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**

NCT Number: NCT04442490

Document Dates:
Protocol Version 6.0: 02 March 2020
Protocol Version 5.0: 25 March 2019
Protocol Version 4.0: 07 March 2019
Protocol Version 3.0: 11 October 2018
Protocol Version 2.0: 25 September 2018
Protocol Version 1.0: 16 July 2018

1. PROTOCOL AND PROTOCOL AMENDMENTS

The original protocol (Version 6) was amended 2 times. Links to each version of the protocol are provided below.

Protocol Versions

Amendment 5, Version 6, 02 March 2020
Summary of Changes from Amendment 5, 02 March 2020
Amendment 6, Version 7, 14 September 2020
Summary of Changes from Amendment 6, 14 September 2020
Amendment 7, Version 8, 14 December 2020
Summary of Changes from Amendment 7, 14 December 2020

Administrative Letters

Administrative Letter #4, 14 October 2020

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. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Tel: [redacted] email: [redacted]
Sponsor Medical Monitor	[redacted], MD, MBA Tel: [redacted] 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
Date of Amendment 5	Version 6.0, 02 March 2020

Protocol Number:	217-MDD-301
Study Drug:	SAGE-217
Study Phase:	Phase 3
Sponsor:	Sage Therapeutics, Inc.
Protocol Date:	Version 6.0, 02 March 2020

Sponsor Approval

[redacted]

02 MAR 2020

Date (DD MMM YYYY)

[redacted]
Sage Therapeutics

[redacted]

[redacted]

DVM, MS, MPH

Date (DD MMM YYYY)

[redacted]

[redacted]

Date (DD MMM YYYY)

[redacted]

Date (DD MMM YYYY)

[redacted]
Sage Therapeutics

[redacted]

[redacted]

Date (DD MMM YYYY)

[redacted]
Sage Therapeutics

[redacted]

[redacted]

PhD

Date (DD MMM YYYY)

[redacted]
Sage Therapeutics

Protocol Number:	217-MDD-301
Study Drug:	SAGE-217
Study Phase:	Phase 3
Sponsor:	Sage Therapeutics, Inc.
Protocol Date:	Version 6.0, 02 March 2020

Sponsor Approval

[redacted] MD, MBA
[redacted]
Sage Therapeutics

Date (DD MMM YYYY)

[redacted]

[redacted] DVM, MS, MPH
[redacted]

Date (DD MMM YYYY)

[redacted]

Date (DD MMM YYYY)

[redacted]

Date (DD MMM YYYY)

[redacted]
Sage Therapeutics

[redacted]

Date (DD MMM YYYY)

[redacted]
Sage Therapeutics

[redacted]

Date (DD MMM YYYY)

[redacted] PhD
[redacted]
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)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Syneos Health Medical Monitor	[redacted], MD	Email: [redacted] Office: [redacted] Cell: [redacted]
Sage Study Physician	[redacted], MD, MBA	Email: [redacted] Tel: [redacted]
24-Hour Serious Adverse Event Reporting	IQVIA Lifecycle Safety	Email: Sage.Safety@iqvia.com Telephone: +1 855-564-2229 Fax: +1 855-638-1674
Product Complaint Reporting	Sage Therapeutics, Inc.	Email: productcomplaints@sagerx.com Tel: +1 833-554-7243

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics

Name of Investigational Product:
SAGE-217 Capsules

Name of Active Ingredient:
SAGE-217

Title of Study: 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

Number of Sites and Study Location: Part A: Approximately 55 sites in the United States

Part B: Approximately 40 sites in the United States

Phase of development: 3

Planned Duration of Subject Participation:

Part A: 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)

Part B: up to 70 days (up to 28-day Screening Period, 14-day Double-blind Treatment Period, and a 28-day double-blind Follow-up Period)

Objectives:

Primary:

- To evaluate the efficacy of SAGE-217 in the treatment of major depressive disorder (MDD) compared to placebo.

Secondary:

- Part A only: 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.

Safety:

- To evaluate the safety and tolerability of SAGE-217.

[redacted]

Endpoints:

Primary:

- 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.

Part A - Secondary:

- Change from baseline in the 17-item HAM-D total score at other timepoints
- HAM-D response at Day 15 and all other time points, defined as a ≥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 ≤7
- Clinical Global Impression - Improvement (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 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)

Part B - Key Secondary:

- CGI-S at Day 15
- HAM-D total score at Day 3, Day 28, and Day 42

Part B – Other Secondary:

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as "much improved" or "very much improved", at Day 15
- MADRS total score at Day 15
- HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline in PRO measures of health-related quality of life, as assessed by responses to SF-36v2, and of depressive symptoms, as assessed by the 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]

[redacted]

Study Description:

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD. This study will be conducted in 2 parts – Part A and Part B. Part B will commence after all subjects in Part A have completed the Day 42 visit. Parts A and B will enroll unique subjects. For both study parts, 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. Each study part is described below.

Part A

Part A 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. 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 ≥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 2.

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.

Part B

Part B will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day follow-up period. Part B of the study may run concurrently with the extended follow-up period in Part A.

The Screening Period begins with the signing of the ICF at the Screening Visit; the ICF must be signed prior to beginning any screening activities. 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 ≥60 days) and randomized within each stratum to one of 2 treatment groups (SAGE-217 50 mg or matching placebo) in a 1:1 ratio. Subjects will self-administer study drug once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 3.

During the treatment period, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the Investigator, subjects who cannot tolerate the 40-mg dose may be discontinued from study drug.

Subjects who discontinue treatment early should return to the site for an 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 ET visit. If necessary, 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 EOT visit assessments should be conducted in addition to an abbreviated physical exam.

Number of Subjects (planned):

Part A: approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects.

Part B: approximately 240 subjects will be randomized and dosed to obtain 216 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 64 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. For Part A, subject has a MADRS total score of ≥32 and a HAM-D total score ≥22 at screening and Day 1 (prior to dosing). For Part B, subject has a HAM-D total score ≥24 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 who have stopped taking antidepressants within 60 days must have stopped for longer than 5 half-lives of the antidepressant 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 or without 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 is currently at significant risk of suicide, as judged by the Investigator, or 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. For Part A, a body mass index (BMI) ≤18 or ≥50 kg/m^2 at Screening is exclusionary; a BMI of 40 to 49 kg/m^2, 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. For Part B, a BMI ≤18 or ≥45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
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 $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Subject is taking any benzodiazepine or GABA modulator with a half-life of ≥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.

SAGE-217 Dosage and Mode of Administration:
SAGE-217 is available as hard gelatin capsules for oral administration. Available dose strengths are:

- Part A: a 30-mg or 20-mg dose
- Part B: a 50-mg dose, with the option to reduce to 40 mg for intolerable AEs

Reference Therapy, Dosage, and Mode of Administration:
Placebo will be provided as hard gelatin capsules for oral administration.

Duration of Treatment: 14 days

Statistical methods:

A detailed description of the statistical analyses to be performed in the study will be provided in the Statistical Analysis Plan (SAP). Separate SAPs will be generated for each part of the study. The SAP for each study part will be finalized and approved prior to treatment unblinding of each respective part.

For Part A, 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.

Part B will not include an extended follow-up period, and the database lock will occur at the end of the study after all subjects have completed the Day 42 visit.

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.

[redacted]

Determination of Sample Size

For Part A, 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%.

For Part B, assuming a two-sided alpha level of 0.05, a sample size of 216 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 a standard deviation (SD) of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 240 total randomized subjects will be required to obtain 216 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.

