±3d) or ET |
| Visit Number                                 | V1               | V2  | V3       | V4       | V5        | V6                                | V7               | V8        | V9        | V10       | V11             |
| <b>Study Procedure</b>                       |                  |   |          |          |           |                                   |                  |           |           |           |                 |
| Informed Consent                             | X                |   |          |          |           |                                   |                  |           |           |           |                 |
| Duplicate Subject Check <sup>b</sup>         | X                |   |          |          |           |                                   |                  |           |           |           |                 |
| Inclusion/Exclusion                          | X                | X   |          |          |           |                                   |                  |           |           |           |                 |
| Serum FSH test <sup>c</sup>                  | X                |   |          |          |           |                                   |                  |           |           |           |                 |
| SCID-5-CT                                    | X                |   |          |          |           |                                   |                  |           |           |           |                 |
| MGH ATRQ                                     | X                |   |          |          |           |                                   |                  |           |           |           |                 |
| Demographics                                 | X                |   |          |          |           |                                   |                  |           |           |           |                 |
| Medical/Family History                       | X                |   |          |          |           |                                   |                  |           |           |           |                 |
| Subject training <sup>d</sup>                | X                | X   |          |          |           |                                   |                  |           |           |           |                 |
| Randomization                                |                  | X   |          |          |           |                                   |                  |           |           |           |                 |
| Physical Examination <sup>e</sup>            | X                | X   |          |          |           |                                   |                  |           |           |           | X               |
| Body Weight/Height                           | X                |   |          |          |           | X (wt only)                       |                  |           |           |           | X (wt only)     |
| Clinical Laboratory Assessments <sup>f</sup> | X                | X   |          | X        |           | X                                 |                  | X         | X         |           | X               |
| Drug & Alcohol Screen <sup>g</sup>           | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X         | X               |
| Pregnancy Test <sup>h</sup>                  | X                | X   |          |          |           | X                                 |                  |           | X         |           | X               |
| Hepatitis & HIV Screen                       | X                |   |          |          |           |                                   |                  |           |           |           |                 |
|  |                  |   |          |          |           |                                   |                  |           |           |           |                 |
| Vital Signs <sup>k</sup>                     | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X         | X               |
| 12-Lead ECG <sup>l</sup>                     | X                | X   |          |          |           | X                                 |                  |           |           |           | X               |
| C-SSRS <sup>m</sup>                          | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X         | X               |
| HAM-D <sup>n, o</sup>                        |                  | X   | X        | X        | X         | X                                 | X                | X         | X         | X         | X               |
| MADRS  | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X         | X               |
| HAM-A <sup>o</sup>                           |                  | X   |          | X        |           | X                                 | X                |           | X         |           | X               |

| Visits  | Screening Period | Double-Blind, Placebo-Controlled Treatment Period |             |             |              |  | Follow-up Period |              |              |              |                          |
|---|------------------|---|-------------|-------------|--------------|--|------------------|--------------|--------------|--------------|--------------------------|
|   |                  |   |             |             |              | D15<br>(±1d)<br>and/or<br>EOT <sup>a</sup> |                  |              |              |              | D42<br>(±3d)<br>or<br>ET |
| Visit Days  | D-28 to D-1      | D1  | D3<br>(±1d) | D8<br>(+1d) | D12<br>(±1d) |  | D18<br>(±1d)     | D21<br>(±1d) | D28<br>(±3d) | D35<br>(±3d) |                          |
| Visit Number  | V1               | V2  | V3          | V4          | V5           | V6   | V7               | V8           | V9           | V10          | V11                      |
| <b>Study Procedure</b>                                |                  |   |             |             |              |  |                  |              |              |              |                          |
| CGI-S   | X                | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        |
| CGI-I   |                  |   | X           | X           | X            | X  | X                | X            | X            | X            | X                        |
| SF-36v2   | X                | X   |             | X           |              | X  |                  |              | X            |              | X                        |
| PHQ-9   |                  | X   |             | X           |              | X  |                  | X            |              |              | X                        |
|   |                  |   |             |             |              |  |                  |              |              |              |                          |
| ISI   |                  | X   |             | X           |              | X  | X                | X            | X            |              | X                        |
| PWC-20  |                  | X   |             |             |              | X  | X                | X            |              |              |                          |
| Sleep diary <sup>p</sup>                              | X                |   |             |             |              |  |                  |              |              |              |                          |
|   |                  |   |             |             |              |  |                  |              |              |              |                          |
| Study Drug Dispensation                               |                  | X   |             | X           |              |  |                  |              |              |              |                          |
| Study Drug Administration                             |                  | X (Day 1 through Day 14)                          |             |             |              |  |                  |              |              |              |                          |
| Study Drug Accountability/Return                      |                  |   |             | X           |              | X  |                  |              |              |              | X <sup>r</sup>           |
| Adverse Events/SAEs <sup>s</sup>                      | X                |   |             |             |              |  |                  |              |              |              |                          |
| Prior/Concomitant Medications/Procedures <sup>t</sup> | X                |   |             |             |              |  |                  |              |              |              |                          |

CGI-I = Clinical Global Impression – Improvement; CGI-S – Clinical Global Impression – Severity; ██████████  
 ██████████ C-SSRS = Columbia Suicide Severity Rating Scale; D = day; EOT = end of  
 treatment; ET = early termination; ECG = electrocardiogram; ██████████ FSH = follicle  
 stimulating hormone; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item;  
 HIV = human immunodeficiency virus; ISI = Insomnia Severity Index; MADRS = Montgomery-Åsberg Depression Rating  
 Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; PHQ-9 = 9-item  
 Patient Health Questionnaire; PWC-20 = 20-item Physician Withdrawal Checklist; O = Optional; ██████████; SCID-  
 5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Clinical Trials  
 Version; SF-36v2 = 36-item Short Form survey version 2; V = visit; wt = weight

- <sup>a</sup> Subjects who discontinue treatment early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place every 7 days after the last dose of treatment for a total of 4 follow-up visits. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for both visits will be conducted.
- <sup>b</sup> Subjects will be asked to authorize that their unique subject identifiers be entered into a registry (www.subjectregistry.com) with the intent of identifying subjects who may meet exclusion criteria for participation in another clinical study.
- <sup>c</sup> A serum follicle stimulating hormone test will be conducted at Screening for female subjects that are not surgically sterile to confirm whether a female subject with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being post-menopausal.
- <sup>d</sup> Subjects will be trained on use of software applications and devices necessary for the conduct of the study by site personnel.

- <sup>e</sup> 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).
- <sup>f</sup> Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis.
- <sup>g</sup> Urine toxicology for selected drugs of abuse (as per the lab manual) and breath test for alcohol.
- <sup>h</sup> Serum pregnancy test at screening and urine pregnancy test thereafter for female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal.  
[REDACTED]
- <sup>k</sup> Vital signs include oral temperature (°C), respiratory rate, 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 subject has been resting for 5 minutes and then after 1 minute in the standing position. Vital signs may be repeated at the discretion of the Investigator as clinically indicated.
- <sup>l</sup> Triplicate ECGs will be collected. [REDACTED]
- <sup>m</sup> The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- <sup>n</sup> The HAM-D is to be completed as early during the visit as possible.
- <sup>o</sup> The assessment timeframe for HAM-D scales will refer to the past 7 days (1 week) at Day 1 and “Since Last Visit” for all other visits. The assessment timeframe for HAM-A scale will refer to the past 7 days (1 week) at all visits.
- <sup>p</sup> Subjects are instructed to complete the Core Consensus Sleep Diary starting at least 7 days prior to Day 1 and then daily through Day 28.  
[REDACTED]
- <sup>r</sup> To be performed at the ET visit only.
- <sup>s</sup> Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject’s participation in the study.
- <sup>t</sup> Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.

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**Table 2: Abbreviations and specialist terms (Continued)**

| <b>Abbreviation or specialist term</b> | <b>Explanation</b>   |
|--|--|
| MDD                                    | major depressive disorder  |
| MGH ATRQ                               | Massachusetts General Hospital Antidepressant Treatment Response Questionnaire |
| MMRM                                   | mixed effects model for repeated measures                                      |
| NCS                                    | not clinically significant   |
| PCS                                    | Potentially clinically significant   |
| PHQ-9                                  | 9-item Patient Health Questionnaire  |
| PK                                     | pharmacokinetic  |
| PRO                                    | patient-reported outcome   |
| PWC-20                                 | 20-item Physician Withdrawal Checklist   |
| 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   |
| SF-36v2                                | 36-item Short Form version 2   |
| SUSAR                                  | suspected, unexpected, serious, adverse reactions                              |
| TEAE                                   | treatment-emergent adverse event   |
| WHO                                    | World Health Organization  |

## 5. INTRODUCTION

### 5.1. Background of Major Depressive Disorder and Unmet Medical Need

The World Health Organization (WHO) has identified depression as the leading cause of disability worldwide, and as a major contributor to the overall global burden of disease (<http://www.who.int/mediacentre/factsheets/fs369/en/>). Globally, depression has been estimated to affect over 300 million people.

In the United States, the economic burden of depression, including workplace costs, direct costs and suicide-related costs, was estimated to be \$210.5 billion in 2010 ([Greenberg 2015](#)). As per WHO statistics, over 800,000 people die due to suicide every year, and suicide is the second leading cause of death in 15- to 29-year-olds. The rate of US adults making a suicide attempt has increased (0.62% from 2004 to 2005 to 0.79% from 2012 to 2013), with a shift to more attempts among younger adults (42% to 50%, respectively) and among those with a depressive disorder (26% to 54%, respectively; [Olfson 2017](#)).

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition ([DSM-5](#)), depression refers to an overarching set of diagnoses, including major depressive disorder (MDD). Diagnostic criteria for MDD includes a set of at least 5 depressive symptoms out of 9, including depressed mood and/or loss of interest or pleasure, and other changes affecting appetite or weight, sleep, psychomotor activity, energy level, feelings of guilt, concentration ability and suicidality during the same 2-week period, that represents a change from previous functioning ([DSM-5](#)).

Antidepressants are a mainstay of pharmacological treatment for depressive disorders. Selective serotonin uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other compounds that affect monoaminergic neurotransmission, such as mirtazapine and bupropion, represent the major classes of antidepressants. While antidepressants are widely used, large scale studies have demonstrated their limited efficacy, including low remission rates and untreated symptoms ([Trivedi 2006](#); [Conradi 2011](#); [Romera 2013](#)).

Converging preclinical and clinical evidence ([Gerner 1981](#); [Honig 1988](#); [Drugan 1989](#); [Luscher 2011](#); [Mann 2014](#)) implicates deficits in  $\gamma$ -aminobutyric acid (GABA)-ergic neurotransmission in the pathophysiology of depressive disorders including MDD. Furthermore, experimental data implicate deficiencies in the normal regulation of endogenous neuroactive steroids in depressive disorders ([Maguire 2008](#); [Maguire 2009](#)). Depressed patients show low levels of GABA in the brain and of neurosteroids in the cerebrospinal fluid (CSF) and plasma, and antidepressant therapy restores GABA levels in relevant animal models and neurosteroid concentrations in depressed patients ([Luscher 2011](#); [Schüle 2014](#)).

### 5.2. SAGE-217

SAGE-217 is a synthetic positive allosteric modulator of GABA<sub>A</sub> receptors, the major class of inhibitory neurotransmitter receptors in the brain. 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<sub>A</sub> receptors, and, consistent with the actions of other GABA<sub>A</sub> receptor potentiators ([Rudolph 2011](#)), exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo.

Data from an open-label Phase 2a study of SAGE-217 administered to subjects with moderate to severe MDD showed clinically significant improvements from baseline in depression and anxiety scale scores (Hamilton Rating Scale for Depression [HAM-D], Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Anxiety Rating Scale [HAM-A], and Clinical Global Impression – Improvement [CGI-I]) as early as Day 2 of the 14-day treatment period, with durable responses following the end of treatment. This result was further supported by the randomized, double-blind portion of this study including 89 subjects, in which a rapid and substantial decrease in HAM-D scores was observed at Day 15 (primary endpoint), starting at Day 2. This response pattern was also observed with other efficacy scales, including MADRS, CGI-I, and HAM-A.

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, and dizziness. Most adverse events (AEs) were reported as mild or moderate in intensity. Among the over 260 subjects exposed to SAGE-217 in clinical trials, there have been no deaths and only one subject with essential tremor experienced a serious adverse event (SAE) of transient confusion leading to discontinuation of study drug. No other SAEs have been reported in any study of SAGE-217.

Additional information on nonclinical and clinical data is provided in the [Investigator's Brochure](#).

### **5.3. Potential Risks and Benefits**

Nonserious events of sedation, somnolence, and dizziness were the most commonly reported AEs with SAGE-217. Given the outcome of the Phase 2a study of SAGE-217 in subjects with MDD, the current significant unmet need in the treatment of depression, and a favorable benefit-risk profile, further investigation of SAGE-217 in patients with MDD is justified.

### **5.4. Dose Justification**

There will be 2 dose levels of SAGE-217 in this study in order to study dose ranging: 30 mg per day and 20 mg per day. The higher dose level of 30 mg per day is the maximum tolerated dose in the multiple ascending dose study of SAGE-217 in healthy subjects and is also the dose level that was effective and generally well tolerated in a Phase 2 study in subjects with MDD (217-MDD-201). The lower dose of 20 mg per day will be studied in subjects with MDD for the first time in the current study and is anticipated to be well tolerated as it is lower than the maximum tolerated dose level. Due to sedation/somnolence observed in previous clinical trials when administered in the morning, and improved tolerability when given in the evening, both doses of SAGE-217 will be administered in the evening in this study.

## **6. STUDY OBJECTIVES AND PURPOSE**

### **6.1. Study Objective**

#### **6.1.1. Primary Objective**

The primary objective is to evaluate the efficacy of SAGE-217 in the treatment of MDD compared to placebo.

#### **6.1.2. Secondary Objective(s)**

Secondary objectives are:

- To evaluate the effect of SAGE-217 on sleep
- To assess patient-reported outcome (PRO) measures as they relate to health-related quality of life and depressive symptoms

#### **6.1.3. Safety Objective**

The safety objective is to evaluate the safety and tolerability of SAGE-217.

[REDACTED]

### **6.2. Endpoints**

#### **6.2.1. Primary Endpoint**

The primary endpoint of this study is the change from baseline in the 17-item HAM-D total score at Day 15.

#### **6.2.2. Secondary Endpoint(s)**

- Change from baseline in the 17-item HAM-D total score at other time points
- HAM-D response at Day 15 and all other time points, defined as a  $\geq 50\%$  reduction in HAM-D score from baseline
- HAM-D remission at Day 15 and all other time points, defined as HAM-D total score  $\leq 7$
- CGI-I response at Day 15 and all other time points, defined as “much improved” or “very much improved”
- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at Day 15 and all other time points



## **7. INVESTIGATIONAL PLAN**

### **7.1. Overall Study Design**

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD (MADRS total score  $\geq 30$ ). The study will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, and a 4-week Follow-up Period.

The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. At the time of providing informed consent for the study, subjects will also be asked to authorize that their unique subject identifiers be entered into a registry ([www.subjectregistry.com](http://www.subjectregistry.com)) with the intent of identifying subjects who may meet exclusion criteria due to participation in another clinical study (Section 8.2).

The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and DSM-5 Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the MADRS and CGI-S.

Antidepressants are permitted provided subjects are on a stable dose for at least 60 days prior to Day 1 and agree to continue on the stable dose through the follow-up period (Day 42). Initiation of new antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints is prohibited between screening and completion of the Day 42 assessments.

Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) and randomized within each stratum to one of 3 treatment groups (SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo) in a 1:1:1 ratio. Subjects will self-administer a single dose of study drug with food once daily in the evening on an outpatient basis, for 14 days. Dose reductions are not permitted. Study drug administration will be monitored via a clinical monitoring service (see Section 9.3).

Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 1.

### **7.2. Number of Subjects**

Approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects (see Section 13.8).

### **7.3. Treatment Assignment**

Subjects will be randomly assigned to a treatment group on Day 1. Randomization will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline and performed within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo.

#### **7.4. Dose Adjustment Criteria**

Dose adjustments are not permitted in this study. Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated (see Section 8.3).

#### **7.5. Criteria for Study Termination**

Sage Therapeutics may 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 subjects, 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 ethics committee and initiate withdrawal procedures for participating subjects.

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

### 8.1. Subject Inclusion Criteria

Qualified subjects will meet all of the following criteria:

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is a male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a MADRS total score of  $\geq 30$  at screening and Day 1 (prior to dosing).
7. Subjects taking psychotropic medications used to treat major depressive disorder (eg, antidepressants, atypical antipsychotics) must have been taking these medications at the same dose for at least 60 days prior to Day 1.
8. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, until after study completion.
9. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH]  $>40$  mIU/mL) and/or surgically sterile (hysterectomy or bilateral oophorectomy), or in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s)):
  - 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/occlusion.
  - Vasectomized partner.
  - Sexual abstinence (no sexual intercourse).
10. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, unless the subject is in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s)). Acceptable methods of effective contraception for males includes sexual abstinence, vasectomy, or a condom with spermicide used together with highly effective

female contraception methods if the female partner is of child-bearing potential (see Inclusion Criteria #9 for acceptable contraception methods).

11. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
12. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

## **8.2. Subject Exclusion Criteria**

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

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from two different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.
5. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
7. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.
8. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
9. Subject has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
10. Subject has active psychosis per Investigator assessment.
11. Subject has a medical history of seizures.

12. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
13. Subject 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.
14. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
15. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
16. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to the first dose of study drug.
17. Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
18. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
19. Subject plans to undergo elective surgery during participation in the study.
20. Subject is taking benzodiazepines or GABA<sub>A</sub> modulators/GABA-containing agents (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28.
21. Subject is taking non-GABA anti-insomnia medications (eg melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) at Day -14.
22. Subject has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) within the past year prior to Screening.
23. Subject has a history of sleep apnea.
24. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.

### **8.3. Subject Withdrawal Criteria**

Subjects may withdraw from the study drug or terminate from the study at any time for any reason. The Investigator may withdraw the subject from the study drug or from the study for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol
- The subject experiences an intolerable AE
- Other medical or safety reason, at the discretion of the Investigator and/or the Medical Monitor

The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject withdraws from study drug or terminates the study for any reason. The reason must be recorded in the subject's electronic case report form (eCRF).

If a subject is persistently noncompliant, the Investigator should discuss with the Sponsor the potential discontinuation of the subject. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the subject's eCRF, including:

- missed visits;
- interruptions in the schedule of study drug administration;
- non-permitted medications (see Section 9.2).

Subjects 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.

Subjects who discontinue study drug early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place every 7 days after the last dose of treatment for 28 days. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for the ET visit will be conducted.

A subject will be deemed lost to follow-up after attempts at contacting the subject have been unsuccessful.

### **8.3.1. Replacement of Subjects**

Subjects will not be replaced. Additional subjects may be randomized if the drop-out rate is higher than anticipated (Section 13.8).

## **9. TREATMENT OF SUBJECTS**

### **9.1. Study Drug**

Subjects will self-administer SAGE-217 (20 or 30 mg) or matching placebo orally once daily in the evening with food for 14 days.

### **9.2. Prior Medications, Concomitant Medications, and Restrictions**

#### **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 Screening and throughout the duration of the study will be recorded. In addition, psychotropic medications taken 6 months prior to Screening will be recorded.

Any medication and/or supplement determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study.

Antidepressants or atypical antipsychotics that have been taken at the same dose for at least 60 days prior to Day 1 are permitted if the subject intends to continue the stable dose through the follow-up period (Day 42).

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

- 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**

The following specific classes of medications are prohibited:

- Initiation of new psychotropic medications at any time during the study
- Initiation of new antidepressant therapy from 60 days prior to Day 1 through the duration of the study
- Use of any benzodiazepines, GABA<sub>A</sub> modulators, GABA<sub>A</sub>-like acting drugs, or GABA-containing agents from Day -28 through the duration of the study
- Use of any non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) from Day -14 through the duration of the study
- Exposure to another investigational medication or device from 30 days prior to Screening through the duration of the study

- Any known strong inhibitors CYP3A4 from Day -28 or 5 half-lives prior to Day 1 (whichever is longer) through the duration of the study
- Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort from Day -28 through the duration of the study.

### **9.2.3. Other Restrictions**

The consumption of grapefruit juice, grapefruit, or Seville oranges, or products containing these is prohibited throughout the treatment period.

Consumption of alcohol or use of drugs of abuse is discouraged throughout the duration of the study.

Female subjects 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 study drug.

Elective surgeries or procedures are prohibited during participation in the study.

### **9.3. Treatment Adherence**

SAGE-217 or placebo will be self-administered by subjects once daily in the evening with food. Sites will dispense study drug to the subjects to take at home with instructions for use (see Section 10.4 and Table 1).

Administration of study drug will be monitored by a medication adherence monitoring platform used on smartphones to visually confirm medication ingestion. Subjects will receive a reminder within a predefined time window to take study drug while using the application. Subjects 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 study drug administration by dose level, as well as missed doses.

In addition, the subject will be instructed to bring their dosing kit to the site as outlined in Table 1, 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 subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

The Investigator(s) will record any reasons for non-compliance in the source documents.

### **9.4. Randomization and Blinding**

This is a randomized double-blind, placebo-controlled study. Subjects who meet the entrance criteria will be randomized in a stratified manner based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline; randomization will be done within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matched placebo. Subjects, 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 (SAGE-217 20 mg, SAGE-217 30 mg, or placebo) 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.

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IRT (see Section 12.6 for more details related to unblinding).

## **10. STUDY DRUG MATERIALS AND MANAGEMENT**

### **10.1. Description of Study Drug**

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 (SMCC), colloidal silicon dioxide, and sodium stearyl fumarate as excipients. Colloidal silicon dioxide may be either a component of the SMCC or a standalone excipient in the formulation. 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. Study Drug 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 study drug in appropriately labeled, subject-specific kits containing sealed unit doses. Each unit dose consists of 1 capsule. Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Study drug 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. Study Drug Storage**

SAGE-217 and matched placebo 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. Study Drug Preparation**

Not applicable.

### **10.5. Study Drug Administration**

SAGE-217 is to be administered orally once daily in the evening with food. Practical options include taking SAGE-217 within 1 hour of dinner or taking SAGE-217 later in the evening with solid food. If a subject misses a dose, the subject 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. Study Drug Accountability**

Upon receipt of study drug, the Investigator(s), or the responsible pharmacist or designee, will inspect the study drug and complete and follow the instructions regarding receipt 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 subject-specific kits to subjects at the planned dispensation visit intervals outlined in [Table 1](#).

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

At the subsequent study drug-dispensing visit, the investigator or designee will access the IRT, providing the same subject ID number assigned at Screening, to obtain the medication ID number for the study drug to be dispensed at that visit. The medication ID number, the number of capsules dispensed, and the number of capsules returned by the subject 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 study drug provided is for use only as directed in this protocol. After the study is completed, all unused study drug must be returned as directed or destroyed on site per the Sponsor's instructions. The Investigator or designee must keep a record of all study drug received, dispensed and discarded.

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

### **10.7. Study Drug Handling and Disposal**

At the end of the study, all used and unused study drug will be reconciled and returned to Sage Therapeutics for destruction or destroyed locally; disposition of study drug will be documented.

A copy of the inventory record and a record of any clinical supplies that have been received, dispensed or destroyed must be documented by the site as directed. This documentation must include at least the information below:

- the number of dispensed units;
- the number of unused units;
- the number of units destroyed at the end of the study;
- the date, method and location of destruction.

## 11. ASSESSMENT OF EFFICACY [REDACTED]

All assessments will be conducted according to the schedule of assessments (Table 1). Study assessments that involve subject 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. Efficacy Assessments

#### 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 subject. An assessment timeframe of 7 days will be used on Day 1 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 subjects 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 of  $\leq 7$ .

#### 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 subjects 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 Impression (CGI)**

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 subject'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 subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject 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 subject's condition posttreatment. The Investigator will rate the subject'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. Short Form-36 Version 2 (SF-36v2)**

The Medical Outcomes Study SF-36v2 is a 36-item measure of health status that has undergone validation in many different disease states (Ware 2007). The SF-36v2 covers eight health dimensions including four physical health status domains (physical functioning, role participation with physical health problems [role-physical], bodily pain, and general health) and four mental health status domains (vitality, social functioning, role participation with emotional health problems [role-emotional], and mental health). In addition, two summary scores, physical component summary and mental component summary, are produced by taking a weighted linear combination of the eight individual domains. The SF-36v2 is available with two recall periods: the standard recall period is 4 weeks and the acute recall period is 1 week. This study will use the acute version, which asks patients to respond to questions as they pertain to the past week. Higher SF-36v2 scores indicate a better state of health.

#### **11.1.6. Patient Health Questionnaire (PHQ-9)**

The PHQ-9 is a subject-rated depressive symptom severity scale. To monitor severity over time for newly diagnosed subjects or subjects in current treatment for depression, subjects 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.

**11.1.7. Insomnia Severity Index (ISI)**

The ISI is a validated questionnaire designed to assess the nature, severity, and impact of insomnia (Morin 2011). The ISI uses a 5-point Likert Scale to measure various aspects of insomnia severity (0 = none, 1 = mild, 2 = moderate; 3 = severe; 4 = very severe), satisfaction with current sleep pattern (0 = very satisfied, 1 = satisfied, 2 = neutral, 3 = dissatisfied, 4 = very dissatisfied), and various aspects of the impact of insomnia on daily functioning (0 = not at all, 1 = a little, 2 = somewhat, 3 = much, 4 = very much). A total score of 0 to 7 = “no clinically significant insomnia,” 8 to 14 = subthreshold insomnia,” 15 to 21 = “clinical insomnia (moderate severity),” and 22 to 28 = “clinical insomnia (severe).”

**11.1.8. Core Consensus Sleep Diary**

The Core Consensus Sleep Diary collects subjective sleep parameters, including sleep onset latency, total sleep time, and wake after sleep onset, number of awakenings, and sleep quality. The take-home subject sleep diary assessment will be administered using an eDiary solution. The eDiary will be captured using either a provisioned smartphone device or bring-your-own-device (BYOD) solution, depending on the subject’s preference.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **12. ASSESSMENT OF SAFETY**

### **12.1. Safety Parameters**

All assessments will be conducted according to the schedule of assessments ([Table 1](#)).

#### **12.1.1. Demographic/Medical History**

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including family psychiatric history, will be documented. The diagnosis of MDD will be determined using the SCID-5-CT. If available, the disease code associated with the diagnosis of MDD based on the 10<sup>th</sup> revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used to determine whether the subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment during the current major depressive episode with adequate doses of antidepressants from two different classes for at least 4 weeks of treatment.

#### **12.1.2. Weight and Height**

Height (Screening only) and weight will be measured and documented.

#### **12.1.3. Physical Examination**

Physical examinations assessing body systems (eg, head, eyes, ears, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Whenever possible, the same individual is to perform all physical examinations for a given subject. Unscheduled brief, symptom-driven physical examinations may also be conducted per the Investigator's discretion.

Any abnormality in physical examinations will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section [12.2.1.1](#).

#### **12.1.4. Vital Signs**

Vital signs comprise both supine and standing for systolic and diastolic blood pressure and heart rate measurements. Heart rate and blood pressure are to be collected in supine position after the subject has been resting for 5 minutes and then after 1 minute in the standing position.

Respiratory rate, pulse oximetry and temperature are collected once, in either position. Vital signs will be documented. When vital signs are scheduled at the same time as blood draws, vital signs will be obtained first.

Any abnormality in vital signs will be interpreted by the Investigator as abnormal, NCS or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section [12.2.1.1](#).

### 12.1.5. Electrocardiogram (ECG)

Supine 12-lead ECGs 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.

### 12.1.6. Laboratory Assessments

Samples will be collected in accordance with acceptable laboratory procedures detailed in the laboratory manual.

The clinical laboratory tests to be performed are listed in [Table 3](#).

**Table 3: Clinical Laboratory Tests**

| Hematology                               | Serum Chemistry             | Urinalysis         | Coagulation                           |
|--|-----------------------------|--------------------|---------------------------------------|
| Red blood cell count                     | Alanine aminotransferase    | pH                 | Activated partial thromboplastin time |
| Hemoglobin                               | Albumin                     | Specific gravity   |                                       |
| Hematocrit                               | Alkaline phosphatase        | Protein            | Prothrombin time                      |
| White blood cell count with differential | Aspartate aminotransferase  | Glucose            |                                       |
| Platelet count                           | Total bilirubin             | Red blood cell     | International normalized ratio        |
| Red blood cell morphology                | Direct bilirubin            | Nitrite            |                                       |
|  | Indirect bilirubin          | Leukocyte esterase |                                       |
|  | Total protein               | Ketones            |                                       |
|  | Creatinine                  | Bilirubin          |                                       |
|  | Blood urea nitrogen         | Urobilinogen       |                                       |
|  | Creatine kinase             |                    |                                       |
|  | Gamma-glutamyl transferase  |                    |                                       |
|  | Potassium                   |                    |                                       |
|  | Sodium                      |                    |                                       |
|  | Lactate dehydrogenase       |                    |                                       |
|  | Glucose                     |                    |                                       |
|  | Chloride                    |                    |                                       |
|  | Bicarbonate                 |                    |                                       |
|  | Calcium                     |                    |                                       |
|  | Phosphorus                  |                    |                                       |
|  | Triglycerides               |                    |                                       |
|  | Thyroid stimulating hormone |                    |                                       |

**Table 3: Clinical Laboratory Tests (Continued)**

| <b>Diagnostic</b>  |  |                     |  |
|--|--|---------------------|--|
| <b>Serum</b>   | <b>Urine</b>   | <b>Breathalyzer</b> |  |
| Hepatitis B<br>Hepatitis C<br>Reflex HCV RNA<br>HIV-1 and -2<br>Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: serum hCG<br>Female subjects, if menopause is suspected and not surgically sterile: FSH | Drug screen including:<br>amphetamines,<br>barbiturates,<br>benzodiazepines,<br>cannabinoids, cocaine,<br>opiates, phencyclidine<br><br>Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: urine hCG | Alcohol             |  |

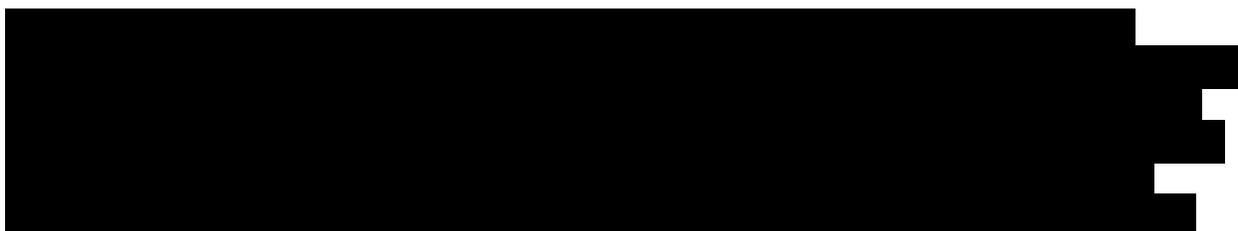
Abbreviations: FSH = follicle stimulating hormone; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus

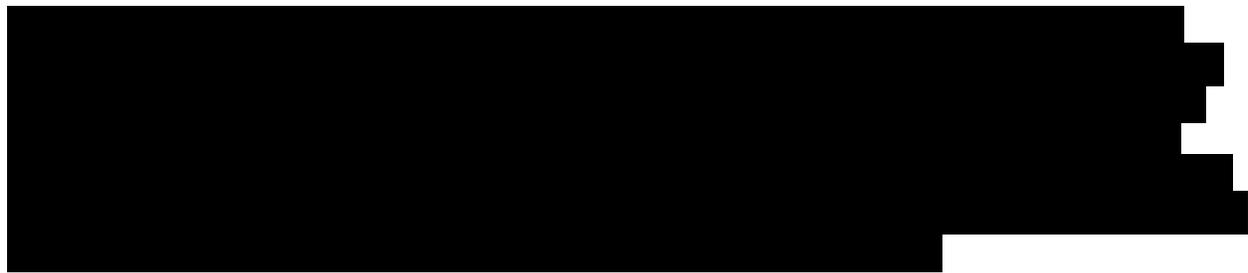
The central laboratory will perform laboratory tests for hematology, serum chemistry, urinalysis, and coagulation. The results of laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to Sage Therapeutics or designee in the format requested by Sage Therapeutics.

Laboratory reports must be signed and dated by the Investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will require clear and complete documentation in the source documents as to the investigator’s assessment of not clinically significant before proceeding with randomization.

All clinical laboratory test results outside the central laboratory’s reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.1. A clinically significant laboratory abnormality following subject randomization will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

A serum follicle stimulating hormone test will be conducted at Screening to confirm whether a female subject with  $\geq 12$  months of spontaneous amenorrhea meets the protocol-defined criteria for being post-menopausal (Section 8.1).





#### **12.1.6.1. Drugs of Abuse and Alcohol**

Urine toxicology tests will be performed for selected drugs of abuse (see [Table 3](#)). A breath test for alcohol will be performed.

#### **12.1.6.2. Pregnancy Screen**

For female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at all other scheduled timepoints thereafter, including the ET visit for subjects who prematurely discontinue.

#### **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 subject with suicidal ideation and behavior, and a post-baseline 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, as outlined in [Table 1](#).

#### **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 trials. 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. Definition of Adverse Events**

#### **12.2.1.1. Adverse Event (AE)**

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 an AE that occurs after the first administration of any study drug. The term study drug includes any Sage investigational product, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) and/or if the Investigator considers them to be clinically significant. Laboratory values and vital signs that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations 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 subject 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.

#### **12.2.1.2. Serious Adverse Event (SAE)**

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 subject or may require medical intervention to prevent one 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 subject 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 within 24 hours of first awareness (Section 12.5). All SAEs should be followed until the event resolved, the condition stabilized, was no longer considered clinically significant or the subject was lost to follow-up. Serious adverse events occurring after a subject’s final visit (including the last follow-up visit) should be reported to Sage or designee only if the Investigator considers the SAE to be related to study treatment.

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject 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 subject’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 the Investigator, between the subject’s consent to participate in the study and at the time of the procedure or treatment.

### 12.3. Relationship to Study Drug

The Investigator must make the determination of relationship to the study drug for each adverse event (not related, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as “not related.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered at least “possibly related.”

**Table 4: Relationship to Study Drug**

| <b>Relationship</b> | <b>Definition</b>  |
|---------------------|--|
| Not Related:        | No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject’s clinical state.  |
| Possibly Related:   | A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.<br>The reaction might have been produced by the subject’s clinical state or other modes of therapy administered to the subject, but this is not known for sure.    |
| Probably Related:   | A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.<br>The reaction cannot be reasonably explained by the known characteristics of the subject’s clinical state or other modes of therapy administered to the subject. |

If the relationship between the adverse event/serious adverse event and the investigational product is determined to be “possible” or “probable”, the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

## 12.4. Recording Adverse Events

Adverse events spontaneously reported by the subject 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, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study drug or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

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 12.2.1.2. An AE of severe intensity may not be considered serious.

If a female subject becomes pregnant during this study, pregnancy information must be collected and recorded on the Sage Therapeutics pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. The Investigator will also attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is participating in study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant female subjects.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication or a complication relating to the pregnancy occurs (e.g., spontaneous abortion). If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly/birth defects), the investigator should follow the procedures for reporting an SAE.

## 12.5. Reporting Serious Adverse Events

All SAEs must be reported to Sage, or designee, immediately. A written account of the SAE must be sent to Sage, or designee, within 24 hours of the first awareness of the event by the investigator and/or his staff. 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 Therapeutics, 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 case report form (CRF) and/or study file.

Any SAEs discovered by the Investigator after the designated follow up time for the study, should be promptly reported to Sage, or designee, according to the timelines noted above.

The contact information for reporting SAEs and/or pregnancies is located in the study reference manual.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the ethics committee 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. Ethics Committee (EC)/Institutional Review Boards (IRBs) will be notified of SAEs and/or SUSARs as required by local law. In addition, appropriate Sponsor Drug Safety and Pharmacovigilance personnel, or designee, will unblind SUSARs for the purpose of regulatory reporting. The Sponsor, or designee, will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. The Sponsor, or designee, will submit SUSARs to investigators in a blinded fashion.

## **12.6. Emergency Identification of Study Drug**

During the study, the blind is to be broken by the Investigator only when the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. Unless a subject is at immediate risk, the Investigator must make diligent attempts to contact Sage prior to unblinding the study treatment administered to a subject. Any request from the Investigator about the treatment administered to study subjects must be discussed with Sage. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented in the source records. Unless a subject is at immediate risk, any request for the unblinding of individual subjects must be made in writing to Sage and approved by the appropriate Sage personnel, according to standard operating procedures.

In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the eCRF. If the subject or study center personnel have been unblinded, the subject will be permanently discontinued from the study.

### **13. STATISTICS**

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the clinical study report.

#### **13.1. Data Analysis Sets**

The Randomized set, defined as all subjects who are randomized, will be used for all data listings, unless otherwise specified.

The Safety Set, defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects in the Safety Set with at least 1 post-baseline HAM-D evaluation, will be used for analysis of efficacy data.



#### **13.2. Handling of Missing Data**

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data. A sensitivity analysis will be used to investigate the impact of missing data if  $\geq 5\%$  of subjects in any treatment group have missing data.

#### **13.3. General Considerations**

For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), 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 (Section 12.1.1) and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized using the Safety Set.

Hepatitis, HIV, drug and alcohol, and pregnancy screening results will be listed, but not summarized as they are considered part of the inclusion/exclusion criteria.

Medical/family history will be listed by subject.

### 13.5. Efficacy Analyses

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment.

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 post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported 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.

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, SF-36v2 score, PHQ-9 score, sleep endpoints (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score and selected individual items and/or subscale scores in HAM-D for change from baseline.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as  $\geq 50\%$  reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of  $\leq 7.0$ ). 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 the 15-day time point. 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 including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.

### 13.6. Safety Analyses

Safety and tolerability of study drug will be evaluated by incidence of adverse events/serious adverse events, concomitant medication usage, 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 subject and summarized by treatment group. All safety summaries will be performed on the

Safety Set. Where applicable, ranges of potentially clinically significant (PCS) values are provided in the SAP.

### **13.6.1. Adverse Events**

The analysis of adverse events will be based on the concept of TEAEs. The incidence of TEAEs will be summarized overall and by Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or higher, System Organ Class (SOC), and preferred term. Incidences will be presented in order of decreasing frequency. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 12.3).

Any TEAEs leading to discontinuation and SAEs with onset after the start of study drug will also be summarized.

All AEs and SAEs (including those with onset or worsening before the start of study drug) 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 range of each parameter is provided by the laboratory; shift from baseline to post-baseline values in abnormality of results will be provided. Potentially clinically significant values will be summarized by treatment. Any abnormal values deemed clinically significant by the investigator will be reported as an AE (see Section 12.2). Clinical laboratory results will be listed by subject and timing of collection.

### **13.6.3. Physical Examinations**

The occurrence of a physical examination (Y/N) and the date performed will be listed by subject. Any clinically significant observation in physical examination will be reported as an AE (see Section 12.2).

### **13.6.4. Vital Signs**

Results from each visit and mean changes from baseline in vital signs will be summarized by scheduled visit. Any abnormality deemed clinically significant by the investigator will be reported as an AE (see Section 12.2). Potentially clinically significant values will be summarized by treatment. Vital sign results will be listed by subject 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 subject: 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 subject 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 signing the ICF through the duration of the study will be recorded. In addition, all psychotropic medications taken 6 months prior to Screening will be recorded. Those medications taken prior to the initiation of the start of study drug will be denoted "Prior". Those medications taken prior to the initiation of the study drug and continuing beyond the initiation of the study drug or those medications started at the same time or after the initiation of the study drug will be denoted "Concomitant" (ie, those with a start date on or after the first dose of study drug, or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug).

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 subject, 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 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 subject.

[REDACTED]

## **13.8. Determination of Sample Size**

Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable subjects 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 SD of 10 points. Assuming an 11% dropout rate and a 1:1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 450 total randomized subjects will be required to obtain 399 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is greater than 11%.

## **14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **14.1. Study Monitoring**

Before an investigational site can enter a subject into the study, a representative of Sage Therapeutics (or designee) 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 investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject'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 subject (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.

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

### **14.2. Audits and Inspections**

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics audit or 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, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

### **14.3. Institutional Review Board (IRB) or Ethics Committee (EC)**

The Principal Investigator must obtain IRB (or EC) approval for the investigation. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the subject 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 Practices and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit. Please see Section [14.2](#) for more details regarding the audit process.

## **16. ETHICS**

### **16.1. Ethics Review**

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or EC as appropriate. The investigator must submit written approval to Sage Therapeutics before he or she can enroll any subject into the study.

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

The Principal Investigator is also responsible for providing the IRB 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 EC according to local regulations and guidelines.

### **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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines, as well as all applicable regulatory requirements.

### **16.3. Written Informed Consent**

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

## **17. DATA HANDLING AND RECORDKEEPING**

### **17.1. Inspection of Records**

Sage Therapeutics will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **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, whichever is longer. If not approved, documentation must be maintained for 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

## **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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## **Protocol 217-MDD-301 Amendment 2**

**Date of Amendment: 11 October 2018**

### **A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy of SAGE-217 in the Treatment of Adult Subjects with Major Depressive Disorder**

#### **Rationale for Protocol Amendment**

The primary purpose for this protocol amendment is as follows:

- Add the 9-item Patient Health Questionnaire (PHQ-9) as a secondary endpoint to supplement efficacy assessments with a patient-reported outcome (PRO) measure that provides balanced assessment of the core symptoms of a major depressive episode
- Add the 20-item Physician Withdrawal Checklist (PWC-20) as a safety endpoint to better characterize the clinical effects of the proposed time-limited use of SAGE-217
- Add a Day 18 follow-up visit to evaluate potential withdrawal symptoms of SAGE-217
- Replace HAM-D with MADRS as the assessment of MDD at screening to better capture depression presentations featuring hypersomnia
- Increase exclusionary period for use of benzodiazepines and GABA<sub>A</sub> modulators/GABA-containing agents to avoid confounding by the natural resolution of prolonged mild GABAergic withdrawal symptoms

Additional changes are being implemented as outlined below:

- Exclude subjects that have taken non-GABA anti-insomnia medications (eg melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) within 14 days of initiation of study drug.
- Remove criterion that subjects must be ambulatory
- Remove duplicate inclusion criterion #8 (reflected in exclusion criteria)
- Include exception to contraception criteria for subjects in same-sex relationship(s) which do not carry a risk of pregnancy
- Enhance exclusion of subjects with treatment-resistant depression within the current major depressive episode
- Exclude subjects with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) within the past year
- Exclude subjects with a history of sleep apnea
- Exclude subjects that have had procedures that interfere with gastrointestinal transit
- Define timeframes for each type of prohibited medication
- Reiterate exclusion criterion prohibiting elective surgeries or procedures during participating in the study
- Offer practical options for taking study drug with food in the evening

- Remove propoxyphene from urine laboratory panel
- Clarify statical analyses of primary efficacy endpoint

A detailed summary of changes is provided in [Table 1](#). Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed individually, nor are administrative updates such as revising the document date, updating the document header and version number, and updating the table of contents.

**Table 1: Protocol Amendment 2 Detailed Summary of Changes**

The primary section of the protocol affected by the changes in Protocol Amendment 2 is indicated. The corresponding related text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

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**Purpose:** Add PHQ-9 as a secondary endpoint to supplement efficacy assessments with a patient-reported outcome (PRO) measure that provides balanced assessment of the core symptoms of a major depressive episode.