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 in Part A only (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score in Part A only, 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 ≥50% reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of ≤7.0). GEE models will include terms for treatment, baseline score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 and matching placebo at 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, 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]

[redacted]

Table 2: Schedule of Events (Part A)

Visits	Screening Period	Double-Blind, Placebo-Controlled Treatment Period					Follow-up Period					Extended Follow-Up
Visit Days	D-28 to D-1	D1	D3 (±1d)	D8 (+1d)	D12 (±1d)	D15 (+1d) and/or EOT[a]	D18 (±1d)	D21 (±1d)	D28 (±3d)	D35 (±3d)	D42 (±3d) or ET	D70, D126, D182 (±7d)
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12, V13, V14
Study Procedure												
Informed Consent	X											
Duplicate Subject Check[b]	X											
Inclusion/Exclusion	X	X										
Serum FSH test[c]	X											
SCID-5-CT	X											
MGH ATRQ	X											
Demographics	X											
Medical/Family History	X											
Subject training[d]	X	X										
Randomization		X										
Physical Examination[e]	X	X									X	
Body Weight/Height	X					X (wt only)					X (wt only)	
Clinical Laboratory Assessments[f]	X	X		X		X		X	X		X	X
Drug & Alcohol Screen[g]	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[h]	X	X				X			X		X	
Hepatitis & HIV Screen	X											
[redacted]												

Visits	**Screening Period**	**Double-Blind, Placebo-Controlled Treatment Period**					**Follow-up Period**					**Extended Follow-Up**
Visit Days	**D-28 to D-1**	**D1**	**D3 (±1d)**	**D8 (+1d)**	**D12 (±1d)**	**D15 (+1d) and/or EOT[a]**	**D18 (±1d)**	**D21 (±1d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d) or ET**	**D70, D126, D182 (±7d)**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12, V13, V14**
Study Procedure												
[redacted]												
Vital Signs[k]	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[l]	X	X				X					X	X (Day 182 only)
C-SSRS[m]	X	X	X	X	X	X	X	X	X	X	X	X
HAM-D[n, o]	X	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[o]		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
[redacted]												
ISI		X		X		X	X	X	X		X	X
PWC-20		X				X	X	X				
Sleep diary[p]	X											
[redacted]												
Study Drug Dispensation		X		X								
Study Drug Administration		X (Day 1 through Day 14)										

Visits	**Screening Period**	**Double-Blind, Placebo-Controlled Treatment Period**					**Follow-up Period**					**Extended Follow-Up**
Visit Days	**D-28 to D-1**	**D1**	**D3 (±1d)**	**D8 (+1d)**	**D12 (±1d)**	**D15 (+1d) and/or EOT[a]**	**D18 (±1d)**	**D21 (±1d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d) or ET**	**D70, D126, D182 (±7d)**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12, V13, V14**
Study Procedure												
Study Drug Accountability/Return				X		X					X[r]	
Adverse Events/SAEs[s]	X											
Prior/Concomitant Medications/Procedures[t]	X											

CGI-I = Clinical Global Impression – Improvement; CGI-S – Clinical Global Impression – Severity; [redacted]
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; PHQ-9 = 9-item Patient Health Questionnaire; PWC-20 = 20-item Physician Withdrawal Checklist; 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

[a] 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. 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.

[b] 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.

[c] 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.

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

[e] A full physical examination will be conducted at Screening and abbreviated physical examinations will be conducted thereafter. A full physical examination includes assessment of body systems (eg, head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities).

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

[g] Urine toxicology for selected drugs of abuse (as per the lab manual) and breath test for alcohol.

[h] 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]

[k] 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.

[l] Triplicate ECGs will be collected. When ECGs and [redacted] collection occur on the same day, the 12-lead ECGs will be performed [redacted] sample collection.

[m] 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.

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

[o] The assessment timeframe for HAM-D scales will refer to the past 7 days (1 week) at Screening and during the extended follow-up period 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.

[p] 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]

[r] To be performed at the ET visit only.

[s] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.

[t] Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.

Table 3: Schedule of Events (Part B)

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 [a]**	**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**
Study Procedure											
Informed Consent	X										
Duplicate Participant Check [b]	X										
Inclusion/Exclusion	X	X									
Serum FSH test [c]	X										
SCID-5-CT	X										
MGH ATRQ	X										
Demographics	X										
Medical/Family History	X										
Subject training [d]	X	X									
Randomization		X									
Physical Examination [e]	X	X									X
Body Weight/Height	X					X (weight only)					X (weight only)
Clinical Laboratory Assessments [f]	X	X		X		X		X	X		X
Drug & Alcohol Screen [g]	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test [h]	X	X				X			X		X

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** [a]	**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**
Study Procedure											
Hepatitis & HIV Screen	X										
[redacted]											
Vital Signs [k]	X	X	X	X	X	X	X		X		X
12-Lead ECG [l]	X	X				X					X
C-SSRS [m]	X	X	X	X	X	X	X	X	X	X	X
HAM-D [n, o]	X	X	X	X	X	X		X	X	X	X
MADRS		X		X		X			X		X
HAM-A [o]		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
SF-36v2	X	X		X		X			X		X
PHQ-9		X		X		X			X		X
PWC-20		X				X	X	X			
[redacted]											
Study Drug Dispensation		X		X							
Study Drug Administration		X (Day 1 through Day 14)									
Study Drug Accountability/Return				X		X					X [q]

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** [a]	**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**
Study Procedure											
Adverse Events/SAEs [r]	X										
Prior/Concomitant Medications/Procedures [s]	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; 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; [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.

[a] 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. If necessary, 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 EOT visit assessments should be conducted in addition to an abbreviated physical exam.

[b] 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.

[c] A serum follicle stimulating hormone test will be conducted at Screening for female participants 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.

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

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

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

[g] Urine toxicology for selected drugs of abuse (as per the lab manual) and breath test for alcohol.

[h] Serum pregnancy test at screening and urine pregnancy test thereafter for female subjects who are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal.

[redacted]

[k] 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 participant has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Vital signs may be repeated at the discretion of the Investigator as clinically indicated.

[l] Triplicate ECGs will be collected. When ECGs [redacted] collection occur on the same day, the 12-lead ECGs will be performed [redacted] sample collection.

[m] 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.
[n] The HAM-D is to be completed as early during the visit as possible.
[o] The assessment timeframe for HAM-D scales will refer to the past 7 days (1 week) at Screening and "Since Last Visit" for all other visits. The assessment timeframe for HAM-A scales will refer to the past 7 days (1 week) at all visits.

[redacted]

[q] To be performed at the ET visit only.
[r] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.
[s] Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.

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

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 4: Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
ADR	adverse drug reaction
AE	adverse event
AUC	area under the curve
C_{avg}	average plasma concentration
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
C_{max}	maximum plasma concentration
CRF	case report form
CS	clinically significant
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ET	early termination
[redacted]	[redacted]
FSH	follicle stimulating hormone
GABA	γ-aminobutyric acid
GEE	generalized estimating equation
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Rating Scale for Depression
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ID	identification

Abbreviation or specialist term	Explanation
IRB	institutional review board
IRT	interactive response technology
ISI	Insomnia Severity Index
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
MTD	maximum tolerated dose
NCS	not clinically significant
NOAEL	no-observed-adverse-effect-level
OS	oral solution
PCS	Potentially clinically significant
PHQ-9	9-item Patient Health Questionnaire
[redacted]	[redacted]
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

This study is being conducted in 2 parts – Part A and Part B. Unless otherwise specified, text in the following sections applies to both study parts.

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 suicide attempts in adults 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).

5.2. SAGE-217

SAGE-217 is a synthetic positive allosteric modulator of $GABA_A$ 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 $GABA_A$ receptors, and, consistent with the actions of other $GABA_A$ receptor potentiators (Rudolph 2011), exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo.

Unlike other neurotropic medications that target $GABA_A$ receptors, SAGE-217 is an allosteric modulator of both synaptic as well as extrasynaptic $GABA_A$ receptors (Martinez Botella 2017).

As such, SAGE-217 may represent a therapeutic advantage in the treatment of depressive disorders by resetting the GABAergic imbalance in depression by affecting both phasic and tonic inhibition.

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 (Gunduz-Bruce 2019). 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. The most common adverse events (AEs) associated with SAGE-217 are somnolence, dizziness, and sedation; most AEs were reported as mild or moderate in intensity. Refer to the Investigator's Brochure for a detailed description of the chemistry, pharmacology, efficacy, and safety of SAGE-217.

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

Part A

There will be 2 dose levels of SAGE-217 in Part A 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 (MTD) for the oral solution formulation 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 Part A.

Part B

To date, the current capsule utilized in clinical studies is not associated with an MTD. Initial MTD assessments were performed using SAGE-217 in an oral solution (OS) at steady-state in healthy subjects, which provided an MTD with a C_{max} of 125 ng/mL at 30 mg OS. While re-identification of the MTD using the capsule formulations was not conducted, steady-state 30 mg

capsules provide a model-derived C_{max} approximately 50% lower (64 ng/mL) than the concentration associated with the MTD of 30 mg OS (125 ng/mL).

Studies 217-MDD-201 and 217-PPD-201, employing 30 mg capsules administered each evening for 14 days, demonstrated significant reduction in symptoms of depression, anxiety and insomnia. The safety profile in these studies is consistent with the $GABA_A$ neurosteroid mechanism, including adverse drug reactions (ADRs) of somnolence, sedation, and dizziness at rates of 4 to 15%; the majority with mild intensity. Phase 3 studies in a broader patient population demonstrate activity of SAGE-217 associated with improvement in depressive symptoms, however, both the efficacy and safety findings support investigation of a higher dose, with predictable ADRs expected to be within an acceptable range.