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The primary change occurs in Section 6.2.2. Secondary Endpoint(s)

Changed text:           **Change from baseline in** patient-reported outcome measures of health-related quality of life, as assessed by responses to the 36-item Short Form survey (SF-36) version 2, **and of depressive symptoms, as assessed by the 9-item Patient Health Questionnaire (PHQ-9)**

Sections also affected by this change:

- Synopsis, Table 1 Schedule of Events, 6.1.2 Secondary Objective, new Section 11.1.6 Patient Health Questionnaire (PHQ-9), 13.5 Efficacy Analyses
- 

**Purpose:** Add PWC-20 as a safety endpoint to better characterize the clinical effects of the proposed time-limited use of SAGE-217.

The primary change occurs in Section 6.2.3. Safety Endpoint(s)

Changed text:

- Incidence and severity of adverse events/serious adverse events
- Changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs)
- Suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)
- **Potential withdrawal symptoms using the 20-item Physician Withdrawal Checklist (PWC-20)**

Sections also affected by this change:

- Synopsis, Table 1 Schedule of Events, new Section 12.1.8 Physician Withdrawal Checklist, 13.6 Safety Analyses, new section 13.6.8 Physician Withdrawal Checklist, 19 List of References
-

**Purpose:** Add a Day 18 follow-up visit to evaluate potential withdrawal symptoms of SAGE-217.

The primary change occurs in Table 1 Schedule of Events

Changed text:

| Visits       | Screening Period | Double-Blind, Placebo-Controlled Treatment Period |             |             |              |  | Follow-up Period     |              |              |              |                          |
|--------------|------------------|---|-------------|-------------|--------------|--|----------------------|--------------|--------------|--------------|--------------------------|
| Visit Days   | D-28 to D-1      | D1  | D3<br>(±1d) | D8<br>(+1d) | D12<br>(±1d) | D15<br>(±1d)<br>and/or<br>EOT <sup>a</sup> | <b>D18<br/>(±1d)</b> | D21<br>(±1d) | D28<br>(±3d) | D35<br>(±3d) | D42<br>(±3d)<br>or<br>ET |
| Visit Number | V1               | V2  | V3          | V4          | V5           | V6   | <b>V7</b>            | <b>V78</b>   | <b>V89</b>   | <b>V910</b>  | <b>V101</b>              |

Sections also affected by this change:

- Not applicable

**Purpose:** Remove criterion that subjects must be ambulatory.

The primary change occurs in Section 8.1 Subject Inclusion Criteria

Changed text: 2. Subject is ~~an ambulatory~~ male or female between 18 and 65 years of age, inclusive.

Sections also affected by this change:

- Synopsis

**Purpose:** Replace HAM-D with MADRS as assessment of MDD at screening to better capture depression presentations featuring hypersomnia.

The primary change occurs in Section 8.1 Subject Inclusion Criteria

Changed text: 6. Subject has a **MADRS** ~~HAM-D~~ total score of ~~≥22~~**≥30** at screening and Day 1 (prior to dosing).

Sections also affected by this change:

- Synopsis, 7.1. Overall Study Design

**Purpose:** Remove HAM-D at Screening and update timeframe of assessments to reflect first HAM-D assessment on Day 1.

The primary change occurs in Table 1 Schedule of Events

Changed text:

| Visits                | Screening Period | Double-Blind, Placebo-Controlled Treatment Period |          |          |           |                                   | Follow-up Period |           |           |           |                 |
|-----------------------|------------------|---|----------|----------|-----------|-----------------------------------|------------------|-----------|-----------|-----------|-----------------|
| Visit Days            | D-28 to D-1      | D1  | D3 (±1d) | D8 (+1d) | D12 (±1d) | D15 (±1d) and/or EOT <sup>a</sup> | D18 (±1d)        | D21 (±1d) | D28 (±3d) | D35 (±3d) | D42 (±3d) or ET |
| HAM-D <sup>n, °</sup> | ✕                | X   | X        | X        | X         | X                                 | X                | X         | X         | X         | X               |

<sup>°</sup> The assessment timeframe for HAM-D scales will refer to the past 7 days (1 week) at **Screening Day 1** and “Since Last Visit” for all other visits. The assessment timeframe for HAM-A scale will refer to the past 7 days (1 week) at all visits.

Sections also affected by this change:

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

**Purpose:** Remove duplicate inclusion criterion #8 (reflected in exclusion criteria).

The primary change occurs in Section 8.1. Subject Inclusion Criteria

Deleted text: ~~8. Subjects taking benzodiazepines or GABAA modulators for insomnia (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) have had these medications discontinued by Day 14.~~

Sections also affected by this change:

- Synopsis

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**Purpose:** Include exception to contraception criteria for subjects in same-sex relationship(s) which do not carry a risk of pregnancy.

The primary change occurs in Section 8.1. Subject Inclusion Criteria

Changed text: ~~109.~~ Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH] >40 mIU/mL) and/or surgically sterile (hysterectomy or bilateral oophorectomy), **or in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s)):**

- 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/occlusion.
- Vasectomized partner.
- Sexual abstinence (no sexual intercourse).

~~140.~~ Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, **unless the subject is in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s))**. Acceptable methods of effective contraception for males includes sexual abstinence, vasectomy, or a condom with spermicide used together with highly effective female contraception methods if the female partner is of child-bearing potential (see Inclusion Criteria #9 for acceptable contraception methods).

Sections also affected by this change:

- Synopsis

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**Purpose:** Enhance exclusion of subjects with treatment-resistant depression within the current major depressive episode.

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Added text: **5. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.**

Sections also affected by this change:

- Synopsis
-

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**Purpose:** Increase exclusionary period for use of benzodiazepines and GABA<sub>A</sub> modulators/GABA-containing agents to avoid confounding by the natural resolution of prolonged mild GABAergic withdrawal symptoms.

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Changed text: ~~1920.~~ Subject is taking benzodiazepines or GABA<sub>A</sub> modulators at Day -14/GABA-containing agents (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28.

Sections also affected by this change:

- Synopsis, 9.2.2 Prohibited Medications

---

**Purpose:** Exclude subjects that have taken non-GABA anti-insomnia medications (eg melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) within 14 days of initiation of study drug.

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Added text: **21. Subject is taking non-GABA anti-insomnia medications (eg melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) at Day -14.**

Sections also affected by this change:

- Synopsis, 9.2.2 Prohibited Medications

---

**Purpose:** Exclude subjects with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) within the past year.

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Added text: **22. Subject has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) within the past year prior to Screening.**

Sections also affected by this change:

- Synopsis

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**Purpose:** Exclude subjects with a history of sleep apnea.

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Added text: **23. Subject has a history of sleep apnea.**

Sections also affected by this change:

- Synopsis

---

**Purpose:** Exclude subjects that have had procedures that interfere with gastrointestinal transit.

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Added text: **24. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.**

Sections also affected by this change:

- Synopsis
- 

**Purpose:** Define timeframes for each type of prohibited medication.

The primary change occurs in Section 9.2.2 Prohibited Medications

Changed text: The following specific classes of medications are prohibited ~~at any time during the treatment period:~~

- Initiation of new psychotropic medications **at any time during the study**
- **Initiation of new antidepressant therapy from 60 days prior to Day 1 through the duration of the study**
- Use of any benzodiazepines, GABAA modulators, ~~or~~ GABAA-like acting drugs, **or GABA-containing agents from Day -28 through the duration of the study**
- **Use of any non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) from Day -14 through the duration of the study**
- Exposure to another investigational medication or device **from 30 days prior to Screening through the duration of the study**
- Any known strong inhibitors CYP3A4 **from Day -28 or 5 half-lives prior to Day 1 (whichever is longer) through the duration of the study**
- Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort **from Day -28 through the duration of the study.**

Sections also affected by this change:

- Not applicable
- 

**Purpose:** Reiterate exclusion criterion prohibiting elective surgeries or procedures during participating in the study.

The primary change occurs in Section 9.2.3 Other Restrictions

Added text: **Elective surgeries or procedures are prohibited during participation in the study.**

Sections also affected by this change:

- Not applicable
-

**Purpose:** Offer practical options for taking study drug with food in the evening.

The primary change occurs in Section 10.5 Study Drug Administration

Added text: SAGE-217 is to be administered orally once daily in the evening with food. **Practical options include taking SAGE-217 within 1 hour of dinner or taking SAGE-217 later in the evening with solid food.** If a subject misses a dose, the subject 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.

Sections also affected by this change:

- Synopsis
- 

**Purpose:** Remove propoxyphene from urine laboratory panel.

The primary change occurs in Table 3 Clinical Laboratory Tests

Removed text: Urine  
Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, ~~and propoxyphene~~  
Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal:  
urine hCG

Sections also affected by this change:

- Not applicable
-

**Purpose:** To clarify statistical analyses of primary efficacy endpoint.

The primary change occurs in Section 13.5 Efficacy Analyses

Changed text:           The **estimand for the primary efficacy analysis is the mean change from baseline in HAM-D total score at Day 15. This primary efficacy endpoint, the change from baseline to each assessment in HAM-D total score, 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 post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. The Toeplitz or compound symmetry covariance structure will be used if there is a convergence issue with the unstructured covariance model. 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.**

Sections also affected by this change:

- Synopsis
-



**A PHASE 3, MULTICENTER, DOUBLE-BLIND,  
RANDOMIZED, PLACEBO-CONTROLLED STUDY  
EVALUATING THE EFFICACY OF SAGE-217 IN THE  
TREATMENT OF ADULT SUBJECTS WITH MAJOR  
DEPRESSIVE DISORDER**

**PROTOCOL NUMBER: 217-MDD-301**

|                           |  |
|---------------------------|--|
| Study Drug                | SAGE-217   |
| Clinical Phase            | Phase 3  |
| Sponsor                   | Sage Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 |
| Sponsor Contact           | [REDACTED]<br>Tel: [REDACTED]<br>email: [REDACTED]                 |
| Sponsor Medical Monitor   | [REDACTED] MD, MBA<br>Tel: [REDACTED]<br>email: [REDACTED]         |
| Date of Original Protocol | Version 1.0, 16 JUL 2018   |
| Date of Amendment 1       | Version 2.0, 25 SEP 2018   |
| Date of Amendment 2       | Version 3.0, 11 OCT 2018   |
| Date of Amendment 3       | Version 4.0, 07 March 2019   |

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.

**Protocol Number:** 217-MDD-301  
**Study Drug:** SAGE-217  
**Study Phase:** Phase 3  
**Sponsor:** Sage Therapeutics, Inc.  
**Protocol Date:** Version 4.0, 07 March 2019

**Sponsor Approval**

[Redacted] [Redacted]  
[Redacted] MD, MBA [Redacted]  
Date (DD MMM YYYY)  
Sage Therapeutics

[Redacted] [Redacted]  
[Redacted] DVM, MS, MPH [Redacted]  
Date (DD MMM YYYY)  
Sage Therapeutics

[Redacted] [Redacted]  
[Redacted] [Redacted]  
Date (DD MMM YYYY)  
Sage Therapeutics

[Redacted] [Redacted]  
[Redacted] [Redacted]  
Date (DD MMM YYYY)  
Sage Therapeutics

[Redacted] [Redacted]  
[Redacted] PhD [Redacted]  
Date (DD MMM YYYY)  
Sage Therapeutics

[Redacted] [Redacted]  
[Redacted] [Redacted]  
Date (DD MMM YYYY)  
Sage Therapeutics

## INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-MDD-301 clinical 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

---

Date (DD Month YYYY)

## 2. SYNOPSIS

|  |
|--|
| <b>Name of Sponsor/Company:</b><br>Sage Therapeutics   |
| <b>Name of Investigational Product:</b><br>SAGE-217 Capsules   |
| <b>Name of Active Ingredient:</b><br>SAGE-217  |
| <b>Title of Study:</b> A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy of SAGE-217 in the Treatment of Adult Subjects with Major Depressive Disorder  |
| <b>Number of Sites and Study Location:</b> Approximately 55 sites in the United States   |
| <b>Phase of development:</b> 3   |
| <b>Planned Duration of Subject Participation:</b><br>Up to 213 days (up to 28-day Screening Period, 14-day Double-blind Treatment Period, and up to 6 months (168 days) of Follow-up)  |
| <b>Objectives:</b><br>Primary: <ul style="list-style-type: none"><li>To evaluate the efficacy of SAGE-217 in the treatment of major depressive disorder (MDD) compared to placebo.</li></ul> Secondary: <ul style="list-style-type: none"><li>To evaluate the effect of SAGE-217 on sleep.</li><li>To assess patient-reported outcome (PRO) measures as they relate to health-related quality of life and depressive symptoms.</li></ul> Safety: <ul style="list-style-type: none"><li>To evaluate the safety and tolerability of SAGE-217.</li></ul> <p>█<br/>█<br/>█</p>   |
| <b>Endpoints:</b><br>Primary: <ul style="list-style-type: none"><li>The primary efficacy endpoint is the change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 15.</li></ul> Secondary: <ul style="list-style-type: none"><li>Change from baseline in the 17-item HAM-D total score at other timepoints</li><li>HAM-D response at Day 15 and all other time points, defined as a <math>\geq 50\%</math> reduction in HAM-D score from baseline</li><li>HAM-D remission at Day 15 and all other time points, defined as HAM-D total score <math>\leq 7</math></li><li>Clinical Global Impression - Improvement (CGI-I) response at Day 15 and all other</li></ul> |

time points, defined as “much improved” or “very much improved”

- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at Day 15 and all other time points
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at Day 15 and all other time points
- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15 and all other time points
- Change from baseline in HAM-D subscale and individual item scores at all time points
- Change in sleep at Day 15 and all other time points, as assessed by
  - Insomnia Severity Index (ISI)
  - Subjective sleep parameters collected with the Core Consensus Sleep Diary
- Change from baseline in PRO measures of health-related quality of life, as assessed by responses to the 36-item Short Form survey version 2 (SF-36v2), and of depressive symptoms, as assessed by the 9-item Patient Health Questionnaire (PHQ-9)

**Safety Endpoints:**

- Incidence and severity of adverse events/serious adverse events
- Changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs)
- Suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Potential withdrawal symptoms using the 20-item Physician Withdrawal Checklist (PWC-20)

[REDACTED]

**Study Description:**

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD (MADRS total score  $\geq 30$ ). Randomization will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline and carried out within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo; subjects will be treated for 14 days beginning on Day 1.

The study will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, a 28-day follow-up period, and an extended follow-up period through Day 182 (6 months following the last dose).

The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the

**MADRS and CGI-S.**

Antidepressants are permitted provided subjects are on a stable dose for at least 60 days prior to Day 1 and agree to continue on the stable dose through the follow-up period (Day 42). Initiation of new antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of the Day 42 assessments.

Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) and randomized within each stratum to one of 3 treatment groups (SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo) in a 1:1:1 ratio. Subjects will self-administer a single dose of study drug once daily in the evening with food, on an outpatient basis, for 14 days. Practical options include taking SAGE-217 within 1 hour of dinner or taking SAGE-217 later in the evening with solid food. Subjects will return to the study center during the treatment and follow-up periods as outlined in [Table 1](#).

Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated. Subjects who discontinue treatment early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place as scheduled relative to the last dose of treatment (eg, if a subject's last dose is on Day 13, their first follow-up visit (Visit 7,) should occur 4 days later). If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for both visits will be conducted.

**Number of Subjects (planned):**

Approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects.

**Eligibility Criteria:**

**Inclusion Criteria:**

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is a male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements, including not participating in night shift work.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a MADRS total score of  $\geq 30$  at screening and Day 1 (prior to dosing).
7. Subjects taking antidepressants must have been taking these medications at the same dose for at least 60 days prior to Day 1. Subjects receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1.
8. Subject is willing to delay 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 42 visit.

9. Female subject agrees to use one of the following methods of contraception during the treatment period and for 30 days following the last dose of study drug, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH] >40 mIU/mL), surgically sterile (hysterectomy or bilateral oophorectomy), or does not engage in sexual relations which carry a risk of pregnancy:
  - 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/occlusion
  - Vasectomized partner
10. Male subject agrees to use an acceptable method of effective contraception during the treatment period and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy. Acceptable methods of effective contraception for males includes vasectomy, or a condom with spermicide used together with highly effective female contraception methods if the female partner(s) is of child-bearing potential (see Inclusion Criteria #9 for acceptable contraception methods).
11. Male subject is willing to abstain from sperm donation during the treatment period and for 5 days after receiving the last dose of the study drug.
12. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

**Exclusion Criteria:**

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study. A body mass index (BMI)  $\leq 18$  or  $\geq 50$  kg/m<sup>2</sup> at Screening is exclusionary; a BMI of 40 to 49 kg/m<sup>2</sup>, inclusive, at Screening is subject to a broader evaluation of medical comorbidities (such as sleep apnea, chronic obstructive pulmonary disease [COPD]), concomitant medications, and prior tolerability of sedating agents.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from two different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment

Response Questionnaire (MGH ATRQ) will be used for this purpose.

5. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
7. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.
8. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
9. Subject has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
10. Subject has active psychosis per Investigator assessment.
11. Subject has a medical history of seizures.
12. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
13. Subject 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.
14. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
15. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
16. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to the first dose of study drug.
17. Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort, within 28 days prior to the first dose of study drug.
18. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
19. Subject plans to undergo elective surgery before completion of the Day 42 visit.
20. Subject is taking benzodiazepines, barbiturates, or GABA<sub>A</sub> modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or has been using these agents daily or near-daily ( $\geq 4$  times per week) for more than 1 year. Subject is taking any

benzodiazepine or GABA modulator with a half-life of  $\geq 48$  hours (eg, diazepam) from 60 days prior to Day 1.

21. Subject is taking non-GABA anti-insomnia medications (eg melatonin, Benadryl [anti-histamines], trazodone), or first or second generation (typical/atypical) antipsychotics at Day -14.
22. Subject 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.
23. Subject has a history of sleep apnea.
24. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
25. Subject is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as-needed, at Day -28.

**Study Drug, Dosage and Mode of Administration:**

SAGE-217 is available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose (SMCC), colloidal silicon dioxide and sodium stearyl fumarate as excipients. Colloidal silicon dioxide may be either a component of the SMCC or a standalone excipient in the formulation. SAGE-217 capsules will be orally administered as a 30-mg or 20-mg dose.

**Reference Therapy, Dosage, and Mode of Administration:**

Placebo will be provided as hard gelatin capsules for oral administration containing only the excipients listed above for the active capsule.

**Duration of Treatment:** 14 days

**Statistical methods:**

A 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 treatment unblinding.

When all subjects complete the Day 42 visit, the database will be locked, followed by treatment unblinding to the Sponsor and data analyses (site personnel and subjects will remain blinded). The extended follow-up period will continue as scheduled; the final database lock will occur when all subjects complete the extended follow-up period.

**General Considerations**

For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration.

Continuous endpoints will be summarized descriptively with 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 Randomized Set is defined as all subjects who are randomized.

The Safety Set is defined as all subjects administered study drug.

The Full Analysis Set is defined as all randomized subjects in the Safety Set with a valid baseline HAM-D total score at least 1 post-baseline HAM-D total score.

### **Determination of Sample Size**

Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable subjects would provide 90% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation (SD) of 10 points. Assuming a 11% dropout rate and a 1:1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 450 total randomized subjects will be required to obtain 399 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is greater than 11%.

### **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 post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported 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, SF-36v2 score, PHQ-9 score, sleep diary endpoints (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score and selected individual items and/or subscale scores in HAM-D for change from baseline.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as  $\geq 50\%$  reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of  $\leq 7.0$ ). 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 the 15-day time point. 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 including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.