Preliminary data through Day 42 of the double-blind period in Part A of this study demonstrated significant anti-depressant effects compared to placebo at Day 3, 8, and 12 but not Day 15 (primary endpoint) for the 30 mg dose. The 20 mg dose did not separate from placebo at any timepoint. The rates of expected ADRs of somnolence, sedation and dizziness in the 30 mg arm were each less than 10%; rates of discontinuation for AEs were lower with SAGE-217 30 mg (2.1%) than with placebo (3.2%). No clinically relevant changes in vital signs, laboratories, electrocardiogram measures, or suicidal thinking were observed in either Part A of the current study or across the full SAGE-217 program, now with over 2000 subjects exposed to treatment. In addition, approximately 112 additional subjects have received blinded study drug (SAGE-217 or placebo) in ongoing blinded clinical studies. Relevant results from Part A of this study are available in the SAGE-217 Investigator's Brochure.

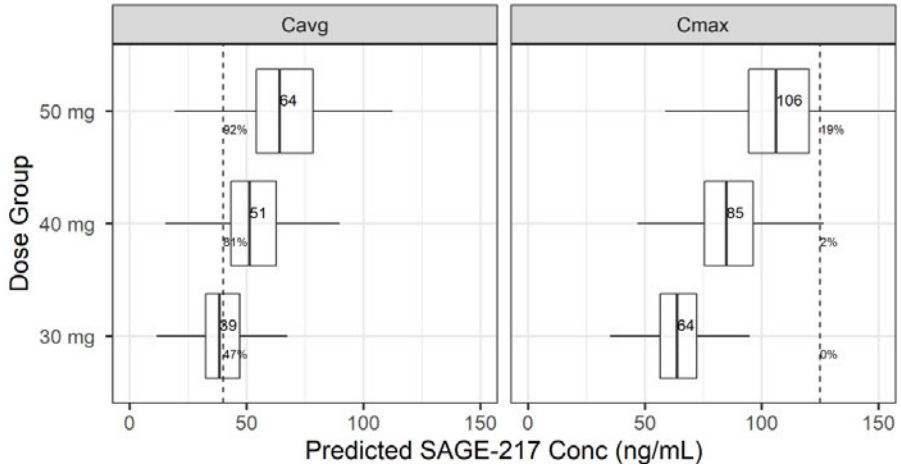
Direct and modeled data from completed studies to date (including efficacy studies 217-MDD-201 and 217-PPD-201) in addition to Part A (through Day 42 of the double-blind period) of the current study, have been used to assess and predict the efficacy and safety outcomes at SAGE-217 concentrations expected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

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

Direct evidence related to efficacy and safety outcomes following administration of SAGE-217 capsules at doses above 30 mg is further provided by results from a Phase 1, placebo-controlled study in healthy subjects using a 5-hour phase advance model of insomnia (Study 217-EXM-101). Administration of single doses of SAGE-217 up to 45 mg improved sleep efficiency, duration, maintenance and sleep quality compared with placebo. Evening administration of SAGE-217 was generally well tolerated, with an acceptable safety and tolerability profile. All reported TEAEs were mild and all resolved. Additional data from Study 217-EXM-101 are provided in the Investigator's Brochure.

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

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



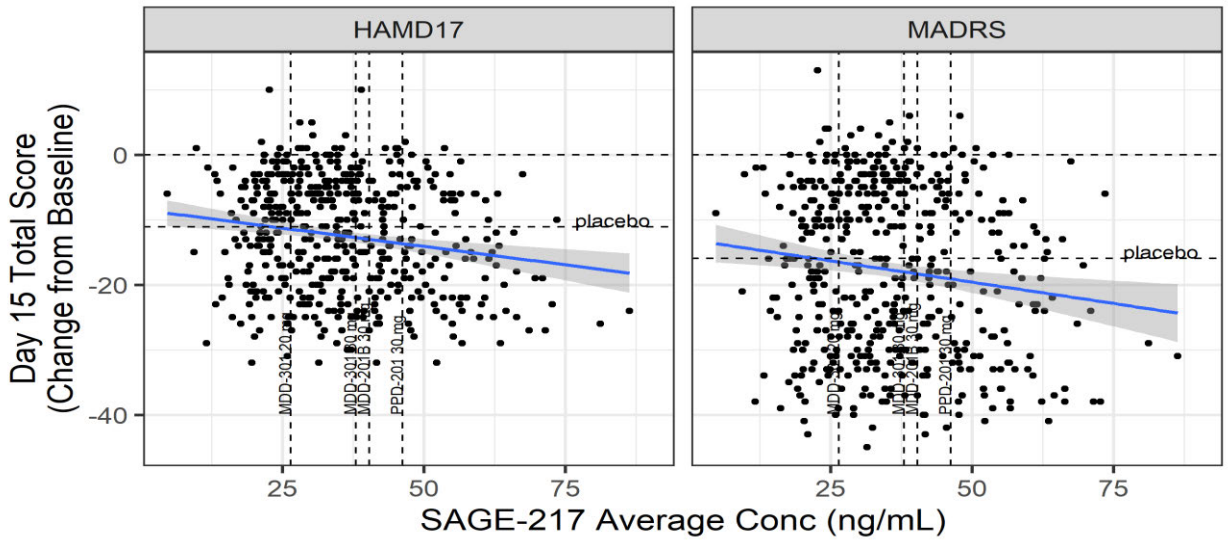
Dashed vertical lines represent target concentrations for efficacy (C_{avg} >40 ng/mL) and safety (C_{max}<125 ng/mL). Percentage next to dashed lines indicate the percentages with C_{avg}>40 ng/mL or with C_{max}>124 ng.

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

Increased granularity of the exposure-efficacy relationship is provided in Figure 2. Across Studies 217-MDD-201B, 217-PPD-201, and Part A of the current study, increased concentrations of SAGE-217 were associated with a larger reduction in depressive symptoms (Figure 2). Based on linear regression modeling, effect sizes for HAM-D were dose dependent, with a 50 mg dose administered once daily for 14 days predicted to provide greater therapeutic

benefit compared to daily doses of 40 and 30 mg. Based on preliminary results from Part A of this study, a dose of 30 mg may be considered the minimally effective dose.

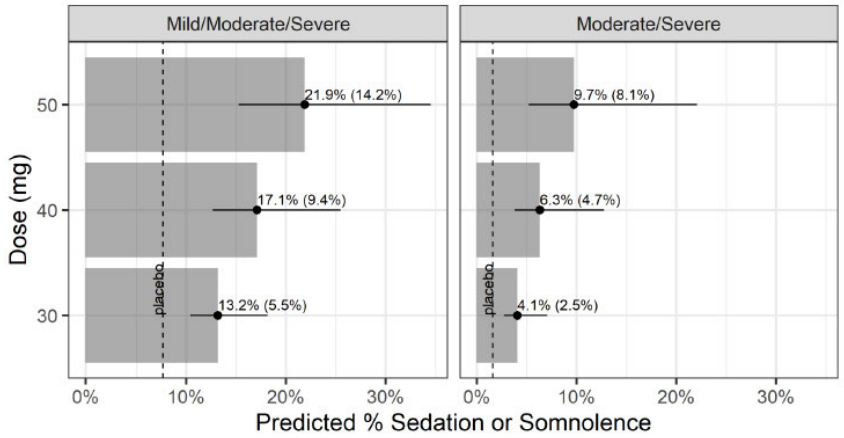
Figure 2: Total score change on Day 15 (Studies 217-MDD-201B, 217-PPD-201, Part A of the current study)



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

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

Figure 3: Predicted incidence of sedation or somnolence by dose



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

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

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

Sedation, an extension of the pharmacologic mechanism of SAGE-217, was the primary dose-limiting effect in toxicity studies in rats and dogs. In dogs, the toxicologic 'effect dose' levels of 2.5 mg/kg/day (9-month study, episodic dosing study) or 2 mg/kg/day (3-month study) associated with a low incidence of convulsion and/or early mortality during or following the dosing phase, were associated with exposures 7- to 11-fold above clinically relevant C_{max} following administration of 30 mg capsules. Similar margin calculations for adverse effect levels in dogs to potential higher SAGE-217 dose levels (40 or 50 mg/day) remain at or above 4.5x for both C_{max} and AUC. All non-clinical findings are provided in the SAGE-217 Investigator's Brochure. The totality of the nonclinical safety data supports the use of SAGE-217 for the

treatment of patients at the higher clinical dose regimen, particularly in the context of the current safety database of greater than 2000 subjects exposed to SAGE-217 treatment.

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

6. STUDY OBJECTIVES AND 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:

- Part A only: 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. Part A - Secondary Endpoints

- 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 ≥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 ≤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. Part B – Key Secondary Endpoints

- CGI-S at Day 15
- HAM-D total score at Day 3, Day 28, and Day 42

6.2.4. Part B – Other Secondary Endpoints

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as “much improved” or “very much improved”, at Day 15
- MADRS total score at Day 15
- HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline in PRO measures of health-related quality of life, as assessed by responses to the SF-36v2, and of depressive symptoms as assessed by the PHQ-9

6.2.5. 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]

- [redacted]
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- [redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD. This study will be conducted in 2 parts – Part A and Part B. Bart B will commence after all subjects in Part A have completed the Day 42 visit. Part A and Part B will enroll unique subjects. For both study parts, 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. Each study part is described below.

Part A

Part A 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) with the intent of identifying subjects who may meet exclusion criteria due to participation in another clinical study (Section 8.2). 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 ≥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 2.

Part B

Part B will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, and a 28-day double-blind follow-up period. Part B of the study may run concurrently with the extended follow-up period in Part A.

The Screening Period begins with the signing of the 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) with the intent of identifying subjects who may meet

exclusion criteria due to participation in another clinical study (Section 8.2). 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 ≥60 days) and randomized within each stratum to one of 2 treatment groups (SAGE-217 50 mg or matching placebo) in a 1:1 ratio. Subjects will self-administer study drug once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat or with a fat-containing snack), on an outpatient basis, for 14 days. See Section 10.5 for examples of fat-containing snacks. Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 3.

During the treatment period, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the Investigator, subjects who cannot tolerate the 40-mg dose may be discontinued from study drug.

Subjects who discontinue treatment early should return to the site for an 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 ET visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and decides to terminate the study on the same day during a clinic visit; in this case, all EOT visit assessments should be conducted in addition to an abbreviated physical exam.

7.2. Number of Subjects

In Part A, approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects (see Section 13.8). In Part B, approximately 240 subjects will be randomized and dosed to obtain 216 evaluable subjects.

7.3. Treatment Assignment

For both study parts, subjects will be randomly assigned to a treatment group on Day 1 and will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥60 days) at baseline. In Part A, randomization will be performed within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo. In Part B, randomization will be performed within each stratum in a 1:1 ratio to receive SAGE-217 50 mg or matching placebo.

7.4. Dose Adjustment Criteria

In Part A, dose adjustments are not permitted and subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated (see Section 8.3).

During the treatment period in Part B, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the Investigator, subjects who cannot tolerate the 40-mg dose may be discontinued from study drug (refer to Section 8.3 for procedures for early study drug discontinuation). If dose adjustment is deemed necessary by the Investigator at any time during the treatment period, the subject will return to the site to return any remaining study drug and for the adjusted dose to be dispensed.

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 64 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. For Part A, subject has a MADRS total score of ≥32 and a HAM-D total score ≥22 at screening and Day 1 (prior to dosing). For Part B, subject has a HAM-D total score ≥24 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 who have stopped taking antidepressants within 60 days must have stopped for longer than 5 half-lives of the antidepressant 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 or without 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 is currently at significant risk of suicide, as judged by the Investigator, or 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. For Part A, a body mass index (BMI) $\leq$18 or $\geq$50 kg/m^2 at Screening is exclusionary; a BMI of 40 to 49 kg/m^2, 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. For Part B, a BMI $\leq$18 or $\geq$45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
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 $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Subject is taking any benzodiazepine or GABA modulator with a half-life of ≥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, including suicidality, at the discretion of the Investigator

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 may withdraw the subject from the study at his/her discretion. 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.

In Part A, 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.

In Part B, subjects who discontinue study drug early should return to the site for an 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. If necessary, 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 EOT visit assessments should be conducted in addition to an abbreviated physical exam.

For both study parts, 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

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

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

9.2. Prior Medications, Concomitant Medications, 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, $GABA_A$ 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 ≥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 who are feeling sedated, somnolent, and/or dizzy are to refrain from driving or engaging in any activity requiring alertness.

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 10.5, Table 2, and Table 3).

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 2 and Table 3, 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. For both study parts, 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 ≥60 days) at baseline.

In Part A, 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. In Part B, randomization will be done within each stratum in a 1:1 ratio to receive SAGE-217 50 mg or matched placebo.

In both study parts, 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 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 Part A, 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 Part B, the Sponsor, site personnel and subjects will remain blinded until the database lock when all subjects complete the Day 42 visit.

9.4.1. Emergency Identification of Study Drug

During the study, the blind is to be broken 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 should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a subject. Requests from the Investigator about the treatment administered to study subjects should be discussed with the Sage Medical Monitor. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the 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. At the of withdrawal from the study/stopping participation, if possible, an EOT and/or ET visit should be conducted.

If a subject or study personnel become unblinded to treatment, the subject will be excluded from the Full Analysis Set, as detailed further in the statistical analysis plan.

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. 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. For Part A, each unit dose consists of 1 capsule. For Part B, each unit dose consists of 2 capsules (see Section 9.1). 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

In Part A, 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.

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

In both study parts, 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 2 and Table 3.

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.

10.8. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness or performance (applicable for approved marketed products) of a drug product after it is released for distribution. In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in Table 1. Where possible, personnel should segregate any product, materials, or packaging associated with the product complaint.

11. ASSESSMENT OF EFFICACY [redacted]

All assessments will be conducted according to the schedule of assessments (Table 2 and Table 3). 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 past 7 days (1 week) will be used at Screening and during the extended Follow-up Period (Part A only), 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 ≤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; Part A Only)

The ISI will be assessed in Part A only. 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 (Part A Only)

The Core Consensus Sleep Diary will be assessed in Part A only. This instrument 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]

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

All assessments will be conducted according to the schedule of assessments (Table 2 and Table 3).

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, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, persistent depressive disorder, postpartum depression, substance use disorder, alcohol use disorder, major depressive disorder with seasonal pattern, major depressive disorder with psychotic features, premenstrual dysphoric disorder, major depressive disorder with atypical features, schizophrenia; or schizoaffective disorder will be documented. The 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 10th 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. An abbreviated physical exam includes a brief medical history followed by a targeted physical exam. 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. When ECG [redacted] sample collection occur during the same visit, the ECGs will be conducted first.

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 5.

Table 5: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Coagulation
Red blood cell count Hemoglobin Hematocrit White blood cell count with differential Platelet count Red Blood Cell Indices (MCV, MCH, MCHC) Reflex to Red blood cell morphology if indices are abnormal	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase Gamma-glutamyl transferase Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphorus Triglycerides	pH Specific gravity Protein Glucose Red blood cell Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio

	Thyroid stimulating hormone (TSH) Reflex to free T3/T4 if TSH is abnormal		
Diagnostic			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C Reflex HCV RNA HIV-1 and -2 Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: serum hCG Female subjects, if menopause is suspected and not surgically sterile: FSH	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine 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).

[redacted]

[redacted]

12.1.6.1. Drugs of Abuse and Alcohol

Urine toxicology tests will be performed for selected drugs of abuse (see Table 5). 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 2 and Table 3).

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 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.

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 6: Relationship to Study Drug

Relationship	Definition
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. 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. 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. Any complication during pregnancy (eg, anemia, infections, pre-eclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, 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. Overdose

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

13. STATISTICS

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. Separate SAPs will be generated for each part of the study. The SAP for each study part will be finalized and approved prior to treatment unblinding of each respective part.

In Part A, 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. Data from Part A may be analyzed and reported following final database lock and before Part B is complete. For Part B, the final database lock will occur when all subjects complete the study; treatment unblinding and analyses will follow the database lock.

Separate clinical study reports will be produced for each part of the study.

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.

[redacted]

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 ≥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 in Part A only (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score in Part A only, 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 ≥50% reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of ≤7.0). GEE models will include terms for treatment, baseline score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 and matching placebo at 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]

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

For Part A, 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%.

For Part B, assuming a two-sided alpha level of 0.05, a sample size of 216 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 a standard deviation (SD) of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 240 total randomized subjects will be required to obtain 216 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 postbaseline HAM-D assessment.