### **Safety Analysis**

Safety and tolerability of study drug will be evaluated by incidence of adverse events/serious adverse events, 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.  
[REDACTED]

**Table 1: Schedule of Events**

| Visits                                       | Screening Period | Double-Blind, Placebo-Controlled Treatment Period |          |          |           |                                   | Follow-up Period |           |           |           |                 | Extended Follow-Up |
|--|------------------|---|----------|----------|-----------|-----------------------------------|------------------|-----------|-----------|-----------|-----------------|--------------------|
|  |                  | D1  | D3 (±1d) | D8 (+1d) | D12 (±1d) | D15 (+1d) and/or EOT <sup>a</sup> | D18 (±1d)        | D21 (±1d) | D28 (±3d) | D35 (±3d) | D42 (±3d) or ET |                    |
| Visit Days                                   | D-28 to D-1      | V2  | V3       | V4       | V5        | V6                                | V7               | V8        | V9        | V10       | V11             | V12, V13, V14      |
| Visit Number                                 | V1               | V2  | V3       | V4       | V5        | V6                                | V7               | V8        | V9        | V10       | V11             | V12, V13, V14      |
| <b>Study Procedure</b>                       |                  |   |          |          |           |                                   |                  |           |           |           |                 |                    |
| Informed Consent                             | X                |   |          |          |           |                                   |                  |           |           |           |                 |                    |
| Duplicate Subject Check <sup>b</sup>         | X                |   |          |          |           |                                   |                  |           |           |           |                 |                    |
| Inclusion/Exclusion                          | X                | X   |          |          |           |                                   |                  |           |           |           |                 |                    |
| Serum FSH test <sup>c</sup>                  | X                |   |          |          |           |                                   |                  |           |           |           |                 |                    |
| SCID-5-CT                                    | X                |   |          |          |           |                                   |                  |           |           |           |                 |                    |
| MGH ATRQ                                     | X                |   |          |          |           |                                   |                  |           |           |           |                 |                    |
| Demographics                                 | X                |   |          |          |           |                                   |                  |           |           |           |                 |                    |
| Medical/Family History                       | X                |   |          |          |           |                                   |                  |           |           |           |                 |                    |
| Subject training <sup>d</sup>                | X                | X   |          |          |           |                                   |                  |           |           |           |                 |                    |
| Randomization                                |                  | X   |          |          |           |                                   |                  |           |           |           |                 |                    |
| Physical Examination <sup>e</sup>            | X                | X   |          |          |           |                                   |                  |           |           |           | X               |                    |
| Body Weight/Height                           | X                |   |          |          |           | X (wt only)                       |                  |           |           |           | X (wt only)     |                    |
| Clinical Laboratory Assessments <sup>f</sup> | X                | X   |          | X        |           | X                                 |                  | X         | X         |           | X               | X                  |
| Drug & Alcohol Screen <sup>g</sup>           | X                | X   | X        | X        | X         | X                                 | X                | X         | X         | X         | X               |                    |
| Pregnancy Test <sup>h</sup>                  | X                | X   |          |          |           | X                                 |                  |           | X         |           | X               |                    |
| Hepatitis & HIV Screen                       | X                |   |          |          |           |                                   |                  |           |           |           |                 |                    |

| Visits                    | Screening Period | Double-Blind, Placebo-Controlled Treatment Period |             |             |              |  | Follow-up Period |              |              |              |                          | Extended Follow-Up       |
|---------------------------|------------------|---|-------------|-------------|--------------|--|------------------|--------------|--------------|--------------|--------------------------|--------------------------|
|                           |                  | D1  | D3<br>(±1d) | D8<br>(+1d) | D12<br>(±1d) | D15<br>(+1d)<br>and/or<br>EOT <sup>a</sup> | D18<br>(±1d)     | D21<br>(±1d) | D28<br>(±3d) | D35<br>(±3d) | D42<br>(±3d)<br>or<br>ET |                          |
| Visit Days                | D-28 to D-1      |   |             |             |              |  |                  |              |              |              |                          | D70, D126, D182<br>(±7d) |
| Visit Number              | V1               | V2  | V3          | V4          | V5           | V6   | V7               | V8           | V9           | V10          | V11                      | V12, V13, V14            |
| Study Procedure           |                  |   |             |             |              |  |                  |              |              |              |                          |                          |
| Vital Signs <sup>k</sup>  | X                | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        | X                        |
| 12-Lead ECG <sup>l</sup>  | X                | X   |             |             |              | X  |                  |              |              |              | X                        | X (Day 182 only)         |
| C-SSRS <sup>m</sup>       | X                | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        | X                        |
| HAM-D <sup>n, o</sup>     |                  | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        | X                        |
| MADRS                     | X                | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        |                          |
| HAM-A <sup>o</sup>        |                  | X   |             | X           |              | X  | X                |              | X            |              | X                        |                          |
| CGI-S                     | X                | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        | X                        |
| CGI-I                     |                  |   | X           | X           | X            | X  | X                | X            | X            | X            | X                        | X                        |
| SF-36v2                   | X                | X   |             | X           |              | X  |                  |              | X            |              | X                        | X                        |
| PHQ-9                     |                  | X   |             | X           |              | X  |                  | X            |              |              | X                        | X                        |
| ISI                       |                  | X   |             | X           |              | X  | X                | X            | X            |              | X                        | X                        |
| PWC-20                    |                  | X   |             |             |              | X  | X                | X            |              |              |                          |                          |
| Sleep diary <sup>p</sup>  | X                |   |             |             |              |  |                  |              |              |              |                          |                          |
| Study Drug Dispensation   |                  | X   |             | X           |              |  |                  |              |              |              |                          |                          |
| Study Drug Administration |                  | X (Day 1 through Day 14)                          |             |             |              |  |                  |              |              |              |                          |                          |



- <sup>k</sup> Vital signs include oral temperature (°C), respiratory rate, 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 subject 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.
- <sup>l</sup> Triplicate ECGs will be collected. [REDACTED]
- <sup>m</sup> The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- <sup>n</sup> The HAM-D is to be completed as early during the visit as possible.
- <sup>o</sup> The assessment timeframe for HAM-D scales will refer to the past 7 days (1 week) at Day 1 and “Since Last Visit” for all other visits. The assessment timeframe for HAM-A scale will refer to the past 7 days (1 week) at all visits.
- <sup>p</sup> Subjects are instructed to complete the Core Consensus Sleep Diary starting at least 7 days prior to Day 1 and then daily through Day 28.  
[REDACTED]
- <sup>r</sup> To be performed at the ET visit only.
- <sup>s</sup> Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject’s participation in the study.
- <sup>t</sup> Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.



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**Table 2: Abbreviations and specialist terms (Continued)**

| <b>Abbreviation or specialist term</b> | <b>Explanation</b>   |
|--|--|
| MADRS                                  | Montgomery Åsberg Depression Rating Scale                                      |
| MDD                                    | major depressive disorder  |
| MGH ATRQ                               | Massachusetts General Hospital Antidepressant Treatment Response Questionnaire |
| MMRM                                   | mixed effects model for repeated measures                                      |
| NCS                                    | not clinically significant   |
| PCS                                    | Potentially clinically significant   |
| PHQ-9                                  | 9-item Patient Health Questionnaire  |
| PK                                     | pharmacokinetic  |
| PRO                                    | patient-reported outcome   |
| PWC-20                                 | 20-item Physician Withdrawal Checklist   |
| 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   |
| SF-36v2                                | 36-item Short Form version 2   |
| SUSAR                                  | suspected, unexpected, serious, adverse reactions                              |
| TEAE                                   | treatment-emergent adverse event   |
| WHO                                    | World Health Organization  |

## 5. INTRODUCTION

### 5.1. Background of Major Depressive Disorder and Unmet Medical Need

The World Health Organization (WHO) has identified depression as the leading cause of disability worldwide, and as a major contributor to the overall global burden of disease (<http://www.who.int/mediacentre/factsheets/fs369/en/>). Globally, depression has been estimated to affect over 300 million people.

In the United States, the economic burden of depression, including workplace costs, direct costs and suicide-related costs, was estimated to be \$210.5 billion in 2010 ([Greenberg 2015](#)). As per WHO statistics, over 800,000 people die due to suicide every year, and suicide is the second leading cause of death in 15- to 29-year-olds. The rate of US adults making a suicide attempt has increased (0.62% from 2004 to 2005 to 0.79% from 2012 to 2013), with a shift to more attempts among younger adults (42% to 50%, respectively) and among those with a depressive disorder (26% to 54%, respectively; [Olfson 2017](#)).

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition ([DSM-5](#)), depression refers to an overarching set of diagnoses, including major depressive disorder (MDD). Diagnostic criteria for MDD includes a set of at least 5 depressive symptoms out of 9, including depressed mood and/or loss of interest or pleasure, and other changes affecting appetite or weight, sleep, psychomotor activity, energy level, feelings of guilt, concentration ability and suicidality during the same 2-week period, that represents a change from previous functioning ([DSM-5](#)).

Antidepressants are a mainstay of pharmacological treatment for depressive disorders. Selective serotonin uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other compounds that affect monoaminergic neurotransmission, such as mirtazapine and bupropion, represent the major classes of antidepressants. While antidepressants are widely used, large scale studies have demonstrated their limited efficacy, including low remission rates and untreated symptoms ([Trivedi 2006](#); [Conradi 2011](#); [Romera 2013](#)).

Converging preclinical and clinical evidence ([Gerner 1981](#); [Honig 1988](#); [Drugan 1989](#); [Luscher 2011](#); [Mann 2014](#)) implicates deficits in  $\gamma$ -aminobutyric acid (GABA)-ergic neurotransmission in the pathophysiology of depressive disorders including MDD. Furthermore, experimental data implicate deficiencies in the normal regulation of endogenous neuroactive steroids in depressive disorders ([Maguire 2008](#); [Maguire 2009](#)). Depressed patients show low levels of GABA in the brain and of neurosteroids in the cerebrospinal fluid (CSF) and plasma, and antidepressant therapy restores GABA levels in relevant animal models and neurosteroid concentrations in depressed patients ([Luscher 2011](#); [Schüle 2014](#)).

### 5.2. SAGE-217

SAGE-217 is a synthetic positive allosteric modulator of GABA<sub>A</sub> receptors, the major class of inhibitory neurotransmitter receptors in the brain. 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<sub>A</sub> receptors, and, consistent with the actions of other GABA<sub>A</sub> receptor potentiators (Rudolph 2011), exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo.

Data from an open-label Phase 2a study of SAGE-217 administered to subjects with moderate to severe MDD showed clinically significant improvements from baseline in depression and anxiety scale scores (Hamilton Rating Scale for Depression [HAM-D], Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Anxiety Rating Scale [HAM-A], and Clinical Global Impression – Improvement [CGI-I]) as early as Day 2 of the 14-day treatment period, with durable responses following the end of treatment. This result was further supported by the randomized, double-blind portion of this study including 89 subjects, in which a rapid and substantial decrease in HAM-D scores was observed at Day 15 (primary endpoint), starting at Day 2. This response pattern was also observed with other efficacy scales, including MADRS, CGI-I, and HAM-A.

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, and dizziness. Most adverse events (AEs) were reported as mild or moderate in intensity. There have been no deaths and only one subject with essential tremor experienced a serious adverse event (SAE) of transient confusion leading to discontinuation of study drug. No other SAEs have been reported in any study of SAGE-217.

Additional information on nonclinical and clinical data is provided in the [Investigator's Brochure](#).

### **5.3. Potential Risks and Benefits**

Non-serious events of sedation, somnolence, and dizziness were the most commonly reported AEs with SAGE-217. Given the outcome of the Phase 2 study of SAGE-217 in subjects with MDD, the current significant unmet need in the treatment of depression, and a favorable benefit-risk profile, further investigation of SAGE-217 in patients with MDD is justified.

### **5.4. Dose Justification**

There will be 2 dose levels of SAGE-217 in this study in order to study dose ranging: 30 mg per day and 20 mg per day. The higher dose level of 30 mg per day is the maximum tolerated dose in the multiple ascending dose study of SAGE-217 in healthy subjects and is also the dose level that was effective and generally well tolerated in a Phase 2 study in subjects with MDD (217-MDD-201). The lower dose of 20 mg per day will be studied in subjects with MDD for the first time in the current study and is anticipated to be well tolerated as it is lower than the maximum tolerated dose level. Due to sedation/somnolence observed in previous clinical trials when administered in the morning, and improved tolerability when given in the evening, both doses of SAGE-217 will be administered in the evening in this study.

## 6. STUDY OBJECTIVES AND PURPOSE

### 6.1. Study Objective

#### 6.1.1. Primary Objective

The primary objective is to evaluate the efficacy of SAGE-217 in the treatment of MDD compared to placebo.

#### 6.1.2. Secondary Objective(s)

Secondary objectives are:

- To evaluate the effect of SAGE-217 on sleep.
- To assess patient-reported outcome (PRO) measures as they relate to health-related quality of life and depressive symptoms.

#### 6.1.3. Safety Objective

The safety objective is to evaluate the safety and tolerability of SAGE-217.

[REDACTED]

### 6.2. Endpoints

#### 6.2.1. Primary Endpoint

The primary endpoint of this study is the change from baseline in the 17-item HAM-D total score at Day 15.

#### 6.2.2. Secondary Endpoint(s)

- Change from baseline in the 17-item HAM-D total score at other time points
- HAM-D response at Day 15 and all other time points, defined as a  $\geq 50\%$  reduction in HAM-D score from baseline
- HAM-D remission at Day 15 and all other time points, defined as HAM-D total score  $\leq 7$
- CGI-I response at Day 15 and all other time points, defined as “much improved” or “very much improved”

- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at Day 15 and all other time points
- Change from baseline in HAM-A total score at Day 15 and all other time points
- Change from baseline in the MADRS total score at Day 15 and all other time points
- Change from baseline in HAM-D subscale and individual item scores at all time points
- Change in sleep at Day 15 and all other time points, as assessed by:
  - Insomnia Severity Index (ISI)
  - Subjective sleep parameters collected with the Core Consensus Sleep Diary
- Change from baseline in PRO measures of health-related quality of life, as assessed by responses to the 36-item Short Form survey version 2 (SF-36v2), and of depressive symptoms, as assessed by the 9-item Patient Health Questionnaire (PHQ-9)

**6.2.3. Safety Endpoint(s)**

- Incidence and severity of adverse events/serious adverse events
- Changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs)
- Suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Potential withdrawal symptoms using the 20-item Physician Withdrawal Checklist (PWC-20)

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

## 7. INVESTIGATIONAL PLAN

### 7.1. Overall Study Design

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD (MADRS total score  $\geq 30$ ). The study will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, a 28-day follow-up period, and an extended follow-up period through Day 182 (6 months following the last dose).

The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. At the time of providing informed consent for the study, subjects will also be asked to authorize that their unique subject identifiers be entered into a registry ([www.subjectregistry.com](http://www.subjectregistry.com)) with the intent of identifying subjects who may meet exclusion criteria due to participation in another clinical study (Section 8.2).

The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and DSM-5 Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the MADRS and CGI-S.

Antidepressants are permitted provided subjects are on a stable dose for at least 60 days prior to Day 1 and agree to continue on the stable dose through the 28-day follow-up period (Day 42). Initiation of new antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints is prohibited between screening and completion of the Day 42 assessments.

Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) and randomized within each stratum to one of 3 treatment groups (SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo) in a 1:1:1 ratio. Subjects will self-administer a single dose of study drug with food once daily in the evening on an outpatient basis, for 14 days. Dose reductions are not permitted. Study drug administration will be monitored via a clinical monitoring service (see Section 9.3).

Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 1.

### 7.2. Number of Subjects

Approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects (see Section 13.8).

### 7.3. Treatment Assignment

Subjects will be randomly assigned to a treatment group on Day 1. Randomization will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline and performed within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo.

#### **7.4. Dose Adjustment Criteria**

Dose adjustments are not permitted in this study. Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated (see Section 8.3).

#### **7.5. Criteria for Study Termination**

Sage Therapeutics may 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 subjects, 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 ethics committee and initiate withdrawal procedures for participating subjects.

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

### 8.1. Subject Inclusion Criteria

Qualified subjects will meet all of the following criteria:

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is a male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements, including not participating in night shift work.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a MADRS total score of  $\geq 30$  at screening and Day 1 (prior to dosing).
7. Subjects taking antidepressants must have been taking these medications at the same dose for at least 60 days prior to Day 1. Subjects receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1.
8. Subject is willing to delay 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 42 visit.
9. Female subject agrees to use one of the following methods of contraception during the treatment period and for 30 days following the last dose of study drug, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH]  $>40$  mIU/mL), surgically sterile (hysterectomy or bilateral oophorectomy), or does not engage in sexual relations which carry a risk of pregnancy:
  - 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/occlusion.
  - Vasectomized partner.
10. Male subject agrees to use an acceptable method of effective contraception during the treatment period and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy. Acceptable methods of effective contraception for males includes vasectomy, or a condom with spermicide used together with highly effective female contraception methods if the

female partner is of child-bearing potential (see Inclusion Criteria #9 for acceptable contraception methods).

11. Male subject is willing to abstain from sperm donation the treatment period and for 5 days after receiving the last dose of the study drug.
12. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

## 8.2. Subject Exclusion Criteria

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

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study. A body mass index (BMI)  $\leq 18$  or  $\geq 50$  kg/m<sup>2</sup> at Screening is exclusionary; a BMI of 40 to 49 kg/m<sup>2</sup>, inclusive, at Screening is subject to a broader evaluation of medical comorbidities (such as sleep apnea, chronic obstructive pulmonary disease [COPD]), concomitant medications, and prior tolerability of sedating agents.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from two different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.
5. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
7. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.
8. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
9. Subject has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of

>450 msec in males or >470 msec in females will be the basis for exclusion from the study.

10. Subject has active psychosis per Investigator assessment.
11. Subject has a medical history of seizures.
12. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
13. Subject 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.
14. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
15. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
16. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to the first dose of study drug.
17. Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort, within 28 days prior to the first dose of study drug.
18. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
19. Subject plans to undergo elective surgery before completion of the Day 42 visit.
20. Subject is taking benzodiazepines, barbiturates, or GABA<sub>A</sub> modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or has been using these agents daily or near-daily ( $\geq 4$  times per week) for more than 1 year. Subject is taking any benzodiazepine or GABA modulator with a half-life of  $\geq 48$  hours (eg, diazepam) from 60 days prior to Day 1.
21. Subject is taking non-GABA anti-insomnia medications (eg melatonin, Benadryl [anti-histamines], trazodone), or first or second generation (typical/atypical) antipsychotics at Day -14.
22. Subject 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.
23. Subject has a history of sleep apnea.
24. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
25. Subject is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as-needed, at Day -28.

### **8.3. Subject Withdrawal Criteria**

Subjects may withdraw from the study drug or terminate from the study at any time for any reason. The Investigator may withdraw the subject from the study drug or from the study for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol
- The subject experiences an intolerable AE
- Other medical or safety reason, at the discretion of the Investigator and/or the Medical Monitor

The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject withdraws from study drug or terminates the study for any reason. The reason must be recorded in the subject's electronic case report form (eCRF).

If a subject is persistently noncompliant, the Investigator should discuss with the Sponsor the potential discontinuation of the subject. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the subject's eCRF, including:

- missed visits;
- interruptions in the schedule of study drug administration;
- non-permitted medications (see Section 9.2).

Subjects 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.

Subjects who discontinue study drug early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place as scheduled relative to the last dose of treatment (eg, if a subject's last dose is on Day 13, their first follow-up visit (Visit 7) should occur 4 days later). If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for the ET visit will be conducted.

A subject will be deemed lost to follow-up after attempts at contacting the subject have been unsuccessful.

#### **8.3.1. Replacement of Subjects**

Subjects will not be replaced. Additional subjects may be randomized if the drop-out rate is higher than anticipated (Section 13.8).

## **9. TREATMENT OF SUBJECTS**

### **9.1. Study Drug**

Subjects will self-administer SAGE-217 (20 or 30 mg) or matching placebo orally once daily in the evening with food for 14 days.

### **9.2. Prior Medications, Concomitant Medications, and Restrictions**

#### **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 Screening and throughout the duration of the study will be recorded. In addition, psychotropic medications taken 6 months prior to Screening will be recorded.

Any medication and/or supplement determined necessary for the welfare of the subject 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 60 days prior to Day 1 are permitted if the subject intends to continue the stable dose through Day 42.

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

- 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**

The following specific classes of medications are prohibited:

- Initiation of new psychotropic medications through the Day 42 visit
- Initiation of new antidepressant therapy from 60 days prior to Day 1 through the Day 42 visit
- Use of any benzodiazepines, barbiturates, GABA<sub>A</sub> modulators, GABA-containing agents from Day -28 through the Day 42 visit (from Day -60 for benzodiazepine or GABA modulators with a half-life of  $\geq 48$  hours)
- Chronic or as-needed psychostimulants (eg, methylphenidate, amphetamine) or opioids from Day -28 through the Day 42 visit

- First generation (typical) antipsychotics (eg, haloperidol, perphenazine) and second generation (atypical) antipsychotics (eg, aripiprazole, quetiapine) from Day -14 through the Day 42 visit
- Use of any non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) from Day -14 through the Day 42 visit
- Exposure to another investigational medication or device from 30 days prior to Screening through the Day 42 visit
- Any known strong inhibitors CYP3A4 from Day -28 or 5 half-lives prior to Day 1 (whichever is longer) through the treatment period
- Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort from Day -28 through the treatment period.

### 9.2.3. Other Restrictions

The consumption of grapefruit juice, grapefruit, or Seville oranges, or products containing these is prohibited throughout the treatment period.

Consumption of alcohol or use of drugs of abuse is discouraged throughout the duration of the study.

Female subjects 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 study drug.

Elective surgeries or procedures are prohibited through the Day 42 visit.

Subjects must not participate in night shift work.

Subjects receiving psychotherapy on a regular schedule for at least 60 days prior to Day 1 are permitted if the subject intends to continue the stable dose through the follow-up period (Day 42).

### 9.3. Treatment Adherence

SAGE-217 or placebo will be self-administered by subjects once daily in the evening with food. Sites will dispense study drug to the subjects to take at home with instructions for use (see Section 10.4 and Table 1).

Administration of study drug will be monitored by a medication adherence monitoring platform used on smartphones to visually confirm medication ingestion. Subjects will receive a reminder within a predefined time window to take study drug while using the application. Subjects 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 study drug administration by dose level, as well as missed doses.

In addition, the subject will be instructed to bring their dosing kit to the site as outlined in Table 1, 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 subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

The Investigator(s) will record any reasons for non-compliance in the source documents.

#### **9.4. Randomization and Blinding**

This is a randomized double-blind, placebo-controlled study. Subjects who meet the entrance criteria will be randomized in a stratified manner based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline; randomization will be done within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matched placebo. Subjects, 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 (SAGE-217 20 mg, SAGE-217 30 mg, or placebo) 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 Sponsor will be unblinded following the first database lock when all subjects complete the Day 42 visit; site personnel and subjects will remain blinded throughout the extended follow-up until the final database lock when all subjects complete the Day 182 visit.

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IRT (see Section 12.6 for more details related to unblinding).

## **10. STUDY DRUG MATERIALS AND MANAGEMENT**

### **10.1. Description of Study Drug**

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 (SMCC), colloidal silicon dioxide, and sodium stearyl fumarate as excipients. Colloidal silicon dioxide may be either a component of the SMCC or a standalone excipient in the formulation. 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. Study Drug 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 study drug in appropriately labeled, subject-specific kits containing sealed unit doses. Each unit dose consists of 1 capsule. Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Study drug 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. Study Drug 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. Study Drug Preparation**

Not applicable.

### **10.5. Study Drug Administration**

SAGE-217 is to be administered orally once daily in the evening with food. Practical options include taking SAGE-217 within 1 hour of dinner or taking SAGE-217 later in the evening with solid food. If a subject misses a dose, the subject 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. Study Drug Accountability**

Upon receipt of study drug, the Investigator(s), or the responsible pharmacist or designee, will inspect the study drug and complete and follow the instructions regarding receipt 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 subject-specific kits to subjects at the planned dispensation visit intervals outlined in [Table 1](#).

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

At the subsequent study drug-dispensing visit, the investigator or designee will access the IRT, providing the same subject ID number assigned at Screening, to obtain the medication ID number for the study drug to be dispensed at that visit. The medication ID number, the number of capsules dispensed, and the number of capsules returned by the subject 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 study drug provided is for use only as directed in this protocol. After the study is completed, all unused study drug must be returned as directed or destroyed on site per the Sponsor's instructions. The Investigator or designee must keep a record of all study drug received, dispensed and discarded.

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

## **10.7. Study Drug Handling and Disposal**

At the end of the study, all used and unused study drug will be reconciled and returned to Sage Therapeutics for destruction or destroyed locally; disposition of study drug will be documented.