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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Protocol 217-MDD-301, Amendment 5

Date of Amendment: 02 March 2020

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 add a new study part (Part B) to evaluate a 50-mg dose (to align with changes to the dose level applied to other active clinical studies of SAGE-217), for further evaluation of the safety and efficacy of SAGE-217. Associated changes to the Part B-specific study objectives and endpoints, subject eligibility criteria, planned number of subjects, schedule of assessments, study drug dose and administration, and dose justification based on the addition of Part B have been incorporated.

Other changes implemented with this amendment include the following:

- Background information was changed to update the SAGE-217 mechanism of action to reflect current data
- Safety information presented in the introduction was simplified with reference to the SAGE-217 Investigator's Brochure for detailed safety information
- Clarified that the decision to withdraw a subject from the study is solely at the discretion of the investigator
- Added a restriction for subjects feeling sedated, somnolent, or dizzy to refrain from driving or engaging in other activities requiring alertness
- Added an overdose section
- Clarified AEs/SAEs related to pregnancy
- Edited the description of the study drug to pertain to autofill formulation only
- Emergency identification of the study drug was moved to the randomization and blinding section for improved organization
- Clarified timing of dose administration and dosing instructions for subjects in Part B

Separately, for interstudy consistency, other minor updates have been made to align with changes applied in other SAGE-217 studies.

Other minor administrative changes have been made, including changes identified in administrative letters dated 19 August 2019 and 29 August 2019, as well as inclusion of emergency contact information and product complaint reporting information.

A detailed summary of changes is provided in Table 1. Updated references, protocol signatories, and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

Table 1: Protocol Amendment 5 Detailed Summary of Changes

The primary section of the protocol affected by the changes in Protocol Amendment 5 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: Revise the overall study design to include a new study part (Part B) designed to evaluate a 50-mg dose. Clarify that the study will be conducted in 2 parts.

The primary change occurs in Section 7.1 Overall Study Design.

Now reads: This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD ~~(MADRS total score ≥32 and a HAM-D total score ≥22)~~. **This study will be conducted in 2 parts – Part A and Part B. Bart B will commence after all subjects in Part A have completed the Day 42 visit. Part A and Part B will enroll unique subjects. For both study parts, 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. Each study part is described below.**

Part A

Part A ~~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) with the intent of identifying subjects who may meet exclusion criteria due to participation in another clinical study (Section 8.2). Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the MADRS, HAM-D, and CGI-S.

~~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 ≥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 2**.

Part B

Part B will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, and a 28-day double-blind follow-up period. Part B of the study may run concurrently with the extended follow-up period in Part A.

The Screening Period begins with the signing of the 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) with the intent of identifying subjects who may meet exclusion criteria due to participation in another clinical study (Section 8.2). 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 ≥60 days) and randomized within each stratum to one of 2 treatment groups (SAGE-217 50 mg or matching placebo) in a 1:1 ratio. Subjects will self-administer study drug once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat or with a fat-containing snack), on an outpatient basis, for 14 days. See Section 10.5 for examples of fat-containing snacks. Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 3.

During the treatment period, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the Investigator, subjects who cannot tolerate the 40-mg dose may be discontinued from study drug.

Subjects who discontinue treatment early should return to the site for an 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 ET visit. The EOT and ET visits can be on the same

day if a subject discontinues study drug and decides to terminate the study on the same day during a clinic visit; in this case, all EOT visit assessments should be conducted in addition to an abbreviated physical exam.

Sections also affected by this change:

- Synopsis
- Section 5 Introduction
- Section 6 Objectives and Purpose
- Section 7 Investigational Plan
- Section 8 Selection and Withdrawal Criteria
- Section 9 Treatment of Subjects
- Section 10 Study Drug Materials and Management
- Section 11 Assessment of Efficacy [redacted]
- Section 13 Statistics

Purpose: Update objectives and endpoints to identify those that pertain to Part A only, identify key secondary endpoints for Part B; secondary endpoints related to sleep (Insomnia Severity Index and subjective sleep parameters collected with the Core Consensus Sleep Diary), [redacted] will not be evaluated in Part B

The primary change occurs in Section 6 Objectives and Purpose.

Now reads:

6.1.2. Secondary Objective(s)

Secondary objectives are:

- **Part A only**: To evaluate the effect of SAGE-217 on sleep.

[redacted]

[redacted]

6.2.2 **Part A -** Secondary Endpoints

6.2.3 Part B – Key Secondary Endpoints

- **CGI-S at Day 15**
- **HAM-D total score at Day 3, Day 28, and Day 42**

6.2.4 Part B – Other Secondary Endpoints

- **HAM-D response at Day 15 and Day 42**
- **HAM-D remission at Day 15 and Day 42**
- **CGI-I response, defined as "much improved" or "very much improved", at Day 15**
- **MADRS total score at Day 15**
- **HAM-A total score at Day 15**
- **Time to first HAM-D response**
- **Change from baseline in PRO measures of health-related quality of life, as assessed by responses to the SF-36v2, and of depressive symptoms as assessed by the PHQ-9**

[redacted]

Sections also affected by this change:

- Synopsis
- Section 11 Assessment of Efficacy [redacted]

Purpose: Update the number of subjects to reflect the addition of Part B

The primary change occurs in Section 7.2 Number of Subjects

Now reads:

In Part A, a~~A~~pproximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects (see Section 13.8). **In Part B, approximately 240 subjects will be randomized and dosed to obtain 216 evaluable subjects.**

Sections also affected by this change:

- Synopsis

Purpose: Update randomization and blinding to include the randomization and blinding plan for Part B.

The primary change occurs in Section 9.4 Randomization and Blinding

Now reads:

This is a randomized double-blind, placebo-controlled study. **For both study parts, ~~S~~s**ubjects who meet the entrance criteria will be randomized in a stratified manner based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥60 days) at baseline.

In Part A, 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. **In Part B, randomization will be done within each stratum in a 1:1 ratio to receive SAGE-217 50 mg or matched placebo.**

In both study parts, ~~S~~s**ubjects, 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 Part A, ~~T~~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 and individual subject's treatment in the study via the IRT (see Section for more details related to unblinding).~~

In Part B, the Sponsor, site personnel and subjects will remain blinded until the database lock when all subjects complete the Day 42 visit.

Sections also affected by this change:

- 7.3 Treatment Assignment
- Synopsis

Purpose: Add dose justification language to support the SAGE-217 50-mg dose. Clarify that the MTD of 30 mg was determined using the oral solution formulation.

The primary change occurs in Section 5.4 Dose Justification

Now reads:

Part A

There will be 2 dose levels of SAGE-217 in **Part A** ~~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 **(MTD) for the oral solution formulation** 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~~ **Part A**.

Part B

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

Studies 217-MDD-201 and 217-PPD-201, employing 30 mg capsules administered each evening for 14 days, demonstrated significant reduction in symptoms of depression, anxiety and insomnia. The safety profile in these studies is consistent with the $GABA_A$ neurosteroid mechanism, including adverse drug reactions (ADRs) of somnolence, sedation, and dizziness at rates of 4 to 15%; the majority with mild intensity. Phase 3 studies in a broader patient population demonstrate activity of SAGE-217 associated with improvement in depressive symptoms, however, both the efficacy and safety findings support investigation of a higher dose, with predictable ADRs expected to be within an acceptable range.

Preliminary data through Day 42 of the double-blind period in Part A of this study demonstrated significant anti-depressant effects compared to placebo at Day 3, 8, and 12 but not Day 15 (primary endpoint) for the 30 mg dose. The 20 mg dose did not separate from placebo at any timepoint. The rates of expected ADRs of somnolence, sedation and dizziness in the 30 mg arm were each less than 10%; rates of discontinuation for AEs were lower with SAGE-217 30 mg (2.1%) than with placebo (3.2%). No clinically relevant changes in vital signs, laboratories, electrocardiogram measures, or suicidal thinking were observed in either Part A of the current study or across the full SAGE-217 program, now with over 2000 subjects exposed to treatment. In addition, approximately 112 additional subjects have received blinded study drug (SAGE-217 or placebo) in ongoing blinded clinical studies. Relevant results from Part A of this study are available in the SAGE-217 Investigator's Brochure.

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

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

Direct evidence related to efficacy and safety outcomes following administration of SAGE-217 capsules at doses above 30 mg is further provided by results from a Phase 1, placebo-controlled study in healthy subjects using a 5-hour phase advance model of insomnia (Study 217-EXM-101). Administration of single doses of SAGE-217 up to 45 mg improved sleep efficiency, duration, maintenance and sleep quality compared with placebo. Evening administration of SAGE-217 was generally well tolerated, with an acceptable safety and tolerability profile. All reported TEAEs were mild and all resolved. Additional data from Study 217-EXM-101 are provided in the Investigator's Brochure.