A copy of the inventory record and a record of any clinical supplies that have been received, dispensed or destroyed must be documented by the site as directed. This documentation must include at least the information below:

- the number of dispensed units;
- the number of unused units;
- the number of units destroyed at the end of the study;
- the date, method and location of destruction.

## 11. ASSESSMENT OF EFFICACY [REDACTED]

All assessments will be conducted according to the schedule of assessments (Table 1). Study assessments that involve subject 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. Efficacy Assessments

#### 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 subject. An assessment timeframe of 7 days will be used on Day 1 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 subjects 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 of  $\leq 7$ .

#### 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 subjects 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 Impression (CGI)**

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 subject'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 subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject 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 subject's condition posttreatment. The Investigator will rate the subject'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. Short Form-36 Version 2 (SF-36v2)**

The Medical Outcomes Study SF-36v2 is a 36-item measure of health status that has undergone validation in many different disease states ([Ware 2007](#)). The SF-36v2 covers eight health dimensions including four physical health status domains (physical functioning, role participation with physical health problems [role-physical], bodily pain, and general health) and four mental health status domains (vitality, social functioning, role participation with emotional health problems [role-emotional], and mental health). In addition, two summary scores, physical component summary and mental component summary, are produced by taking a weighted linear combination of the eight individual domains. The SF-36v2 is available with two recall periods: the standard recall period is 4 weeks and the acute recall period is 1 week. This study will use the acute version, which asks patients to respond to questions as they pertain to the past week. Higher SF-36v2 scores indicate a better state of health.

#### **11.1.6. Patient Health Questionnaire (PHQ-9)**

The PHQ-9 is a subject-rated depressive symptom severity scale. To monitor severity over time for newly diagnosed subjects or subjects in current treatment for depression, subjects 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.

#### **11.1.7. Insomnia Severity Index (ISI)**

The ISI is a validated questionnaire designed to assess the nature, severity, and impact of insomnia (Morin 2011). The ISI uses a 5-point Likert Scale to measure various aspects of insomnia severity (0 = none, 1 = mild, 2 = moderate; 3 = severe; 4 = very severe), satisfaction with current sleep pattern (0 = very satisfied, 1 = satisfied, 2 = neutral, 3 = dissatisfied, 4 = very dissatisfied), and various aspects of the impact of insomnia on daily functioning (0 = not at all, 1 = a little, 2 = somewhat, 3 = much, 4 = very much). A total score of 0 to 7 = “no clinically significant insomnia,” 8 to 14 = subthreshold insomnia,” 15 to 21 = “clinical insomnia (moderate severity),” and 22 to 28 = “clinical insomnia (severe).”

#### **11.1.8. Core Consensus Sleep Diary**

The Core Consensus Sleep Diary collects subjective sleep parameters, including sleep onset latency, total sleep time, and wake after sleep onset, number of awakenings, and sleep quality. The take-home subject sleep diary assessment will be administered using an eDiary solution. The eDiary will be captured using either a provisioned smartphone device or bring-your-own-device solution, depending on the subject’s preference.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **12. ASSESSMENT OF SAFETY**

### **12.1. Safety Parameters**

All assessments will be conducted according to the schedule of assessments ([Table 1](#)).

#### **12.1.1. Demographic/Medical History**

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including family psychiatric history, will be documented. The diagnosis of MDD will be determined using the SCID-5-CT. If available, the disease code associated with the diagnosis of MDD based on the 10<sup>th</sup> revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used to determine whether the subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment during the current major depressive episode with adequate doses of antidepressants from two different classes for at least 4 weeks of treatment.

#### **12.1.2. Weight and Height**

Height (Screening only) and weight will be measured and documented.

#### **12.1.3. Physical Examination**

Physical examinations assessing body systems (eg, head, eyes, ears, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Whenever possible, the same individual is to perform all physical examinations for a given subject. Unscheduled brief, symptom-driven physical examinations may also be conducted per the Investigator's discretion.

Any abnormality in physical examinations will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section [12.2.1.1](#).

#### **12.1.4. Vital Signs**

Vital signs comprise both supine and standing for systolic and diastolic blood pressure and heart rate measurements. Heart rate and blood pressure are to be collected in supine position after the subject has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Respiratory rate and temperature are collected once, in either position. Vital signs will be documented. When vital signs are scheduled at the same time as blood draws, vital signs will be obtained first.

Any abnormality in vital signs will be interpreted by the Investigator as abnormal, NCS or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section [12.2.1.1](#).

### 12.1.5. Electrocardiogram (ECG)

Supine 12-lead ECGs 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.

### 12.1.6. Laboratory Assessments

Samples will be collected in accordance with acceptable laboratory procedures detailed in the laboratory manual.

The clinical laboratory tests to be performed are listed in [Table 3](#).

**Table 3: Clinical Laboratory Tests**

| Hematology  | Serum Chemistry                         | Urinalysis         | Coagulation                           |
|---|---|--------------------|---------------------------------------|
| Red blood cell count  | Alanine aminotransferase                | pH                 | Activated partial thromboplastin time |
| Hemoglobin  | Albumin                                 | Specific gravity   | Prothrombin time                      |
| Hematocrit  | Alkaline phosphatase                    | Protein            | International normalized ratio        |
| White blood cell count with differential                    | Aspartate aminotransferase              | Glucose            |                                       |
| Platelet count  | Total bilirubin                         | Red blood cell     |                                       |
| Red Blood Cell Indices (MCV, MCH, MCHC)                     | Direct bilirubin                        | Nitrite            |                                       |
| Reflex to Red blood cell morphology if indices are abnormal | Indirect bilirubin                      | Leukocyte esterase |                                       |
|   | Total protein                           | Ketones            |                                       |
|   | Creatinine                              | Bilirubin          |                                       |
|   | Blood urea nitrogen                     | Urobilinogen       |                                       |
|   | Creatine kinase                         |                    |                                       |
|   | Gamma-glutamyl transferase              |                    |                                       |
|   | Potassium                               |                    |                                       |
|   | Sodium                                  |                    |                                       |
|   | Lactate dehydrogenase                   |                    |                                       |
|   | Glucose                                 |                    |                                       |
|   | Chloride                                |                    |                                       |
|   | Bicarbonate                             |                    |                                       |
|   | Calcium                                 |                    |                                       |
|   | Phosphorus                              |                    |                                       |
|   | Triglycerides                           |                    |                                       |
|   | Thyroid stimulating hormone (TSH)       |                    |                                       |
|   | Reflex to free T3/T4 if TSH is abnormal |                    |                                       |

**Table 3: Clinical Laboratory Tests (Continued)**

| <b>Diagnostic</b>  |  |                     |  |
|--|--|---------------------|--|
| <b>Serum</b>   | <b>Urine</b>   | <b>Breathalyzer</b> |  |
| Hepatitis B<br>Hepatitis C<br>Reflex HCV RNA<br>HIV-1 and -2<br>Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: serum hCG<br>Female subjects, if menopause is suspected and not surgically sterile: FSH | Drug screen including:<br>amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine<br><br>Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: urine hCG | Alcohol             |  |

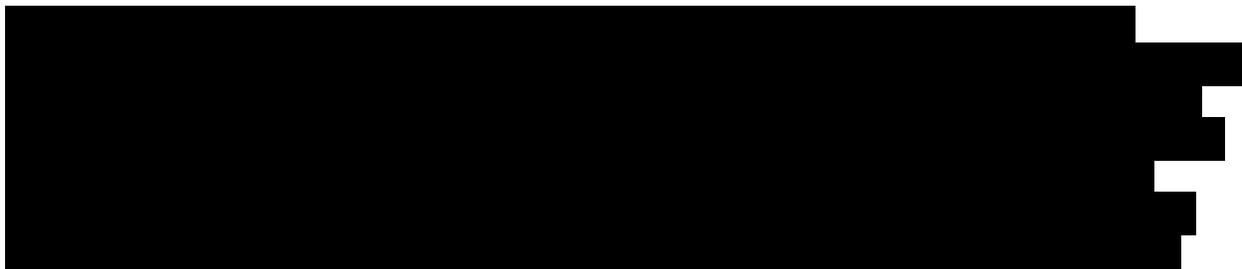
Abbreviations: FSH = follicle stimulating hormone; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus

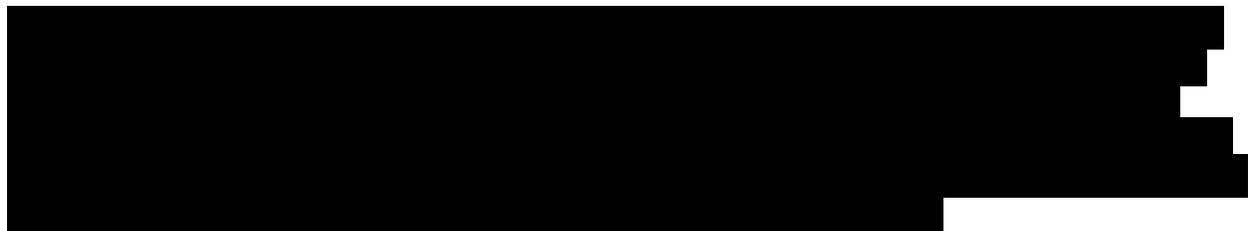
The central laboratory will perform laboratory tests for hematology, serum chemistry, urinalysis, and coagulation. The results of laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to Sage Therapeutics or designee in the format requested by Sage Therapeutics.

Laboratory reports must be signed and dated by the Investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will require clear and complete documentation in the source documents as to the investigator’s assessment of not clinically significant before proceeding with randomization.

All clinical laboratory test results outside the central laboratory’s reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.1. A clinically significant laboratory abnormality following subject randomization will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

A serum follicle stimulating hormone test will be conducted at Screening to confirm whether a female subject with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being post-menopausal (Section 8.1).





#### **12.1.6.1. Drugs of Abuse and Alcohol**

Urine toxicology tests will be performed for selected drugs of abuse (see [Table 3](#)). A breath test for alcohol will be performed.

#### **12.1.6.2. Pregnancy Screen**

For female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at all other scheduled timepoints thereafter, including the ET visit for subjects who prematurely discontinue.

#### **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 subject with suicidal ideation and behavior, and a post-baseline 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, as outlined in [Table 1](#).

#### **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 trials. 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. Definition of Adverse Events**

#### **12.2.1.1. Adverse Event (AE)**

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 an AE that occurs after the first administration of any study drug. The term study drug includes any Sage investigational product, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) and/or if the Investigator considers them to be clinically significant. Laboratory values and vital signs that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations 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 subject 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.

Any AEs that are unresolved at the subject'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 subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

#### **12.2.1.2. Serious Adverse Event (SAE)**

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 subject or may require medical intervention to prevent one 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 subject 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 within 24 hours of first awareness (Section 12.5). All SAEs should be followed until the event resolved, the condition stabilized, was no longer considered clinically significant or the subject was lost to follow-up. Serious adverse events occurring after a subject’s final visit (including the last follow-up visit) should be reported to Sage or designee only if the Investigator considers the SAE to be related to study treatment.

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject 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 subject’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 the Investigator, between the subject’s consent to participate in the study and at the time of the procedure or treatment.

### 12.3. Relationship to Study Drug

The Investigator must make the determination of relationship to the study drug for each adverse event (not related, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as “not related.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered at least “possibly related.”

**Table 4: Relationship to Study Drug**

| <b>Relationship</b> | <b>Definition</b>  |
|---------------------|--|
| Not Related:        | No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject’s clinical state.  |
| Possibly Related:   | A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.<br>The reaction might have been produced by the subject’s clinical state or other modes of therapy administered to the subject, but this is not known for sure.    |
| Probably Related:   | A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.<br>The reaction cannot be reasonably explained by the known characteristics of the subject’s clinical state or other modes of therapy administered to the subject. |

If the relationship between the adverse event/serious adverse event and the investigational product is determined to be “possible” or “probable”, the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

#### **12.4. Recording Adverse Events**

Adverse events spontaneously reported by the subject 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, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study drug or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

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 12.2.1.2. An AE of severe intensity may not be considered serious.

If a female subject becomes pregnant during this study, pregnancy information must be collected and recorded on the Sage Therapeutics pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. The Investigator will also attempt to collect pregnancy information on any male subject’s female partner who becomes pregnant while the male subject is participating in study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant female subjects.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication or a complication relating to the pregnancy occurs (e.g., spontaneous abortion). If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly/birth defects), the investigator should follow the procedures for reporting an SAE.

#### **12.5. Reporting Serious Adverse Events**

All SAEs must be reported to Sage, or designee, immediately. A written account of the SAE must be sent to Sage, or designee, within 24 hours of the first awareness of the event by the investigator and/or his staff. 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 Therapeutics, 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 case report form (CRF) and/or study file.

Any SAEs discovered by the Investigator after the designated follow up time for the study, should be promptly reported to Sage, or designee, according to the timelines noted above.

The contact information for reporting SAEs and/or pregnancies is located in the study reference manual.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the ethics committee 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. Ethics Committee (EC)/Institutional Review Boards (IRBs) will be notified of SAEs and/or SUSARs as required by local law. In addition, appropriate Sponsor Drug Safety and Pharmacovigilance personnel, or designee, will unblind SUSARs for the purpose of regulatory reporting. The Sponsor, or designee, will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. The Sponsor, or designee, will submit SUSARs to investigators in a blinded fashion.

## **12.6. Emergency Identification of Study Drug**

During the study, the blind is to be broken by the Investigator only when the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. Unless a subject is at immediate risk, the Investigator must make diligent attempts to contact Sage prior to unblinding the study treatment administered to a subject. Any request from the Investigator about the treatment administered to study subjects must be discussed with Sage. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented in the source records. Unless a subject is at immediate risk, any request for the unblinding of individual subjects must be made in writing to Sage and approved by the appropriate Sage personnel, according to standard operating procedures.

In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the eCRF. If the subject or study center personnel have been unblinded, the subject will be permanently discontinued from the study.

## 13. STATISTICS

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to treatment unblinding.

When all subjects complete the Day 42 visit, the database will be locked, followed by treatment unblinding to the Sponsor and data analyses (site personnel and subjects will remain blinded). The extended follow-up period will continue as scheduled; the final database lock will occur when all subjects complete the extended follow-up period.

### 13.1. Data Analysis Sets

The Randomized set is defined as all subjects who are randomized.

The Safety Set is defined as all subjects administered study drug.

The Full Analysis Set is defined as all randomized subjects in the Safety Set with a valid baseline HAM-D total score and at least 1 post-baseline HAM-D total score.



### 13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data. A sensitivity analysis will be used to investigate the impact of missing data if  $\geq 5\%$  of subjects in any treatment group have missing data.

### 13.3. General Considerations

For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), 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 (Section 12.1.1) and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized using the Safety Set.

Hepatitis, HIV, drug and alcohol, and pregnancy screening results will be listed, but not summarized as they are considered part of the inclusion/exclusion criteria.

Medical/family history will be listed by subject.

### 13.5. Efficacy Analyses

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment.

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 post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported 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. 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, SF-36v2 score, PHQ-9 score, sleep diary endpoints (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score and selected individual items and/or subscale scores in HAM-D for change from baseline.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as  $\geq 50\%$  reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of  $\leq 7.0$ ). 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 the 15-day time point. 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 including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.

### 13.6. Safety Analyses

Safety and tolerability of study drug will be evaluated by incidence of AEs/SAEs, 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 subject and summarized by treatment group. All safety summaries will be performed on the Safety Set. Where applicable, ranges of potentially clinically significant (PCS) values are provided in the SAP.

### **13.6.1. Adverse Events**

The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized overall and by Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or higher, System Organ Class (SOC), and preferred term. Incidences will be presented in order of decreasing frequency. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 12.3).

Any TEAEs leading to discontinuation and SAEs with onset after the start of study drug will also be summarized.

All AEs and SAEs (including those with onset or worsening before the start of study drug) 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 range of each parameter is provided by the laboratory; shift from baseline to post-baseline values in abnormality of results will be provided. Potentially clinically significant values will be summarized by treatment. Any abnormal values deemed clinically significant by the investigator will be reported as an AE (see Section 12.2). Clinical laboratory results will be listed by subject and timing of collection.

### **13.6.3. Physical Examinations**

The occurrence of a physical examination (Y/N) and the date performed will be listed by subject. Any clinically significant observation in physical examination will be reported as an AE (see Section 12.2).

### **13.6.4. Vital Signs**

Results from each visit and mean changes from baseline in vital signs will be summarized by scheduled visit. Any abnormality deemed clinically significant by the investigator will be reported as an AE (see Section 12.2). Potentially clinically significant values will be summarized by treatment. Vital sign results will be listed by subject 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 subject: 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 subject 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 signing the ICF through the duration of the study will be recorded. In addition, all psychotropic medications taken 6 months prior to Screening will be recorded. Those medications taken prior to the initiation of the start of study drug will be denoted “Prior”. Those medications taken prior to the initiation of the study drug and continuing beyond the initiation of the study drug or those medications started at the same time or after the initiation of the study drug will be denoted “Concomitant” (ie, those with a start date on or after the first dose of study drug, or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug).

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 subject, 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 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 subject.

[REDACTED]

## **13.8. Determination of Sample Size**

Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable subjects 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 SD of 10 points. Assuming an 11% dropout rate and a 1:1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 450 total randomized subjects will be required to obtain 399 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is greater than 11%.

## **14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **14.1. Study Monitoring**

Before an investigational site can enter a subject into the study, a representative of Sage Therapeutics (or designee) 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 investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject'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 subject (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.

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

### **14.2. Audits and Inspections**

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics audit or 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, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The

investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

### **14.3. Institutional Review Board (IRB) or Ethics Committee (EC)**

The Principal Investigator must obtain IRB (or EC) approval for the investigation. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the subject 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 Practices and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit. Please see Section [14.2](#) for more details regarding the audit process.

## **16. ETHICS**

### **16.1. Ethics Review**

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or EC as appropriate. The investigator must submit written approval to Sage Therapeutics before he or she can enroll any subject into the study.

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

The Principal Investigator is also responsible for providing the IRB 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 EC according to local regulations and guidelines.

### **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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines, as well as all applicable regulatory requirements.

### **16.3. Written Informed Consent**

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

## **17. DATA HANDLING AND RECORDKEEPING**

### **17.1. Inspection of Records**

Sage Therapeutics will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **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, whichever is longer. If not approved, documentation must be maintained for 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

## **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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### **Protocol 217-MDD-301 Amendment 3**

**Date of Amendment: 07 March 2019**

#### **A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy of SAGE-217 in the Treatment of Adult Subjects with Major Depressive Disorder**

##### **Rationale for Protocol Amendment**

The primary purpose for this protocol amendment is to extend the follow-up period (total of 6 months). Additional changes are being implemented as outlined below:

- Prohibit subjects from participating in night shift work for subject safety with evening dosing
- Specify subjects receiving psychotherapy at Screening must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1 and plan to continue the psychotherapy schedule through Day 42
- Specify body mass index parameters that would be exclusionary or that would require further evaluation prior to admission to the study
- Restrict only strong CYP3A inducers due to results from a drug-drug interaction study of SAGE-217 with CYP inducers
- Exclude subjects who have been taking benzodiazepines, barbiturates, or GABA<sub>A</sub> modulators daily or near-daily for more than 1 year at Screening and exclude subjects taking any benzodiazepine or GABA modulator with a half-life of  $\geq 48$  hours (eg, diazepam) from 60 days prior to Day 1 to avoid any confounding effects with SAGE-217
- Exclude all atypical and typical antipsychotics
- Exclude psychostimulants and opioids
- Specify 2 database locks (the first after all subjects complete 4 weeks of follow-up and the final after all subjects complete the 6-month follow-up period)
- Increase time required for subject to be standing before standing vital signs are taken
- Remove pulse oximetry that was inadvertently listed in Section 12.1.4 Vital Signs
- Specify additional clinical laboratory tests that the laboratory performs
- Specify conduct for unresolved adverse events after the last scheduled visit
- Update terminology and definition of the Efficacy Set (now Full Analysis Set) to specify that subjects in this set must have a valid baseline HAM-D score
- Remove concomitant medication usage that was inadvertently listed in Section 13.6 Safety Analyses

A detailed summary of changes is provided in [Table 1](#)~~Table 1~~. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed individually, nor are administrative updates such as revising the document date, updating the document header and version number, and updating the table of contents.

**Table 1: Protocol Amendment 3 Detailed Summary of Changes**

The primary section of the protocol affected by the changes in Protocol Amendment 3 is indicated. The corresponding related text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

---

**Purpose:** Extend the follow-up period (total of 6 months) resulting in an additional 3 visits

---

The primary change occurs in Section 7.1 Overall Study Design

Changed text: This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD (MADRS total score  $\geq 30$ ). The study will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, [a 28-day follow-up period](#), and [an extended follow-up period through Day 182 \(6 months following the last dose\)](#)~~a 4-week Follow-up Period~~.

Sections also affected by this change:

- Synopsis, Planned Duration of Subject Participation
- Synopsis, Study Description
- Table 1 Schedule of Events
- Synopsis and Section 8.1 Subject Inclusion Criteria #8, #9, #10, and #11
- Synopsis and Section 8.2 Subject Exclusion Criteria #19
- Section 8.3 Subject Withdrawal Criteria
- Section 9.2.2 Prohibited Medications
- Section 9.2.3 Other Restrictions

---

**Purpose:** Prohibit subjects from participating in night shift work for subject safety with evening dosing

---

The primary change occurs in Section 8.1 Subject Inclusion Criteria

Changed text: 4. Subject agrees to adhere to the study requirements, [including not participating in night shift work](#).

Sections also affected by this change:

- Synopsis, Subject Inclusion Criteria
  - 9.2.3 Other Restrictions
-

---

**Purpose:** Specify subjects receiving psychotherapy at Screening must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1 and plan to continue the psychotherapy schedule through Day 42

---

The primary change occurs in Section 8.1 Subject Inclusion Criteria

Added text:                   7. Subjects taking ~~antidepressants psychotropic medications used to treat major depressive disorder (eg, antidepressants, atypical antipsychotics)~~ must have been taking these medications at the same dose for at least 60 days prior to Day 1. Subjects receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1.

Sections also affected by this change:

- Synopsis, Subject Inclusion Criteria
- 9.2.3 Other Restrictions

---

**Purpose:** Specify body mass index parameters that would be exclusionary or that would require further evaluation prior to admission to the study

---

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Added text:                   3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study. A body mass index (BMI)  $\leq 18$  or  $\geq 50$  kg/m<sup>2</sup> at Screening is exclusionary; a BMI of 40 to 49 kg/m<sup>2</sup>, inclusive, at Screening is subject to a broader evaluation of medical co-morbidities (such as sleep apnea, chronic obstructive pulmonary disease [COPD]), concomitant medications, and prior tolerability of sedating agents.

Sections also affected by this change:

- Synopsis, Subject Exclusion Criteria
-

---

**Purpose:** Restrict only strong CYP3A inducers due to results from a drug-drug interaction study of SAGE-217 with CYP inducers

---

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Changed text: 17. Use of any strong CYP3A inducer, such as ~~such as~~ rifampin, carbamazepine, ~~ritonavir~~, enzalutamide, ~~mitotane~~ ~~efavirenz~~, nevirapine, phenytoin, ~~phenobarbital and/or~~ St John's Wort, within 28 days prior to the first dose of study drug.

Sections also affected by this change:

- Synopsis, Subject Exclusion Criteria
- Section 9.2.2 Prohibited Medications

---

**Purpose:** Exclude subjects that have been taking benzodiazepines, barbiturates, or GABA<sub>A</sub> modulators daily or near-daily for more than 1 year at Screening and exclude subjects taking any benzodiazepine or GABA modulator with a half-life of  $\geq 48$  hours (eg, diazepam) from 60 days prior to Day 1 to avoid any confounding effects with SAGE-217

---

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Changed text: 20. Subject is taking benzodiazepines, barbiturates, or GABA<sub>A</sub> modulators ~~GABA-containing agents~~ (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or has been using these agents daily or near-daily ( $\geq 4$  times per week) for more than 1 year. Subject is taking any benzodiazepine or GABA modulator with a half-life of  $\geq 48$  hours (eg, diazepam) from 60 days prior to Day 1.

Sections also affected by this change:

- Synopsis, Subject Exclusion Criteria
  - Section 9.2.2 Prohibited Medications
-

---

**Purpose:** Exclude all atypical and typical antipsychotics

---

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Changed text:           21. Subject is taking non-GABA anti-insomnia medications (eg melatonin, Benadryl [anti-histamines], trazodone, ~~low dose quetiapine, mirtazapine, etc~~), or first or second generation (typical/atypical) antipsychotics at Day -14.

Sections also affected by this change:

- Synopsis, Subject Exclusion Criteria
- Synopsis and Section 8.1 Subject Inclusion Criterion #7
- Section 9.2.1 Prior and Concomitant Medications and/or Supplements
- Section 9.2.2 Prohibited Medications

---

**Purpose:** Exclude psychostimulants and opioids

---

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Added text:           25. Subject is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as-needed, at Day -28.

Sections also affected by this change:

- Synopsis, Subject Exclusion Criteria
- Section 9.2.2 Prohibited Medications

---

**Purpose:** Specify 2 database locks (the first after all subjects complete 4 weeks of follow-up and the final after all subjects complete the 6-month follow-up period)

---

The primary change occurs in Section 9.4 Randomization and Blinding

Added text:           The Sponsor will be unblinded following the first database lock when all subjects complete the Day 42 visit; site personnel and subjects will remain blinded throughout the extended follow-up until the final database lock when all subjects complete the Day 182 visit.

Sections also affected by this change:

- Synopsis, Statistical Methods
  - Section 13 Statistics
-

---

**Purpose:** Increase time required for subject to be standing before standing vital signs are taken

---

The primary change occurs in Section 12.1.4 Vital Signs

Changed text: Vital signs comprise both supine and standing for systolic and diastolic blood pressure and heart rate measurements. Heart rate and blood pressure are to be collected in supine position after the subject has been resting for 5 minutes and then after [approximately 34 minutes](#) in the standing position.

Sections also affected by this change:

- Table 1 footnote 'k'

---

**Purpose:** Remove pulse oximetry that was inadvertently listed in Section 12.1.4 Vital Signs

---

The primary change occurs in Section 12.1.4 Vital Signs

Removed text: Respiratory rate, ~~pulse oximetry~~ and temperature are collected once, in either position.

Sections also affected by this change:

- Not applicable

---

**Purpose:** Specify additional clinical laboratory tests that the laboratory performs

---

The primary change occurs in Table 3 Clinical Laboratory Tests

Changed text: Added red blood cell indices to the hematology panel which will reflex to red blood cell morphology if the indices are abnormal.

Added that the thyroid stimulation hormone (TSH) test in the serum chemistry panel will reflex to free T3/T4 if TSH is abnormal

Sections also affected by this change:

- Not applicable
-

---

**Purpose:** Specify conduct for unresolved adverse events after the last scheduled visit

---

The primary change occurs in 12.2.1.1 Adverse Event (AE)

Added text: Any AEs that are unresolved at the subject'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 subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Sections also affected by this change:

- Not applicable

---

**Purpose:** Update terminology and definition of the Efficacy Set (now Full Analysis Set) to specify that subjects in this set must have a valid baseline HAM-D score

---

The primary change occurs in 13.1 Data Analysis Sets

Changed text: The ~~Efficacy-Full Analysis~~ Set ~~is~~, defined as all randomized subjects in the Safety Set with a valid baseline HAM-D total score and at least 1 post-baseline HAM-D total score evaluation, will be used for analysis of efficacy data.

Sections also affected by this change:

- Synopsis, Analysis Sets

---

**Purpose:** Remove concomitant medication usage that was inadvertently listed in Section 13.6 Safety Analyses

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The primary change occurs in 13.6 Safety Analyses

Removed text: Safety and tolerability of study drug will be evaluated by incidence of ~~adverse events/serious adverse events~~ AEs/SAEs, ~~concomitant medication usage~~, vital signs, clinical laboratory evaluations, and 12-lead ECG.

Sections also affected by this change:

- Synopsis, Safety Analysis



**A PHASE 3, MULTICENTER, DOUBLE-BLIND,  
RANDOMIZED, PLACEBO-CONTROLLED STUDY  
EVALUATING THE EFFICACY OF SAGE-217 IN THE  
TREATMENT OF ADULT SUBJECTS WITH MAJOR  
DEPRESSIVE DISORDER**

**PROTOCOL NUMBER: 217-MDD-301**

|                           |  |
|---------------------------|--|
| Study Drug                | SAGE-217   |
| Clinical Phase            | Phase 3  |
| Sponsor                   | Sage Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 |
| Sponsor Contact           | [REDACTED]<br>Tel: [REDACTED]<br>email: [REDACTED]                 |
| Sponsor Medical Monitor   | [REDACTED] MD, MBA<br>Tel: [REDACTED]<br>email: [REDACTED]         |
| Date of Original Protocol | Version 1.0, 16 JUL 2018   |
| Date of Amendment 1       | Version 2.0, 25 SEP 2018   |
| Date of Amendment 2       | Version 3.0, 11 OCT 2018   |
| Date of Amendment 3       | Version 4.0, 07 March 2019   |
| Date of Amendment 4       | Version 5.0, 25 March 2019   |

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.

**Protocol Number:** 217-MDD-301  
**Study Drug:** SAGE-217  
**Study Phase:** Phase 3  
**Sponsor:** Sage Therapeutics, Inc.  
**Protocol Date:** Version 5.0, 25 March 2019

**Sponsor Approval**

[Redacted] [Redacted]  
[Redacted] MD, MBA Date (DD MMM YYYY)  
Sage Therapeutics

[Redacted] [Redacted]  
[Redacted] DVM, MS, MPH Date (DD MMM YYYY)  
Sage Therapeutics

[Redacted] [Redacted]  
[Redacted] RAC Date (DD MMM YYYY)  
Sage Therapeutics

[Redacted] [Redacted]  
[Redacted] Date (DD MMM YYYY)  
Sage Therapeutics

[Redacted] [Redacted]  
[Redacted] PhD Date (DD MMM YYYY)  
Sage Therapeutics

[Redacted] [Redacted]  
[Redacted] Date (DD MMM YYYY)  
Sage Therapeutics

## INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-MDD-301 clinical 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.

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Printed name of Investigator

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Signature of Investigator

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Date (DD Month YYYY)

## 2. SYNOPSIS

|  |
|--|
| <b>Name of Sponsor/Company:</b><br>Sage Therapeutics   |
| <b>Name of Investigational Product:</b><br>SAGE-217 Capsules   |
| <b>Name of Active Ingredient:</b><br>SAGE-217  |
| <b>Title of Study:</b> A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy of SAGE-217 in the Treatment of Adult Subjects with Major Depressive Disorder  |
| <b>Number of Sites and Study Location:</b> Approximately 55 sites in the United States   |
| <b>Phase of development:</b> 3   |
| <b>Planned Duration of Subject Participation:</b><br>Up to 213 days (up to 28-day Screening Period, 14-day Double-blind Treatment Period, and up to 6 months (168 days) of Follow-up)  |
| <b>Objectives:</b><br>Primary: <ul style="list-style-type: none"><li>To evaluate the efficacy of SAGE-217 in the treatment of major depressive disorder (MDD) compared to placebo.</li></ul> Secondary: <ul style="list-style-type: none"><li>To evaluate the effect of SAGE-217 on sleep.</li><li>To assess patient-reported outcome (PRO) measures as they relate to health-related quality of life and depressive symptoms.</li></ul> Safety: <ul style="list-style-type: none"><li>To evaluate the safety and tolerability of SAGE-217.</li></ul> <p>█</p> <p>█</p> <p>█</p>   |
| <b>Endpoints:</b><br>Primary: <ul style="list-style-type: none"><li>The primary efficacy endpoint is the change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 15.</li></ul> Secondary: <ul style="list-style-type: none"><li>Change from baseline in the 17-item HAM-D total score at other timepoints</li><li>HAM-D response at Day 15 and all other time points, defined as a <math>\geq 50\%</math> reduction in HAM-D score from baseline</li><li>HAM-D remission at Day 15 and all other time points, defined as HAM-D total score <math>\leq 7</math></li><li>Clinical Global Impression - Improvement (CGI-I) response at Day 15 and all other</li></ul> |

time points, defined as “much improved” or “very much improved”

- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at Day 15 and all other time points
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at Day 15 and all other time points
- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15 and all other time points
- Change from baseline in HAM-D subscale and individual item scores at all time points
- Change in sleep at Day 15 and all other time points, as assessed by
  - Insomnia Severity Index (ISI)
  - Subjective sleep parameters collected with the Core Consensus Sleep Diary
- Change from baseline in PRO measures of health-related quality of life, as assessed by responses to the 36-item Short Form survey version 2 (SF-36v2), and of depressive symptoms, as assessed by the 9-item Patient Health Questionnaire (PHQ-9)

**Safety Endpoints:**

- Incidence and severity of adverse events/serious adverse events
- Changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs)
- Suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Potential withdrawal symptoms using the 20-item Physician Withdrawal Checklist (PWC-20)

[REDACTED]

**Study Description:**

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD (MADRS total score  $\geq 32$  and a HAM-D total score  $\geq 22$ ). Randomization will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline and carried out within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo; subjects will be treated for 14 days beginning on Day 1. The study will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, a 28-day follow-up period, and an extended follow-up period through Day 182 (6 months following the last dose).

The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the

MADRS, HAM-D and CGI-S.

Antidepressants are permitted provided subjects are on a stable dose for at least 60 days prior to Day 1 and agree to continue on the stable dose through the follow-up period (Day 42). Initiation of new antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of the Day 42 assessments.

Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) and randomized within each stratum to one of 3 treatment groups (SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo) in a 1:1:1 ratio. Subjects will self-administer a single dose of study drug once daily in the evening with food, on an outpatient basis, for 14 days. Practical options include taking SAGE-217 within 1 hour of dinner or taking SAGE-217 later in the evening with solid food. Subjects will return to the study center during the treatment and follow-up periods as outlined in [Table 1](#).

Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated. Subjects who discontinue treatment early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place as scheduled relative to the last dose of treatment (eg, if a subject's last dose is on Day 13, their first follow-up visit (Visit 7,) should occur 4 days later). If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for both visits will be conducted.

**Number of Subjects (planned):**

Approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects.

**Eligibility Criteria:**

**Inclusion Criteria:**

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is a male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements, including not participating in night shift work.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a MADRS total score of  $\geq 32$  and a HAM-D total score  $\geq 22$  at screening and Day 1 (prior to dosing).
7. Subjects taking antidepressants must have been taking these medications at the same dose for at least 60 days prior to Day 1. Subjects receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1.
8. Subject is willing to delay start of other antidepressant or anti-anxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics

and sleep aids, until after completion of the Day 42 visit.

9. Female subject agrees to use one of the following methods of contraception during the treatment period and for 30 days following the last dose of study drug, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH] >40 mIU/mL), surgically sterile (hysterectomy or bilateral oophorectomy), or does not engage in sexual relations which carry a risk of pregnancy:
  - 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/occlusion
  - Vasectomized partner
10. Male subject agrees to use an acceptable method of effective contraception during the treatment period and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy. Acceptable methods of effective contraception for males includes vasectomy, or a condom with spermicide used together with highly effective female contraception methods if the female partner(s) is of child-bearing potential (see Inclusion Criteria #9 for acceptable contraception methods).
11. Male subject is willing to abstain from sperm donation during the treatment period and for 5 days after receiving the last dose of the study drug.
12. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

**Exclusion Criteria:**

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study. A body mass index (BMI)  $\leq 18$  or  $\geq 50$  kg/m<sup>2</sup> at Screening is exclusionary; a BMI of 40 to 49 kg/m<sup>2</sup>, inclusive, at Screening is subject to a broader evaluation of medical comorbidities (such as sleep apnea, chronic obstructive pulmonary disease [COPD]), concomitant medications, and prior tolerability of sedating agents.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major

- depressive episode (excluding antipsychotics) from two different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.
5. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
  6. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
  7. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.
  8. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
  9. Subject has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
  10. Subject has active psychosis per Investigator assessment.
  11. Subject has a medical history of seizures.
  12. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
  13. Subject 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.
  14. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
  15. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
  16. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to the first dose of study drug.
  17. Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort, within 28 days prior to the first dose of study drug.
  18. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
  19. Subject plans to undergo elective surgery before completion of the Day 42 visit.
  20. Subject is taking benzodiazepines, barbiturates, or GABA<sub>A</sub> modulators (eg, eszopiclone,

zopiclone, zaleplon, and zolpidem) at Day -28, or has been using these agents daily or near-daily ( $\geq 4$  times per week) for more than 1 year. Subject is taking any benzodiazepine or GABA modulator with a half-life of  $\geq 48$  hours (eg, diazepam) from 60 days prior to Day 1.

21. Subject is taking non-GABA anti-insomnia medications (eg melatonin, Benadryl [anti-histamines], trazodone), or first or second generation (typical/atypical) antipsychotics at Day -14.
22. Subject 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.
23. Subject has a history of sleep apnea.
24. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
25. Subject is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as-needed, at Day -28.

**Study Drug, Dosage and Mode of Administration:**

SAGE-217 is available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose (SMCC), colloidal silicon dioxide and sodium stearyl fumarate as excipients. Colloidal silicon dioxide may be either a component of the SMCC or a standalone excipient in the formulation. SAGE-217 capsules will be orally administered as a 30-mg or 20-mg dose.

**Reference Therapy, Dosage, and Mode of Administration:**

Placebo will be provided as hard gelatin capsules for oral administration containing only the excipients listed above for the active capsule.

**Duration of Treatment:** 14 days

**Statistical methods:**

A 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 treatment unblinding.

When all subjects complete the Day 42 visit, the database will be locked, followed by treatment unblinding to the Sponsor and data analyses (site personnel and subjects will remain blinded). The extended follow-up period will continue as scheduled; the final database lock will occur when all subjects complete the extended follow-up period.

**General Considerations**

For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration.

Continuous endpoints will be summarized descriptively with 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 Randomized Set is defined as all subjects who are randomized.

The Safety Set is defined as all subjects administered study drug.

The Full Analysis Set is defined as all randomized subjects in the Safety Set with a valid baseline HAM-D total score at least 1 post-baseline HAM-D total score.

### **Determination of Sample Size**

Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable subjects would provide 90% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation (SD) of 10 points. Assuming a 11% dropout rate and a 1:1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 450 total randomized subjects will be required to obtain 399 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is greater than 11%.

### **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 post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported 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, SF-36v2 score, PHQ-9 score, sleep diary endpoints (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score and selected individual items and/or subscale scores in HAM-D for change from baseline.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as  $\geq 50\%$  reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of  $\leq 7.0$ ). 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 the 15-day time point. 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 including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.

**Safety Analysis**

Safety and tolerability of study drug will be evaluated by incidence of adverse events/serious adverse events, 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.

[REDACTED]

**Table 1: Schedule of Events**

| Visits                                       | Screening Period | Double-Blind, Placebo-Controlled Treatment Period |             |             |              |  | Follow-up Period |              |              |              |                          | Extended Follow-Up |
|--|------------------|---|-------------|-------------|--------------|--|------------------|--------------|--------------|--------------|--------------------------|--------------------|
|  |                  | D1  | D3<br>(±1d) | D8<br>(+1d) | D12<br>(±1d) | D15<br>(+1d)<br>and/or<br>EOT <sup>a</sup> | D18<br>(±1d)     | D21<br>(±1d) | D28<br>(±3d) | D35<br>(±3d) | D42<br>(±3d)<br>or<br>ET |                    |
| Visit Days                                   | D-28 to D-1      |   |             |             |              |  |                  |              |              |              |                          |                    |
| Visit Number                                 | V1               | V2  | V3          | V4          | V5           | V6   | V7               | V8           | V9           | V10          | V11                      | V12, V13, V14      |
| <b>Study Procedure</b>                       |                  |   |             |             |              |  |                  |              |              |              |                          |                    |
| Informed Consent                             | X                |   |             |             |              |  |                  |              |              |              |                          |                    |
| Duplicate Subject Check <sup>b</sup>         | X                |   |             |             |              |  |                  |              |              |              |                          |                    |
| Inclusion/Exclusion                          | X                | X   |             |             |              |  |                  |              |              |              |                          |                    |
| Serum FSH test <sup>c</sup>                  | X                |   |             |             |              |  |                  |              |              |              |                          |                    |
| SCID-5-CT                                    | X                |   |             |             |              |  |                  |              |              |              |                          |                    |
| MGH ATRQ                                     | X                |   |             |             |              |  |                  |              |              |              |                          |                    |
| Demographics                                 | X                |   |             |             |              |  |                  |              |              |              |                          |                    |
| Medical/Family History                       | X                |   |             |             |              |  |                  |              |              |              |                          |                    |
| Subject training <sup>d</sup>                | X                | X   |             |             |              |  |                  |              |              |              |                          |                    |
| Randomization                                |                  | X   |             |             |              |  |                  |              |              |              |                          |                    |
| Physical Examination <sup>e</sup>            | X                | X   |             |             |              |  |                  |              |              |              | X                        |                    |
| Body Weight/Height                           | X                |   |             |             |              | X (wt only)                                |                  |              |              |              | X (wt only)              |                    |
| Clinical Laboratory Assessments <sup>f</sup> | X                | X   |             | X           |              | X  |                  | X            | X            |              | X                        | X                  |
| Drug & Alcohol Screen <sup>g</sup>           | X                | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        |                    |
| Pregnancy Test <sup>h</sup>                  | X                | X   |             |             |              | X  |                  |              | X            |              | X                        |                    |
| Hepatitis & HIV Screen                       | X                |   |             |             |              |  |                  |              |              |              |                          |                    |

| Visits                    | Screening Period | Double-Blind, Placebo-Controlled Treatment Period |             |             |              |  | Follow-up Period |              |              |              |                          | Extended Follow-Up |                          |
|---------------------------|------------------|---|-------------|-------------|--------------|--|------------------|--------------|--------------|--------------|--------------------------|--------------------|--------------------------|
|                           |                  | D1  | D3<br>(±1d) | D8<br>(+1d) | D12<br>(±1d) | D15<br>(+1d)<br>and/or<br>EOT <sup>a</sup> | D18<br>(±1d)     | D21<br>(±1d) | D28<br>(±3d) | D35<br>(±3d) | D42<br>(±3d)<br>or<br>ET |                    |                          |
| Visit Days                | D-28 to D-1      | V1  | V2          | V3          | V4           | V5   | V6               | V7           | V8           | V9           | V10                      | V11                | D70, D126, D182<br>(±7d) |
| Visit Number              | V1               | V2  | V3          | V4          | V5           | V6   | V7               | V8           | V9           | V10          | V11                      | V12, V13, V14      |                          |
| Study Procedure           |                  |   |             |             |              |  |                  |              |              |              |                          |                    |                          |
| Vital Signs <sup>k</sup>  | X                | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        | X                  | X                        |
| 12-Lead ECG <sup>l</sup>  | X                | X   |             |             |              | X  |                  |              |              |              | X                        |                    | X (Day 182 only)         |
| C-SSRS <sup>m</sup>       | X                | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        | X                  | X                        |
| HAM-D <sup>n, o</sup>     | X                | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        | X                  | X                        |
| MADRS                     | X                | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        | X                  |                          |
| HAM-A <sup>o</sup>        |                  | X   |             | X           |              | X  | X                |              | X            |              | X                        |                    |                          |
| CGI-S                     | X                | X   | X           | X           | X            | X  | X                | X            | X            | X            | X                        | X                  | X                        |
| CGI-I                     |                  |   | X           | X           | X            | X  | X                | X            | X            | X            | X                        | X                  | X                        |
| SF-36v2                   | X                | X   |             | X           |              | X  |                  |              | X            |              | X                        |                    | X                        |
| PHQ-9                     |                  | X   |             | X           |              | X  |                  | X            |              |              | X                        |                    | X                        |
| ISI                       |                  | X   |             | X           |              | X  | X                | X            | X            |              | X                        |                    | X                        |
| PWC-20                    |                  | X   |             |             |              | X  | X                | X            |              |              |                          |                    |                          |
| Sleep diary <sup>p</sup>  | X                |   |             |             |              |  |                  |              |              |              |                          |                    |                          |
| Study Drug Dispensation   |                  | X   |             | X           |              |  |                  |              |              |              |                          |                    |                          |
| Study Drug Administration |                  | X (Day 1 through Day 14)                          |             |             |              |  |                  |              |              |              |                          |                    |                          |



- <sup>k</sup> Vital signs include oral temperature (°C), respiratory rate, 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 subject 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.
- <sup>l</sup> Triplicate ECGs will be collected. [REDACTED]
- <sup>m</sup> The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- <sup>n</sup> The HAM-D is to be completed as early during the visit as possible.
- <sup>o</sup> 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 scale will refer to the past 7 days (1 week) at all visits.
- <sup>p</sup> Subjects are instructed to complete the Core Consensus Sleep Diary starting at least 7 days prior to Day 1 and then daily through Day 28.  
[REDACTED]
- <sup>r</sup> To be performed at the ET visit only.
- <sup>s</sup> Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject’s participation in the study.
- <sup>t</sup> Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.