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

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

------Figure 1 image------

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

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

Figure 1: Total score change on Day 15 (Studies 217-MDD-201B, 217-PPD-201, Part A of the current study)

------Figure 2 image------

Exposure-response modeling for safety quantified the relationship between maximum plasma concentration (C_{max}) and safety from studies 217-MDD-201, 217-PPD-201, and Part A of the current study. The safety endpoint for modeling was selected as the incidence of sedation or somnolence during SAGE-217 treatment, as they represent on-target effects at the $GABA_A$

receptor and are the most commonly occurring adverse events with SAGE-217 when considering all doses and formulations. Logistic regression modeling indicated higher C_{max} values were associated with an increased incidence of sedation or somnolence across mild, moderate and severe intensities. Based on this observed relationship, the predicted incidence rates of sedation or somnolence were simulated at SAGE-217 doses of 30, 40 or 50 mg administered once daily (Figure 3).

Figure 2: Predicted incidence of sedation or somnolence by dose

------Figure 3 image------

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

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

Sedation, an extension of the pharmacologic mechanism of SAGE-217, was the primary dose-limiting effect in toxicity studies in rats and dogs. In dogs, the toxicologic 'effect dose' levels of 2.5 mg/kg/day (9-month study, episodic dosing study) or 2 mg/kg/day (3-month study) associated with a low incidence of convulsion and/or early mortality during or following the dosing phase, were associated with exposures 7- to 11-fold above clinically relevant C_{max} following administration of 30 mg capsules. Similar margin calculations for adverse effect levels in dogs to potential higher SAGE-217 dose levels (40 or 50 mg/day) remain at or above 4.5x for both C_{max} and AUC. All non-clinical findings are provided in the SAGE-217 Investigator's Brochure. The totality of the nonclinical safety data supports the use of SAGE-217 for the treatment of patients at the higher clinical dose regimen, particularly in the context of the current safety database of greater than 2000 subjects exposed to SAGE-217 treatment.

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

Sections also affected by this change:

- Added Figures 1 to 3

Purpose: Modify background information to align with current understanding of the mechanisms of action of SAGE-217 and update safety information to include a high-level summary with reference to the Investigator's Brochure for more detailed safety information.

The primary change occurs in Section 5 Introduction

Now reads:

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 mirtrazapine 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 γ-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 $GABA_A$ 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 $GABA_A$ receptors, and, consistent with the actions of other $GABA_A$ receptor potentiators (Rudolph 2011), exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo.

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

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 **(Gunduz-Bruce 2019)**. 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 adverse events associated with SAGE-217 are somnolence, dizziness, and sedation; most adverse events were reported as mild or moderate in intensity. Refer to the Investigator's Brochure for a detailed description of the chemistry, pharmacology, efficacy, and safety of SAGE-217.** ~~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.~~

Sections also affected by this change:

- Not applicable

Purpose: Modify dose adjustment criteria to indicate that dose reductions are permitted in Part B for subjects who cannot tolerate the 50-mg dose.

The primary change occurs in Section 7.4 Dose Adjustment Criteria

Now reads:

In Part A, d~~D~~ose adjustments are not permitted ~~in this study~~ **and s**~~S~~ubjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated (see Section 8.3).

During the treatment period in Part B, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subject who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the Investigator, subjects who cannot tolerate the 40-mg dose may be discontinued from study drug (refer to Section 8.3 **for procedures for early study drug discontinuation). If dose adjustment is deemed necessary by the Investigator at any time during the treatment period, the subject will return to the site to return any remaining study drug and for the adjusted dose to be dispensed.**

Sections also affected by this change:

- Synopsis
- Section 5.4 Dose Justification
- Section 7.1 Overall Study Design
- Section 9.1 Study Drug

Purpose: Add product complaint reporting information.

The primary change occurs in added Section 10.8 Product Complaints.

Now reads:

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

In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in Table 1. Where possible, personnel should segregate any product, materials, or packaging associated with the product complaint.

Sections also affected by this change:

- Added Table 1 Emergency Contact Information

Purpose: Revise subject withdrawal criteria to indicate that the decision to withdraw a subject from the study is solely at the discretion of the Investigator

The primary change occurs in Section 8.3 Subject Withdrawal Criteria

Now reads:

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, **including suicidality,** 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~~ **may withdraw the subject from the study at his/her discretion**.~~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.

Sections also affected by this change:

- Not applicable

Purpose: Update subject inclusion criteria to: 1) modify the upper age limit to 64 years, inclusive for subjects in Part B to conform with the accepted definition of non-elderly subjects; 2) allow subjects with higher HAM-D score to be eligible for Part B; 3) clarify that if subjects have stopped taking antidepressants within 60 days of Day 1, they must also have stopped taking them for longer than 5 half-lives to ensure full wash-out prior to study start; 4) lower the upper BMI limit for subjects in Part B to 45 kg/m^2; and 5) specify that use of condoms with or without spermicide is an acceptable method of contraception.

The primary change occurs in Section 8.1 Subject Inclusion Criteria

Now reads:

2. Subject is a male or female between 18 and ~~65~~**54** years of age, inclusive.

6. **For Part A, s**~~S~~ubject has a MADRS total score of ≥32 and a HAM-D total score ≥22 at screening and Day 1 (prior to dosing). **For Part B, subject has a HAM-D total score ≥24 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 who have stopped taking antidepressants within 60 days must have stopped for longer than 5 half-lives of the antidepressant 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.** Subjects receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1.

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 **or without** 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

Purpose: Clarify the exclusion criterion of suicide risk. Lower the upper BMI limit for subjects in Part B to 45kg/m^2.

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Now reads:

1. Subject **is currently at significant risk of suicide, as judged by the Investigator, or** has attempted suicide associated with the current episode of MDD.

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. **For Part A, a** ~~A~~ body mass index (BMI) ≤18 or ≥50 kg/m^2 at Screening is exclusionary; a BMI of 40 to 49 kg/m^2, 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. **For Part B, a BMI ≤18 or ≥45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.**

Sections also affected by this change:

- Synopsis

Purpose: Update description of study drug to delete information pertaining to the profill formulation, which is not being used in this study.

The primary change occurs in Section 10.1 Description of Study Drug

Now reads:

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.

Sections also affected by this change:

- Synopsis

Purpose: Update description of study drug to delete information pertaining to the profill formulation, which is not being used in this study.

The primary change occurs in Section 10.1 Description of Study Drug

Now reads:

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.

Sections also affected by this change:

- Synopsis

Purpose: Update study drug information to include the dose-specific information for Part B.

The primary change occurs in Section 9.1 Study Drug

Now reads:

In Part A, ~~S~~subjects will self-administer SAGE-217 (20 or 30 mg) or matching placebo orally once daily in the evening with food for 14 days.

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

Sections also affected by this change:

- Section 10.2 Study Drug Packaging and Labeling
- Synopsis

Purpose: Add a section to define overdose and procedures in the event of overdose.

The primary change is a new Section 12.6 Overdose

Now reads:

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

Sections also affected by this change:

- Not applicable

Purpose: Specify procedures for subjects who discontinue study drug early during Part B.

The primary change occurs in Section 8.3 Subject Withdrawal Criteria

Now reads:

In Part B, subjects who discontinue study drug early should return to the site for an EOT visit as soon as possible, preferably the day after treatment is discontinued, and an ET visit should be conducted 7 days later. If necessary, 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 EOT visit assessments should be conducted in addition to an abbreviated physical exam.

For both study parts, a~~A~~ subject will be deemed lost to follow-up after attempts at contacting the subject have been unsuccessful.

Sections also affected by this change:

- Synopsis
- Section 7.1 Overall Study Design

Purpose: Specify that separate SAPs and clinical study reports will be generated for each study. Additionally, data from Part A may be analyzed and reported following final database lock and before Part B is complete.

The primary change occurs in Section 13 Statistics

Now reads:

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. **Separate SAPs will be generated for each part of the study.** The SAP **for each study part** will be finalized and approved prior to treatment unblinding **of each respective part.**

In Part A, **w**~~W~~hen 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. **Data from Part A may be analyzed and reported following final database lock and before Part B is complete. For Part B, the final database lock will occur when all subjects complete the study; treatment unblinding and analyses will follow the database lock.**

Separate clinical study reports will be produced for each part of the study.

Sections also affected by this change:

- Synopsis

Purpose: Update determination of sample size to include Part B.

The primary change occurs in Section 13.8 Determination of Sample Size

Now reads:

For Part A, ~~A~~**a**ssuming 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%.