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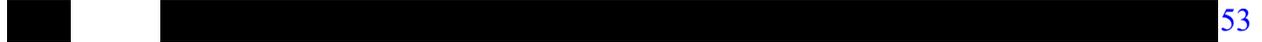
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**Table 2: Abbreviations and specialist terms (Continued)**

| <b>Abbreviation or specialist term</b> | <b>Explanation</b>   |
|--|--|
| MADRS                                  | Montgomery Åsberg Depression Rating Scale                                      |
| MDD                                    | major depressive disorder  |
| MGH ATRQ                               | Massachusetts General Hospital Antidepressant Treatment Response Questionnaire |
| MMRM                                   | mixed effects model for repeated measures                                      |
| NCS                                    | not clinically significant   |
| PCS                                    | Potentially clinically significant   |
| PHQ-9                                  | 9-item Patient Health Questionnaire  |
| PK                                     | pharmacokinetic  |
| PRO                                    | patient-reported outcome   |
| PWC-20                                 | 20-item Physician Withdrawal Checklist   |
| 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   |
| SF-36v2                                | 36-item Short Form version 2   |
| SUSAR                                  | suspected, unexpected, serious, adverse reactions                              |
| TEAE                                   | treatment-emergent adverse event   |
| WHO                                    | World Health Organization  |

## 5. INTRODUCTION

### 5.1. Background of Major Depressive Disorder and Unmet Medical Need

The World Health Organization (WHO) has identified depression as the leading cause of disability worldwide, and as a major contributor to the overall global burden of disease (<http://www.who.int/mediacentre/factsheets/fs369/en/>). Globally, depression has been estimated to affect over 300 million people.

In the United States, the economic burden of depression, including workplace costs, direct costs and suicide-related costs, was estimated to be \$210.5 billion in 2010 ([Greenberg 2015](#)). As per WHO statistics, over 800,000 people die due to suicide every year, and suicide is the second leading cause of death in 15- to 29-year-olds. The rate of US adults making a suicide attempt has increased (0.62% from 2004 to 2005 to 0.79% from 2012 to 2013), with a shift to more attempts among younger adults (42% to 50%, respectively) and among those with a depressive disorder (26% to 54%, respectively; [Olfson 2017](#)).

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition ([DSM-5](#)), depression refers to an overarching set of diagnoses, including major depressive disorder (MDD). Diagnostic criteria for MDD includes a set of at least 5 depressive symptoms out of 9, including depressed mood and/or loss of interest or pleasure, and other changes affecting appetite or weight, sleep, psychomotor activity, energy level, feelings of guilt, concentration ability and suicidality during the same 2-week period, that represents a change from previous functioning ([DSM-5](#)).

Antidepressants are a mainstay of pharmacological treatment for depressive disorders. Selective serotonin uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other compounds that affect monoaminergic neurotransmission, such as mirtazapine and bupropion, represent the major classes of antidepressants. While antidepressants are widely used, large scale studies have demonstrated their limited efficacy, including low remission rates and untreated symptoms ([Trivedi 2006](#); [Conradi 2011](#); [Romera 2013](#)).

Converging preclinical and clinical evidence ([Gerner 1981](#); [Honig 1988](#); [Drugan 1989](#); [Luscher 2011](#); [Mann 2014](#)) implicates deficits in  $\gamma$ -aminobutyric acid (GABA)-ergic neurotransmission in the pathophysiology of depressive disorders including MDD. Furthermore, experimental data implicate deficiencies in the normal regulation of endogenous neuroactive steroids in depressive disorders ([Maguire 2008](#); [Maguire 2009](#)). Depressed patients show low levels of GABA in the brain and of neurosteroids in the cerebrospinal fluid (CSF) and plasma, and antidepressant therapy restores GABA levels in relevant animal models and neurosteroid concentrations in depressed patients ([Luscher 2011](#); [Schüle 2014](#)).

### 5.2. SAGE-217

SAGE-217 is a synthetic positive allosteric modulator of GABA<sub>A</sub> receptors, the major class of inhibitory neurotransmitter receptors in the brain. 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<sub>A</sub> receptors, and, consistent with the actions of other GABA<sub>A</sub> receptor potentiators (Rudolph 2011), exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo.

Data from an open-label Phase 2a study of SAGE-217 administered to subjects with moderate to severe MDD showed clinically significant improvements from baseline in depression and anxiety scale scores (Hamilton Rating Scale for Depression [HAM-D], Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Anxiety Rating Scale [HAM-A], and Clinical Global Impression – Improvement [CGI-I]) as early as Day 2 of the 14-day treatment period, with durable responses following the end of treatment. This result was further supported by the randomized, double-blind portion of this study including 89 subjects, in which a rapid and substantial decrease in HAM-D scores was observed at Day 15 (primary endpoint), starting at Day 2. This response pattern was also observed with other efficacy scales, including MADRS, CGI-I, and HAM-A.

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, and dizziness. Most adverse events (AEs) were reported as mild or moderate in intensity. There have been no deaths and only one subject with essential tremor experienced a serious adverse event (SAE) of transient confusion leading to discontinuation of study drug. No other SAEs have been reported in any study of SAGE-217.

Additional information on nonclinical and clinical data is provided in the Investigator's Brochure.

### **5.3. Potential Risks and Benefits**

Non-serious events of sedation, somnolence, and dizziness were the most commonly reported AEs with SAGE-217. Given the outcome of the Phase 2 study of SAGE-217 in subjects with MDD, the current significant unmet need in the treatment of depression, and a favorable benefit-risk profile, further investigation of SAGE-217 in patients with MDD is justified.

### **5.4. Dose Justification**

There will be 2 dose levels of SAGE-217 in this study in order to study dose ranging: 30 mg per day and 20 mg per day. The higher dose level of 30 mg per day is the maximum tolerated dose in the multiple ascending dose study of SAGE-217 in healthy subjects and is also the dose level that was effective and generally well tolerated in a Phase 2 study in subjects with MDD (217-MDD-201). The lower dose of 20 mg per day will be studied in subjects with MDD for the first time in the current study and is anticipated to be well tolerated as it is lower than the maximum tolerated dose level. Due to sedation/somnolence observed in previous clinical trials when administered in the morning, and improved tolerability when given in the evening, both doses of SAGE-217 will be administered in the evening in this study.

## 6. STUDY OBJECTIVES AND PURPOSE

### 6.1. Study Objective

#### 6.1.1. Primary Objective

The primary objective is to evaluate the efficacy of SAGE-217 in the treatment of MDD compared to placebo.

#### 6.1.2. Secondary Objective(s)

Secondary objectives are:

- To evaluate the effect of SAGE-217 on sleep.
- To assess patient-reported outcome (PRO) measures as they relate to health-related quality of life and depressive symptoms.

#### 6.1.3. Safety Objective

The safety objective is to evaluate the safety and tolerability of SAGE-217.

[REDACTED]

### 6.2. Endpoints

#### 6.2.1. Primary Endpoint

The primary endpoint of this study is the change from baseline in the 17-item HAM-D total score at Day 15.

#### 6.2.2. Secondary Endpoint(s)

- Change from baseline in the 17-item HAM-D total score at other time points
- HAM-D response at Day 15 and all other time points, defined as a  $\geq 50\%$  reduction in HAM-D score from baseline
- HAM-D remission at Day 15 and all other time points, defined as HAM-D total score  $\leq 7$
- CGI-I response at Day 15 and all other time points, defined as “much improved” or “very much improved”

- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at Day 15 and all other time points
- Change from baseline in HAM-A total score at Day 15 and all other time points
- Change from baseline in the MADRS total score at Day 15 and all other time points
- Change from baseline in HAM-D subscale and individual item scores at all time points
- Change in sleep at Day 15 and all other time points, as assessed by:
  - Insomnia Severity Index (ISI)
  - Subjective sleep parameters collected with the Core Consensus Sleep Diary
- Change from baseline in PRO measures of health-related quality of life, as assessed by responses to the 36-item Short Form survey version 2 (SF-36v2), and of depressive symptoms, as assessed by the 9-item Patient Health Questionnaire (PHQ-9)

**6.2.3. Safety Endpoint(s)**

- Incidence and severity of adverse events/serious adverse events
- Changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs)
- Suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Potential withdrawal symptoms using the 20-item Physician Withdrawal Checklist (PWC-20)

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

## 7. INVESTIGATIONAL PLAN

### 7.1. Overall Study Design

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD (MADRS total score  $\geq 32$  and a HAM-D total score  $\geq 22$ ). The study will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, a 28-day follow-up period, and an extended follow-up period through Day 182 (6 months following the last dose).

The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. At the time of providing informed consent for the study, subjects will also be asked to authorize that their unique subject identifiers be entered into a registry ([www.subjectregistry.com](http://www.subjectregistry.com)) with the intent of identifying subjects who may meet exclusion criteria due to participation in another clinical study (Section 8.2).

The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and DSM-5 Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the MADRS, HAM-D, and CGI-S.

Antidepressants are permitted provided subjects are on a stable dose for at least 60 days prior to Day 1 and agree to continue on the stable dose through the 28-day follow-up period (Day 42). Initiation of new antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints is prohibited between screening and completion of the Day 42 assessments.

Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) and randomized within each stratum to one of 3 treatment groups (SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo) in a 1:1:1 ratio. Subjects will self-administer a single dose of study drug with food once daily in the evening on an outpatient basis, for 14 days. Dose reductions are not permitted. Study drug administration will be monitored via a clinical monitoring service (see Section 9.3).

Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 1.

### 7.2. Number of Subjects

Approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects (see Section 13.8).

### 7.3. Treatment Assignment

Subjects will be randomly assigned to a treatment group on Day 1. Randomization will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline and performed within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo.

#### **7.4. Dose Adjustment Criteria**

Dose adjustments are not permitted in this study. Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated (see Section 8.3).

#### **7.5. Criteria for Study Termination**

Sage Therapeutics may 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 subjects, 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 ethics committee and initiate withdrawal procedures for participating subjects.

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

### 8.1. Subject Inclusion Criteria

Qualified subjects will meet all of the following criteria:

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is a male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements, including not participating in night shift work.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a MADRS total score of  $\geq 32$  and a HAM-D total score  $\geq 22$  at screening and Day 1 (prior to dosing).
7. Subjects taking antidepressants must have been taking these medications at the same dose for at least 60 days prior to Day 1. Subjects receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1.
8. Subject is willing to delay start of other antidepressant or anti-anxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, until after completion of the Day 42 visit.
9. Female subject agrees to use one of the following methods of contraception during the treatment period and for 30 days following the last dose of study drug, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH]  $>40$  mIU/mL), surgically sterile (hysterectomy or bilateral oophorectomy), or does not engage in sexual relations which carry a risk of pregnancy:
  - 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/occlusion.
  - Vasectomized partner.
10. Male subject agrees to use an acceptable method of effective contraception during the treatment period and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy. Acceptable methods of effective contraception for males includes vasectomy, or a condom with

spermicide used together with highly effective female contraception methods if the female partner is of child-bearing potential (see Inclusion Criteria #9 for acceptable contraception methods).

11. Male subject is willing to abstain from sperm donation the treatment period and for 5 days after receiving the last dose of the study drug.
12. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

## 8.2. Subject Exclusion Criteria

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

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study. A body mass index (BMI)  $\leq 18$  or  $\geq 50$  kg/m<sup>2</sup> at Screening is exclusionary; a BMI of 40 to 49 kg/m<sup>2</sup>, inclusive, at Screening is subject to a broader evaluation of medical comorbidities (such as sleep apnea, chronic obstructive pulmonary disease [COPD]), concomitant medications, and prior tolerability of sedating agents.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from two different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.
5. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
7. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.
8. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
9. Subject has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of

>450 msec in males or >470 msec in females will be the basis for exclusion from the study.

10. Subject has active psychosis per Investigator assessment.
11. Subject has a medical history of seizures.
12. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
13. Subject 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.
14. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
15. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
16. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to the first dose of study drug.
17. Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort, within 28 days prior to the first dose of study drug.
18. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
19. Subject plans to undergo elective surgery before completion of the Day 42 visit.
20. Subject is taking benzodiazepines, barbiturates, or GABA<sub>A</sub> modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or has been using these agents daily or near-daily ( $\geq 4$  times per week) for more than 1 year. Subject is taking any benzodiazepine or GABA modulator with a half-life of  $\geq 48$  hours (eg, diazepam) from 60 days prior to Day 1.
21. Subject is taking non-GABA anti-insomnia medications (eg melatonin, Benadryl [anti-histamines], trazodone), or first or second generation (typical/atypical) antipsychotics at Day -14.
22. Subject 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.
23. Subject has a history of sleep apnea.
24. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
25. Subject is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as-needed, at Day -28.

### **8.3. Subject Withdrawal Criteria**

Subjects may withdraw from the study drug or terminate from the study at any time for any reason. The Investigator may withdraw the subject from the study drug or from the study for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol
- The subject experiences an intolerable AE
- Other medical or safety reason, at the discretion of the Investigator and/or the Medical Monitor

The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject withdraws from study drug or terminates the study for any reason. The reason must be recorded in the subject's electronic case report form (eCRF).

If a subject is persistently noncompliant, the Investigator should discuss with the Sponsor the potential discontinuation of the subject. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the subject's eCRF, including:

- missed visits;
- interruptions in the schedule of study drug administration;
- non-permitted medications (see Section 9.2).

Subjects 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.

Subjects who discontinue study drug early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place as scheduled relative to the last dose of treatment (eg, if a subject's last dose is on Day 13, their first follow-up visit (Visit 7) should occur 4 days later). If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for the ET visit will be conducted.

A subject will be deemed lost to follow-up after attempts at contacting the subject have been unsuccessful.

#### **8.3.1. Replacement of Subjects**

Subjects will not be replaced. Additional subjects may be randomized if the drop-out rate is higher than anticipated (Section 13.8).

## **9. TREATMENT OF SUBJECTS**

### **9.1. Study Drug**

Subjects will self-administer SAGE-217 (20 or 30 mg) or matching placebo orally once daily in the evening with food for 14 days.

### **9.2. Prior Medications, Concomitant Medications, and Restrictions**

#### **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 Screening and throughout the duration of the study will be recorded. In addition, psychotropic medications taken 6 months prior to Screening will be recorded.

Any medication and/or supplement determined necessary for the welfare of the subject 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 60 days prior to Day 1 are permitted if the subject intends to continue the stable dose through Day 42.

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

- 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**

The following specific classes of medications are prohibited:

- Initiation of new psychotropic medications through the Day 42 visit
- Initiation of new antidepressant therapy from 60 days prior to Day 1 through the Day 42 visit
- Use of any benzodiazepines, barbiturates, GABA<sub>A</sub> modulators, GABA-containing agents from Day -28 through the Day 42 visit (from Day -60 for benzodiazepine or GABA modulators with a half-life of  $\geq 48$  hours)
- Chronic or as-needed psychostimulants (eg, methylphenidate, amphetamine) or opioids from Day -28 through the Day 42 visit

- First generation (typical) antipsychotics (eg, haloperidol, perphenazine) and second generation (atypical) antipsychotics (eg, aripiprazole, quetiapine) from Day -14 through the Day 42 visit
- Use of any non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) from Day -14 through the Day 42 visit
- Exposure to another investigational medication or device from 30 days prior to Screening through the Day 42 visit
- Any known strong inhibitors CYP3A4 from Day -28 or 5 half-lives prior to Day 1 (whichever is longer) through the treatment period
- Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort from Day -28 through the treatment period.

### 9.2.3. Other Restrictions

The consumption of grapefruit juice, grapefruit, or Seville oranges, or products containing these is prohibited throughout the treatment period.

Consumption of alcohol or use of drugs of abuse is discouraged throughout the duration of the study.

Female subjects 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 study drug.

Elective surgeries or procedures are prohibited through the Day 42 visit.

Subjects must not participate in night shift work.

Subjects receiving psychotherapy on a regular schedule for at least 60 days prior to Day 1 are permitted if the subject intends to continue the stable dose through the follow-up period (Day 42).

### 9.3. Treatment Adherence

SAGE-217 or placebo will be self-administered by subjects once daily in the evening with food. Sites will dispense study drug to the subjects to take at home with instructions for use (see Section 10.4 and Table 1).

Administration of study drug will be monitored by a medication adherence monitoring platform used on smartphones to visually confirm medication ingestion. Subjects will receive a reminder within a predefined time window to take study drug while using the application. Subjects 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 study drug administration by dose level, as well as missed doses.

In addition, the subject will be instructed to bring their dosing kit to the site as outlined in Table 1, 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 subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

The Investigator(s) will record any reasons for non-compliance in the source documents.

#### **9.4. Randomization and Blinding**

This is a randomized double-blind, placebo-controlled study. Subjects who meet the entrance criteria will be randomized in a stratified manner based on use of antidepressant treatment (current/stable or not treated/withdrawn  $\geq 60$  days) at baseline; randomization will be done within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matched placebo. Subjects, 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 (SAGE-217 20 mg, SAGE-217 30 mg, or placebo) 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 Sponsor will be unblinded following the first database lock when all subjects complete the Day 42 visit; site personnel and subjects will remain blinded throughout the extended follow-up until the final database lock when all subjects complete the Day 182 visit.

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IRT (see Section 12.6 for more details related to unblinding).

## **10. STUDY DRUG MATERIALS AND MANAGEMENT**

### **10.1. Description of Study Drug**

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 (SMCC), colloidal silicon dioxide, and sodium stearyl fumarate as excipients. Colloidal silicon dioxide may be either a component of the SMCC or a standalone excipient in the formulation. 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. Study Drug 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 study drug in appropriately labeled, subject-specific kits containing sealed unit doses. Each unit dose consists of 1 capsule. Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Study drug 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. Study Drug 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. Study Drug Preparation**

Not applicable.

### **10.5. Study Drug Administration**

SAGE-217 is to be administered orally once daily in the evening with food. Practical options include taking SAGE-217 within 1 hour of dinner or taking SAGE-217 later in the evening with solid food. If a subject misses a dose, the subject 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. Study Drug Accountability**

Upon receipt of study drug, the Investigator(s), or the responsible pharmacist or designee, will inspect the study drug and complete and follow the instructions regarding receipt 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 subject-specific kits to subjects at the planned dispensation visit intervals outlined in [Table 1](#).

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

At the subsequent study drug-dispensing visit, the investigator or designee will access the IRT, providing the same subject ID number assigned at Screening, to obtain the medication ID number for the study drug to be dispensed at that visit. The medication ID number, the number of capsules dispensed, and the number of capsules returned by the subject 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 study drug provided is for use only as directed in this protocol. After the study is completed, all unused study drug must be returned as directed or destroyed on site per the Sponsor's instructions. The Investigator or designee must keep a record of all study drug received, dispensed and discarded.

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

## **10.7. Study Drug Handling and Disposal**

At the end of the study, all used and unused study drug will be reconciled and returned to Sage Therapeutics for destruction or destroyed locally; disposition of study drug will be documented.

A copy of the inventory record and a record of any clinical supplies that have been received, dispensed or destroyed must be documented by the site as directed. This documentation must include at least the information below:

- the number of dispensed units;
- the number of unused units;
- the number of units destroyed at the end of the study;
- the date, method and location of destruction.

## 11. ASSESSMENT OF EFFICACY [REDACTED]

All assessments will be conducted according to the schedule of assessments (Table 1). Study assessments that involve subject 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. Efficacy Assessments

#### 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 subject. An assessment timeframe of 7 days 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 subjects 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 of  $\leq 7$ .

#### 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 subjects 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 Impression (CGI)**

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 subject'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 subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject 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 subject's condition posttreatment. The Investigator will rate the subject'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. Short Form-36 Version 2 (SF-36v2)**

The Medical Outcomes Study SF-36v2 is a 36-item measure of health status that has undergone validation in many different disease states ([Ware 2007](#)). The SF-36v2 covers eight health dimensions including four physical health status domains (physical functioning, role participation with physical health problems [role-physical], bodily pain, and general health) and four mental health status domains (vitality, social functioning, role participation with emotional health problems [role-emotional], and mental health). In addition, two summary scores, physical component summary and mental component summary, are produced by taking a weighted linear combination of the eight individual domains. The SF-36v2 is available with two recall periods: the standard recall period is 4 weeks and the acute recall period is 1 week. This study will use the acute version, which asks patients to respond to questions as they pertain to the past week. Higher SF-36v2 scores indicate a better state of health.

#### **11.1.6. Patient Health Questionnaire (PHQ-9)**

The PHQ-9 is a subject-rated depressive symptom severity scale. To monitor severity over time for newly diagnosed subjects or subjects in current treatment for depression, subjects 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.

#### 11.1.7. Insomnia Severity Index (ISI)

The ISI is a validated questionnaire designed to assess the nature, severity, and impact of insomnia (Morin 2011). The ISI uses a 5-point Likert Scale to measure various aspects of insomnia severity (0 = none, 1 = mild, 2 = moderate; 3 = severe; 4 = very severe), satisfaction with current sleep pattern (0 = very satisfied, 1 = satisfied, 2 = neutral, 3 = dissatisfied, 4 = very dissatisfied), and various aspects of the impact of insomnia on daily functioning (0 = not at all, 1 = a little, 2 = somewhat, 3 = much, 4 = very much). A total score of 0 to 7 = “no clinically significant insomnia,” 8 to 14 = subthreshold insomnia,” 15 to 21 = “clinical insomnia (moderate severity),” and 22 to 28 = “clinical insomnia (severe).”