For Part B, assuming a two-sided alpha level of 0.05, a sample size of 216 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 a standard deviation (SD) of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 240 total randomized

subjects will be required to obtain 216 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 postbaseline HAM-D assessment.

Sections also affected by this change:

- Synopsis

Purpose: Clarify pregnancy-related AEs/SAEs

The primary change occurs in Section 12.4 Recording Adverse Events

Now reads:

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. **Any complication** ~~or a complication relating to the~~ **during** pregnancy ~~occurs~~ (e~~.~~g~~.~~, **anemia, infections, pre-eclampsia**~~spontaneous abortion~~) **should be reported as an AE/SAE**. 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

[redacted]

[redacted]

Purpose: Update assessment of efficacy section to modify assessments that pertain only to Part A

The primary change occurs in Section 11 Assessment of Efficacy [redacted]

Now reads:

11.1.7 Insomnia Severity Index (ISI**; Part A Only**)

The ISI will be assessed in Part A only. The ISI is a validated questionnaire designed to assess the nature, severity, and impact of insomnia (Morin 2011).

11.1.8 Core Consensus Sleep Diary **(Part A Only)**

The Core Consensus Sleep Diary **will be assessed in Part A only. This instrument** collects subjective sleep parameters, including sleep onset latency, total sleep time, and wake after sleep onset, number of awakenings, and sleep quality.

[redacted]

Sections also affected by this change:

- Not applicable

Purpose: Modify efficacy analysis to indicate the Part A-specific endpoints

The primary change occurs in Section 13.5 Efficacy Analysis

Now reads:

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 **in Part A only** (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score **in Part A only**, and selected individual items and/or subscale scores in HAM-D for change from baseline.

Sections also affected by this change:

- Synopsis

Purpose: Include a restriction for subjects feeling sedated, somnolent, or dizzy to refrain from driving or engaging in other activities requiring alertness.

The primary change occurs in Section 9.2.3 Other Restrictions

Now reads:

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

Sections also affected by this change:

- Not applicable

Purpose: Specify that for Part B, in the event of a dose reduction, an unscheduled [redacted] sample should be collected, if possible, prior to the dose adjustment.

[redacted]

Sections also affected by this change:

- Schedule of Events (Part B) footnote p

Purpose: Add definition of an abbreviated physical exam

The primary change occurs in Section 12.1.3 Physical Examination

Now reads:

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. **An abbreviated physical exam includes a brief medical history followed by a targeted physical exam.** 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.

Sections also affected by this change:

- Schedule of Events (Part B) footnote e

Purpose: Add specific psychiatric diagnoses that are documented as part of medical history.

The primary change occurs in Section 12.1.1 Demographic/Medical History

Now reads:

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including**:** family psychiatric history**, generalized anxiety disorder, obsessive-compulsive disorder, panic**

disorder, persistent depressive disorder, postpartum depression, substance use disorder, alcohol use disorder, major depressive disorder with seasonal pattern, major depressive disorder with psychotic features, premenstrual dysphoric disorder, major depressive disorder with atypical features, schizophrenia, or schizoaffective disorder will be documented. The 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 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

Sections also affected by this change:

- Not applicable

Purpose: In accordance with Administrative Letter #2, dated 15 August 2019, specify that for the extended follow-up period, an assessment timeframe of past 7 days should be used for the HAM-D questionnaire.

The primary change occurs in Section 11.1.1 Hamilton Rating Scale for Depression (HAM-D)

Now reads:

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 **past** 7 days **(1 week)** will be used at Screening **and during the extended Follow-up Period (Part A only)**, and 'Since Last Visit' will be used for all other visits.

Sections also affected by this change:

- Schedule of Events (Part A) footnote o

Purpose: *Correct typographical errors, punctuation, grammar, abbreviations, formatting and updated references list.*

These changes are not listed individually.

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. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Tel: [redacted] email: [redacted]
Sponsor Medical Monitor	[redacted], MD, MBA Tel: [redacted] 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 MAR 2019
Date of Amendment 4	Version 5.0, 25 MAR 2019
Date of Amendment 5	Version 6.0, 02 MAR 2020
Date of Amendment 6	Version 7.0, 14 SEP 2020

SPONSOR APPROVAL

Protocol Number:	217-MDD-301
Study Drug:	SAGE-217
Study Phase:	Phase 3
Sponsor:	Sage Therapeutics, Inc.
Protocol Date:	Version 7.0, 14 September 2020

Sponsor Approval

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9/15/2020

[redacted], MD, MBA — Date
[redacted]
Sage Therapeutics

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9/15/2020

[redacted], MBBS (MD) — Date
[redacted]
Sage Therapeutics

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9/15/2020

[redacted], RAC — Date
[redacted]
Sage Therapeutics

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9/15/2020

[redacted] — Date
[redacted]
Sage Therapeutics

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9/15/2020

[redacted], PhD — Date
[redacted]
Sage Therapeutics

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9/15/2020

[redacted] — Date
[redacted]
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)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Syneos Health Medical Monitor	[redacted], MD [redacted]	Email: [redacted] Office: [redacted] Cell: [redacted]
Sage Study Physician	[redacted], MD, MBA [redacted]	Email: [redacted] Tel: [redacted]
24-Hour Serious Adverse Event Reporting	IQVIA Lifecycle Safety	Email: Sage.Safety@iqvia.com Telephone: +1 855-564-2229 Fax: +1 855-638-1674
Product Complaint Reporting	Sage Therapeutics, Inc.	Email: productcomplaints@sagerx.com Tel: +1 833-554-7243

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics

Name of Investigational Product:
SAGE-217 Capsules

Name of Active Ingredient:
SAGE-217

Title of Study: 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

Number of Sites and Study Location: Part A: Approximately 55 sites in the United States

Part B: Approximately 40 sites in the United States

Phase of development: 3

Planned Duration of Subject Participation:

Part A: 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)

Part B: up to 70 days (up to 28-day Screening Period, 14-day Double-blind Treatment Period, and a 28-day double-blind Follow-up Period)

Objectives:

Primary:

- To evaluate the efficacy of SAGE-217 in the treatment of major depressive disorder (MDD) compared to placebo.

Secondary:

- Part A only: 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.

Safety:

- To evaluate the safety and tolerability of SAGE-217.

[redacted]

Endpoints:

Primary:

- 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.

Part A - Secondary:

- Change from baseline in the 17-item HAM-D total score at other timepoints
- HAM-D response at Day 15 and all other time points, defined as a ≥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 ≤7
- Clinical Global Impression - Improvement (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 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)

Part B - Key Secondary:

- Change from baseline in CGI-S at Day 15
- Change from baseline in HAM-D total score at Day 8, Day 3, and Day 42

Part B – Other Secondary:

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as "much improved" or "very much improved", at Day 15
- Change from baseline in MADRS total score at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline in PRO measures of health-related quality of life, as assessed by responses to SF-36v2, and of depressive symptoms, as assessed by the 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]

[redacted]

Study Description:

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD. This study will be conducted in 2 parts – Part A and Part B. Part B will commence after all subjects in Part A have completed the Day 42 visit. Parts A and B will enroll unique subjects. For both study parts, 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. Each study part is described below.

Part A

Part A 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. 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 ≥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 2.

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.

Part B

Part B will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day follow-up period. Part B of the study may run concurrently with the extended follow-up period in Part A.

The Screening Period begins with the signing of the ICF at the Screening Visit; the ICF must be signed prior to beginning any screening activities. 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 ≥60 days) and randomized within each stratum to one of 2 treatment groups (SAGE-217 50 mg or matching placebo) in a 1:1 ratio. Subjects will self-administer study drug once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 3.

During the treatment period, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the Investigator, subjects who cannot tolerate the 40-mg dose may be discontinued from study drug.

Subjects who discontinue treatment early should return to the site for an 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 ET visit. If necessary, 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 EOT visit assessments should be conducted in addition to an abbreviated physical exam.

Number of Subjects (planned):

Part A: approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects.

Part B: approximately 370 subjects will be randomized and dosed to obtain sufficient evaluable subjects for all analyses.

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 64 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. For Part A, subject has a MADRS total score of ≥32 and a HAM-D total score ≥22 at screening and Day 1 (prior to dosing). For Part B, subject has a HAM-D total score ≥24 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 who have stopped taking antidepressants within 60 days must have stopped for longer than 5 half-lives of the antidepressant 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 or without 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 is currently at significant risk of suicide, as judged by the Investigator, or 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. For Part A, a body mass index (BMI) ≤18 or ≥50 kg/m^2 at Screening is exclusionary; a BMI of 40 to 49 kg/m^2, 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. For Part B, a BMI ≤18 or ≥45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
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 $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Subject is taking any benzodiazepine or GABA modulator with a half-life of ≥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.