#### 11.1.8. Core Consensus Sleep Diary

The Core Consensus Sleep Diary collects subjective sleep parameters, including sleep onset latency, total sleep time, and wake after sleep onset, number of awakenings, and sleep quality. The take-home subject sleep diary assessment will be administered using an eDiary solution. The eDiary will be captured using either a provisioned smartphone device or bring-your-own-device solution, depending on the subject’s preference.

[REDACTED]

[REDACTED]

[Redacted]

[Redacted]

## **12. ASSESSMENT OF SAFETY**

### **12.1. Safety Parameters**

All assessments will be conducted according to the schedule of assessments ([Table 1](#)).

#### **12.1.1. Demographic/Medical History**

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including family psychiatric history, will be documented. The diagnosis of MDD will be determined using the SCID-5-CT. If available, the disease code associated with the diagnosis of MDD based on the 10<sup>th</sup> revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used to determine whether the subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment during the current major depressive episode with adequate doses of antidepressants from two different classes for at least 4 weeks of treatment.

#### **12.1.2. Weight and Height**

Height (Screening only) and weight will be measured and documented.

#### **12.1.3. Physical Examination**

Physical examinations assessing body systems (eg, head, eyes, ears, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Whenever possible, the same individual is to perform all physical examinations for a given subject. Unscheduled brief, symptom-driven physical examinations may also be conducted per the Investigator's discretion.

Any abnormality in physical examinations will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section [12.2.1.1](#).

#### **12.1.4. Vital Signs**

Vital signs comprise both supine and standing for systolic and diastolic blood pressure and heart rate measurements. Heart rate and blood pressure are to be collected in supine position after the subject has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Respiratory rate and temperature are collected once, in either position. Vital signs will be documented. When vital signs are scheduled at the same time as blood draws, vital signs will be obtained first.

Any abnormality in vital signs will be interpreted by the Investigator as abnormal, NCS or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section [12.2.1.1](#).

### 12.1.5. Electrocardiogram (ECG)

Supine 12-lead ECGs 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.

### 12.1.6. Laboratory Assessments

Samples will be collected in accordance with acceptable laboratory procedures detailed in the laboratory manual.

The clinical laboratory tests to be performed are listed in Table 3.

**Table 3: Clinical Laboratory Tests**

| Hematology  | Serum Chemistry                         | Urinalysis         | Coagulation                           |
|---|---|--------------------|---------------------------------------|
| Red blood cell count  | Alanine aminotransferase                | pH                 | Activated partial thromboplastin time |
| Hemoglobin  | Albumin                                 | Specific gravity   | Prothrombin time                      |
| Hematocrit  | Alkaline phosphatase                    | Protein            | International normalized ratio        |
| White blood cell count with differential                    | Aspartate aminotransferase              | Glucose            |                                       |
| Platelet count  | Total bilirubin                         | Red blood cell     |                                       |
| Red Blood Cell Indices (MCV, MCH, MCHC)                     | Direct bilirubin                        | Nitrite            |                                       |
| Reflex to Red blood cell morphology if indices are abnormal | Indirect bilirubin                      | Leukocyte esterase |                                       |
|   | Total protein                           | Ketones            |                                       |
|   | Creatinine                              | Bilirubin          |                                       |
|   | Blood urea nitrogen                     | Urobilinogen       |                                       |
|   | Creatine kinase                         |                    |                                       |
|   | Gamma-glutamyl transferase              |                    |                                       |
|   | Potassium                               |                    |                                       |
|   | Sodium                                  |                    |                                       |
|   | Lactate dehydrogenase                   |                    |                                       |
|   | Glucose                                 |                    |                                       |
|   | Chloride                                |                    |                                       |
|   | Bicarbonate                             |                    |                                       |
|   | Calcium                                 |                    |                                       |
|   | Phosphorus                              |                    |                                       |
|   | Triglycerides                           |                    |                                       |
|   | Thyroid stimulating hormone (TSH)       |                    |                                       |
|   | Reflex to free T3/T4 if TSH is abnormal |                    |                                       |

**Table 3: Clinical Laboratory Tests (Continued)**

| <b>Diagnostic</b>  |  |                     |  |
|--|--|---------------------|--|
| <b>Serum</b>   | <b>Urine</b>   | <b>Breathalyzer</b> |  |
| Hepatitis B<br>Hepatitis C<br>Reflex HCV RNA<br>HIV-1 and -2<br>Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: serum hCG<br>Female subjects, if menopause is suspected and not surgically sterile: FSH | Drug screen including:<br>amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine<br><br>Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: urine hCG | Alcohol             |  |

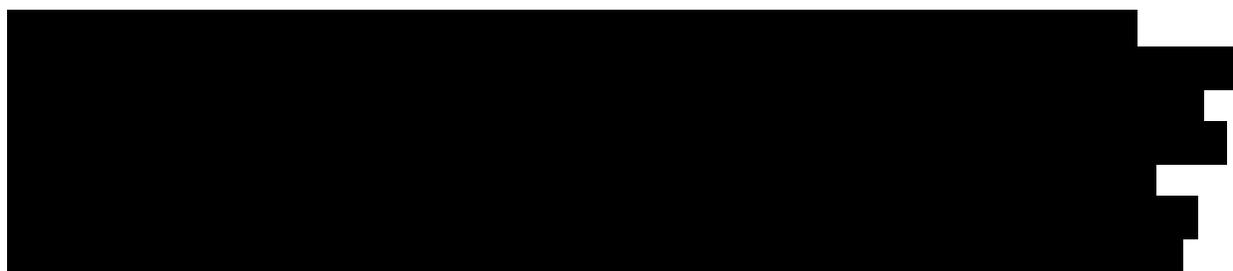
Abbreviations: FSH = follicle stimulating hormone; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus

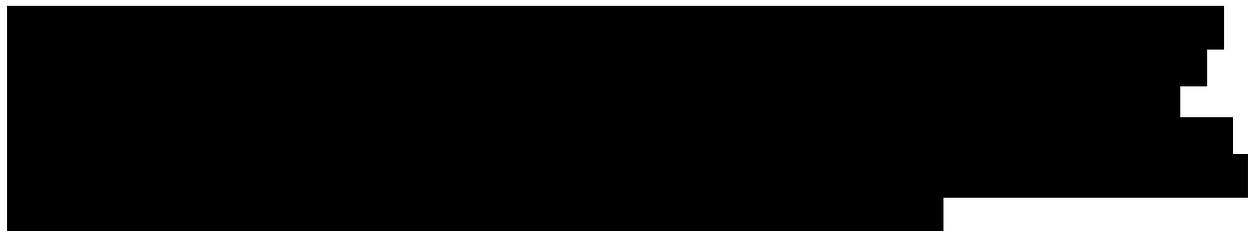
The central laboratory will perform laboratory tests for hematology, serum chemistry, urinalysis, and coagulation. The results of laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to Sage Therapeutics or designee in the format requested by Sage Therapeutics.

Laboratory reports must be signed and dated by the Investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will require clear and complete documentation in the source documents as to the investigator’s assessment of not clinically significant before proceeding with randomization.

All clinical laboratory test results outside the central laboratory’s reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.1. A clinically significant laboratory abnormality following subject randomization will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

A serum follicle stimulating hormone test will be conducted at Screening to confirm whether a female subject with  $\geq 12$  months of spontaneous amenorrhea meets the protocol-defined criteria for being post-menopausal (Section 8.1).





#### **12.1.6.1. Drugs of Abuse and Alcohol**

Urine toxicology tests will be performed for selected drugs of abuse (see [Table 3](#)). A breath test for alcohol will be performed.

#### **12.1.6.2. Pregnancy Screen**

For female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at all other scheduled timepoints thereafter, including the ET visit for subjects who prematurely discontinue.

#### **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 subject with suicidal ideation and behavior, and a post-baseline 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, as outlined in [Table 1](#).

#### **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 trials. 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. Definition of Adverse Events**

#### **12.2.1.1. Adverse Event (AE)**

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 an AE that occurs after the first administration of any study drug. The term study drug includes any Sage investigational product, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) and/or if the Investigator considers them to be clinically significant. Laboratory values and vital signs that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations 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 subject 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.

Any AEs that are unresolved at the subject'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 subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

#### **12.2.1.2. Serious Adverse Event (SAE)**

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 subject or may require medical intervention to prevent one 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 subject 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 within 24 hours of first awareness (Section 12.5). All SAEs should be followed until the event resolved, the condition stabilized, was no longer considered clinically significant or the subject was lost to follow-up. Serious adverse events occurring after a subject’s final visit (including the last follow-up visit) should be reported to Sage or designee only if the Investigator considers the SAE to be related to study treatment.

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject 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 subject’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 the Investigator, between the subject’s consent to participate in the study and at the time of the procedure or treatment.

### 12.3. Relationship to Study Drug

The Investigator must make the determination of relationship to the study drug for each adverse event (not related, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as “not related.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered at least “possibly related.”

**Table 4: Relationship to Study Drug**

| <b>Relationship</b> | <b>Definition</b>  |
|---------------------|--|
| Not Related:        | No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject’s clinical state.  |
| Possibly Related:   | A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.<br>The reaction might have been produced by the subject’s clinical state or other modes of therapy administered to the subject, but this is not known for sure.    |
| Probably Related:   | A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.<br>The reaction cannot be reasonably explained by the known characteristics of the subject’s clinical state or other modes of therapy administered to the subject. |

If the relationship between the adverse event/serious adverse event and the investigational product is determined to be “possible” or “probable”, the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

#### **12.4. Recording Adverse Events**

Adverse events spontaneously reported by the subject 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, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study drug or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

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 12.2.1.2. An AE of severe intensity may not be considered serious.

If a female subject becomes pregnant during this study, pregnancy information must be collected and recorded on the Sage Therapeutics pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. The Investigator will also attempt to collect pregnancy information on any male subject’s female partner who becomes pregnant while the male subject is participating in study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant female subjects.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication or a complication relating to the pregnancy occurs (e.g., spontaneous abortion). If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly/birth defects), the investigator should follow the procedures for reporting an SAE.

#### **12.5. Reporting Serious Adverse Events**

All SAEs must be reported to Sage, or designee, immediately. A written account of the SAE must be sent to Sage, or designee, within 24 hours of the first awareness of the event by the investigator and/or his staff. 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 Therapeutics, 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 case report form (CRF) and/or study file.

Any SAEs discovered by the Investigator after the designated follow up time for the study, should be promptly reported to Sage, or designee, according to the timelines noted above.

The contact information for reporting SAEs and/or pregnancies is located in the study reference manual.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the ethics committee 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. Ethics Committee (EC)/Institutional Review Boards (IRBs) will be notified of SAEs and/or SUSARs as required by local law. In addition, appropriate Sponsor Drug Safety and Pharmacovigilance personnel, or designee, will unblind SUSARs for the purpose of regulatory reporting. The Sponsor, or designee, will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. The Sponsor, or designee, will submit SUSARs to investigators in a blinded fashion.

## **12.6. Emergency Identification of Study Drug**

During the study, the blind is to be broken by the Investigator only when the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. Unless a subject is at immediate risk, the Investigator must make diligent attempts to contact Sage prior to unblinding the study treatment administered to a subject. Any request from the Investigator about the treatment administered to study subjects must be discussed with Sage. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented in the source records. Unless a subject is at immediate risk, any request for the unblinding of individual subjects must be made in writing to Sage and approved by the appropriate Sage personnel, according to standard operating procedures.

In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the eCRF. If the subject or study center personnel have been unblinded, the subject will be permanently discontinued from the study.

## 13. STATISTICS

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to treatment unblinding.

When all subjects complete the Day 42 visit, the database will be locked, followed by treatment unblinding to the Sponsor and data analyses (site personnel and subjects will remain blinded). The extended follow-up period will continue as scheduled; the final database lock will occur when all subjects complete the extended follow-up period.

### 13.1. Data Analysis Sets

The Randomized set is defined as all subjects who are randomized.

The Safety Set is defined as all subjects administered study drug.

The Full Analysis Set is defined as all randomized subjects in the Safety Set with a valid baseline HAM-D total score and at least 1 post-baseline HAM-D total score.

### 13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data. A sensitivity analysis will be used to investigate the impact of missing data if  $\geq 5\%$  of subjects in any treatment group have missing data.

### 13.3. General Considerations

For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), 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 (Section 12.1.1) and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized using the Safety Set.

Hepatitis, HIV, drug and alcohol, and pregnancy screening results will be listed, but not summarized as they are considered part of the inclusion/exclusion criteria.

Medical/family history will be listed by subject.

### 13.5. Efficacy Analyses

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment.

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 post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported 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. 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, SF-36v2 score, PHQ-9 score, sleep diary endpoints (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score and selected individual items and/or subscale scores in HAM-D for change from baseline.

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as  $\geq 50\%$  reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of  $\leq 7.0$ ). 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 the 15-day time point. 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 including terms for treatment, baseline CGI-S score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables.

### 13.6. Safety Analyses

Safety and tolerability of study drug will be evaluated by incidence of AEs/SAEs, 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 subject and summarized by treatment group. All safety summaries will be performed on the Safety Set. Where applicable, ranges of potentially clinical significant (PCS) values are provided in the SAP.

### **13.6.1. Adverse Events**

The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized overall and by Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or higher, System Organ Class (SOC), and preferred term. Incidences will be presented in order of decreasing frequency. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 12.3).

Any TEAEs leading to discontinuation and SAEs with onset after the start of study drug will also be summarized.

All AEs and SAEs (including those with onset or worsening before the start of study drug) 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 range of each parameter is provided by the laboratory; shift from baseline to post-baseline values in abnormality of results will be provided. Potentially clinically significant values will be summarized by treatment. Any abnormal values deemed clinically significant by the investigator will be reported as an AE (see Section 12.2). Clinical laboratory results will be listed by subject and timing of collection.

### **13.6.3. Physical Examinations**

The occurrence of a physical examination (Y/N) and the date performed will be listed by subject. Any clinically significant observation in physical examination will be reported as an AE (see Section 12.2).

### **13.6.4. Vital Signs**

Results from each visit and mean changes from baseline in vital signs will be summarized by scheduled visit. Any abnormality deemed clinically significant by the investigator will be reported as an AE (see Section 12.2). Potentially clinically significant values will be summarized by treatment. Vital sign results will be listed by subject 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 subject: 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 subject 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 signing the ICF through the duration of the study will be recorded. In addition, all psychotropic medications taken 6 months prior to Screening will be recorded. Those medications taken prior to the initiation of the start of study drug will be denoted “Prior”. Those medications taken prior to the initiation of the study drug and continuing beyond the initiation of the study drug or those medications started at the same time or after the initiation of the study drug will be denoted “Concomitant” (ie, those with a start date on or after the first dose of study drug, or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug).

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 subject, 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 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 subject.

[REDACTED]

## **13.8. Determination of Sample Size**

Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable subjects 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 SD of 10 points. Assuming an 11% dropout rate and a 1:1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 450 total randomized subjects will be required to obtain 399 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is greater than 11%.

## **14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **14.1. Study Monitoring**

Before an investigational site can enter a subject into the study, a representative of Sage Therapeutics (or designee) 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 investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject'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 subject (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.

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

### **14.2. Audits and Inspections**

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics audit or 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, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The

investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

### **14.3. Institutional Review Board (IRB) or Ethics Committee (EC)**

The Principal Investigator must obtain IRB (or EC) approval for the investigation. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the subject 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 Practices and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit. Please see Section [14.2](#) for more details regarding the audit process.

## **16. ETHICS**

### **16.1. Ethics Review**

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or EC as appropriate. The investigator must submit written approval to Sage Therapeutics before he or she can enroll any subject into the study.

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

The Principal Investigator is also responsible for providing the IRB 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 EC according to local regulations and guidelines.

### **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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines, as well as all applicable regulatory requirements.

### **16.3. Written Informed Consent**

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

## **17. DATA HANDLING AND RECORDKEEPING**

### **17.1. Inspection of Records**

Sage Therapeutics will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **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, whichever is longer. If not approved, documentation must be maintained for 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

## **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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**Protocol 217-MDD-301 Amendment 4**

**Date of Amendment: 25 March 2019**

**A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating  
the Efficacy of SAGE-217 in the Treatment of Adult Subjects with Major Depressive  
Disorder**

**Rationale for Protocol Amendment**

The purpose for this protocol amendment is to increase the Montgomery-Åsberg Depression Rating Scale (MADRS) score required for entry into the study and include a minimum total score for the 17-item Hamilton Rating Scale for Depression (HAM-D) required for entry into the study. These changes are a result of a blinded data review during which it was discovered that a substantial number of subjects have entered the study with Day 1 HAM-D scores <22, with some as low as 13, which do not correlate with the intended severity of depression to be treated in this study.

A detailed summary of changes is provided in [Table 1](#). Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed individually, nor are administrative updates such as revising the document date, updating the document header and version number, and updating the table of contents.

**Table 1: Protocol Amendment 4 Detailed Summary of Changes**

The primary section of the protocol affected by the changes in Protocol Amendment 4 is indicated. The corresponding related text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

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**Purpose:** Increase the MADRS score required for entry into the study and include a minimum HAM-D total score required for entry into the study in order to ensure enrolment of subjects with the intended severity of depression.

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The primary change occurs in Section 8.1 Subject Inclusion Criteria (#6)

Changed text:           6. Subject has a MADRS total score of  $\geq 32$  ~~0~~ **and a HAM-D total score  $\geq 22$**  at screening and Day 1 (prior to dosing).

Sections also affected by the change:

- Synopsis, Study Description
- Synopsis, Inclusion Criteria
- Table 1 Schedule of Events
- Table 1 footnote 'o'
- Section 7.1 Overall Study Design
- Section 11.1.1 Hamilton Rating Scale for Depression (HAM-D)

November 8, 2018

217-MDD-301 Protocol Memo to Sites

Study title: A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy of SAGE-217 in the Treatment of Adult Subjects with Major Depressive Disorder

This memo is to inform you of additional changes regarding subject eligibility following the finalization of Protocol v3.0, Amendment 2 dated 11-Oct-2018. An amendment incorporating these changes will be forthcoming. Any questions in the meantime can be directed to the CST.

The following outlines all changes for Section 8.2 Exclusion Criteria:

1. Modification of exclusion criteria #20.

From:

20. Subject is taking benzodiazepines or GABA<sub>A</sub> modulators/GABA-containing agents (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28.

To:

20. Subject is taking benzodiazepines, barbiturates, or GABA<sub>A</sub> modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or subjects have been using these agents daily or near-daily ( $\geq 4$  times per week) for more than one year.

Rationale: Per FDA feedback, to avoid confounding effects of potential withdrawal that might result from discontinuation of GABAergic drugs after long-term exposure.

Sections also affected by this change: Synopsis, Prohibited medications, Prior and Concomitant Medications and/or Supplements

2. Addition of exclusion criteria # 22.

Added:

22. Subject has been taking psychostimulants (e.g., methylphenidate, amphetamine) or opioids regularly or as needed, at Day -28.

Rationale: To avoid any confounding antidepressant effects of stimulants, as well as potential pharmacodynamic interactions with opioids.

Sections also affected by this change: Synopsis, Prohibited Medications

Additional edits and clarifications will be made to the following sections:

Section 9.2.1 Prior and Concomitant Medications and/or Supplements

Added:

GABAergic medications taken 12 months prior to Screening will be recorded.

Rationale: Prior medication use will need to be collected in order to properly assess changes to exclusion criteria #20.

Section 12.1.4 Vital Signs

From:

Respiratory rate, pulse oximetry and temperature are collected once, in either position.

To:

Respiratory rate and temperature are collected once, in either position.

Rationale: Pulse oximetry is not collected in this study.

[REDACTED]  
[REDACTED] MD, MBA  
[REDACTED]

Aug 15, 2019

217-MDD-301 Protocol Administrative Letter #2

Study Title: A PHASE 3, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY OF SAGE-217 IN THE TREATMENT OF ADULT SUBJECTS WITH MAJOR DEPRESSIVE DISORDER

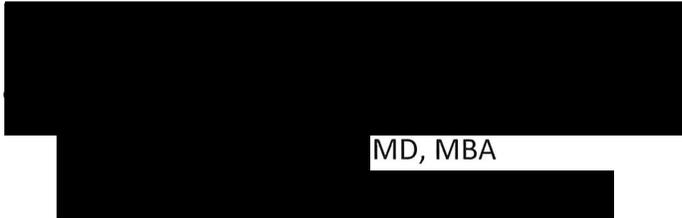
Dear 217-MDD-301 Clinical Sites:

This memo is to inform you of a clarification to the 217-MDD-301 protocol version 5.0, dated 25March2019. The clarification will be incorporated into the next protocol amendment, if one is needed. Any questions may be directed to the study team or to Syneos CST.

The clarification is as follows:

The protocol (Table 1 footnote 'o' and Section 11.1.1) states that the 'Since Last Visit' timeframe for the HAM-D questionnaire will be used at all visits except Screening. However, during the extended follow-up period (Visits 12, 13, and 14), an assessment timeframe of the past 7 days should be used.

Rationale: This is an unintentional error in the protocol. The HAM-D is meant to be assessed within the past 7 days (1 week) during the Extended Follow Up Period.



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August 29, 2019

217-MDD-301 Protocol Administrative Letter #3

Study Title: A PHASE 3, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY OF SAGE-217 IN THE TREATMENT OF ADULT SUBJECTS WITH MAJOR DEPRESSIVE DISORDER

Dear 217-MDD-301 Clinical Sites:

This memo is to inform you of a clarification to the 217-MDD-301 protocol version 5.0, dated 25March2019. The clarification will be incorporated into the next protocol amendment, if one is needed. Any questions may be directed to the study team or to Syneos CST.

The clarification is as follows:

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MD, MBA