SAGE-217 Dosage and Mode of Administration:
SAGE-217 is available as hard gelatin capsules for oral administration. Available dose strengths are:

- Part A: a 30-mg or 20-mg dose
- Part B: a 50-mg dose, with the option to reduce to 40 mg for intolerable AEs

Reference Therapy, Dosage, and Mode of Administration:
Placebo will be provided as hard gelatin capsules for oral administration.

Duration of Treatment: 14 days

Statistical methods:

A detailed description of the statistical analyses to be performed in the study will be provided in the Statistical Analysis Plan (SAP). Separate SAPs will be generated for each part of the study. The SAP for each study part will be finalized and approved prior to treatment unblinding of each respective part.

For Part A, 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.

Part B will not include an extended follow-up period, and the database lock will occur at the end of the study after all subjects have completed the Day 42 visit.

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.

[redacted]

Determination of Sample Size

For Part A, 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%.

For Part B, assuming a two-sided alpha level of 0.05, a sample size of 216 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 a standard deviation (SD) of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 240 total randomized subjects will be required to obtain 216 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. To ensure sufficient power for subgroup analyses, approximately 370 subjects will be randomized for Part B (see SAP for details).

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, 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 in Part A only (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score in Part A only, 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 ≥50% reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of ≤7.0). GEE models will include terms for treatment, baseline score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 and matching placebo at 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, 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 2: Schedule of Events (Part A)

Visits	Screening Period	Double-Blind, Placebo-Controlled Treatment Period					Follow-up Period					Extended Follow-Up
Visit Days	D-28 to D-1	D1	D3 (±1d)	D8 (+1d)	D12 (±1d)	D15 (+1d) and/or EOT[a]	D18 (±1d)	D21 (±1d)	D28 (±3d)	D35 (±3d)	D42 (±3d) or ET	D70, D126, D182 (±7d)
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12, V13, V14
Study Procedure												
Informed Consent	X											
Duplicate Subject Check[b]	X											
Inclusion/Exclusion	X	X										
Serum FSH test[c]	X											
SCID-5-CT	X											
MGH ATRQ	X											
Demographics	X											
Medical/Family History	X											
Subject training[d]	X	X										
Randomization		X										
Physical Examination[e]	X	X									X	
Body Weight/Height	X					X (wt only)					X (wt only)	
Clinical Laboratory Assessments[f]	X	X		X		X		X	X		X	X
Drug & Alcohol Screen[g]	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[h]	X	X				X			X		X	
Hepatitis & HIV Screen	X											
[redacted]												

Visits	**Screening Period**	**Double-Blind, Placebo-Controlled Treatment Period**					**Follow-up Period**					**Extended Follow-Up**
Visit Days	**D-28 to D-1**	**D1**	**D3 (±1d)**	**D8 (+1d)**	**D12 (±1d)**	**D15 (+1d) and/or EOT[a]**	**D18 (±1d)**	**D21 (±1d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d) or ET**	**D70, D126, D182 (±7d)**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12, V13, V14**
Study Procedure												
[redacted]												
Vital Signs[k]	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[l]	X	X				X					X	X (Day 182 only)
C-SSRS[m]	X	X	X	X	X	X	X	X	X	X	X	X
HAM-D[n, o]	X	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[o]		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
[redacted]												
ISI		X		X		X	X	X	X		X	X
PWC-20		X				X	X	X				
Sleep diary[p]	X											
[redacted]												
Study Drug Dispensation		X		X								
Study Drug Administration		X (Day 1 through Day 14)										

Visits	**Screening Period**	**Double-Blind, Placebo-Controlled Treatment Period**					**Follow-up Period**					**Extended Follow-Up**
Visit Days	**D-28 to D-1**	**D1**	**D3 (±1d)**	**D8 (+1d)**	**D12 (±1d)**	**D15 (+1d) and/or EOT[a]**	**D18 (±1d)**	**D21 (±1d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d) or ET**	**D70, D126, D182 (±7d)**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12, V13, V14**
Study Procedure												
Study Drug Accountability/Return				X		X					X[r]	
Adverse Events/SAEs[s]	X											
Prior/Concomitant Medications/Procedures[t]	X											

CGI-I = Clinical Global Impression – Improvement; CGI-S – Clinical Global Impression – Severity; [redacted]
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; PHQ-9 = 9-item Patient Health Questionnaire; PWC-20 = 20-item Physician Withdrawal Checklist; 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

[a] 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. 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.

[b] 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.

[c] 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.

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

[e] A full physical examination will be conducted at Screening and abbreviated physical examinations will be conducted thereafter. A full physical examination includes assessment of body systems (eg, head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities).

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

[g] Urine toxicology for selected drugs of abuse (as per the lab manual) and breath test for alcohol.

[h] 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]

[k] 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.

[l] Triplicate ECGs will be collected. When ECGs [redacted] sample collection occur on the same day, the 12-lead ECGs will be performed [redacted] sample collection.

[m] 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.

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

[o] The assessment timeframe for HAM-D scales will refer to the past 7 days (1 week) at Screening and during the extended follow-up period 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.

[p] 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]

[r] To be performed at the ET visit only.

[s] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.

[t] Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.

[redacted]

Table 3: Schedule of Events (Part B)

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 [a]**	**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**
Study Procedure											
Informed Consent	X										
Duplicate Participant Check [b]	X										
Inclusion/Exclusion	X	X									
Serum FSH test [c]	X										
SCID-5-CT	X										
MGH ATRQ	X										
Demographics	X										
Medical/Family History[d]	X										
Subject training [e]	X	X									
Randomization		X									
Physical Examination [f]	X	X									X
Body Weight/Height	X					X (weight only)					X (weight only)
Clinical Laboratory Assessments [g]	X	X		X		X		X	X		X
Drug & Alcohol Screen [h]	X	X	X	X	X	X	X	X	X	X	X

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** [a]	**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**
Study Procedure											
Pregnancy Test [i]	X	X				X			X		X
Hepatitis & HIV Screen	X										
[redacted]											
Vital Signs [l]	X	X	X	X	X	X	X		X		X
12-Lead ECG [m]	X	X				X					X
C-SSRS [n]	X	X	X	X	X	X	X	X	X	X	X
HAM-D [o, p]	X	X	X	X	X	X		X	X	X	X
MADRS		X		X		X			X		X
HAM-A [o]		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
SF-36v2	X	X		X		X			X		X
PHQ-9		X		X		X			X		X
PWC-20		X				X	X	X			
[redacted]											
Study Drug Dispensation		X		X							
Study Drug Administration		X (Day 1 through Day 14)									

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** [a]	**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**
Study Procedure											
Study Drug Accountability/Return				X		X					X [q]
Adverse Events/SAEs[d, r]	X										
Prior/Concomitant Medications/Procedures[d, s]	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; 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; [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.

[a] 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. If necessary, 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 EOT visit assessments should be conducted in addition to an abbreviated physical exam.

[b] 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.

[c] A serum follicle stimulating hormone test will be conducted at Screening for female participants 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.

[d] Information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of Medical History, AE collection, and prior/concomitant medication/procedure collection at Screening and throughout the study.

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

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

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

[h] Urine toxicology for selected drugs of abuse (as per the lab manual) and breath test for alcohol.

[i] Serum pregnancy test at screening and urine pregnancy test thereafter for female subjects who are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal.

[redacted]

[l] 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 participant has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Vital signs may be repeated at the discretion of the Investigator as clinically indicated.

[m] Triplicate ECGs will be collected. When ECGs [redacted] sample collection occur on the same day, the 12-lead ECGs will be performed [redacted] sample collection.

[n] 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.

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

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

[redacted]

To be performed at the ET visit only.

[s] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.

[t] Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.

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

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 4: Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
ADR	adverse drug reaction
AE	adverse event
AUC	area under the curve
C_{avg}	average plasma concentration
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
C_{max}	maximum plasma concentration
CRF	case report form
CS	clinically significant
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ET	early termination
[redacted]	[redacted]
FSH	follicle stimulating hormone
GABA	γ-aminobutyric acid
GEE	generalized estimating equation
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Rating Scale for Depression
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ID	identification

Abbreviation or specialist term	Explanation
IRB	institutional review board
IRT	interactive response technology
ISI	Insomnia Severity Index
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
MTD	maximum tolerated dose
NCS	not clinically significant
NOAEL	no-observed-adverse-effect-level
OS	oral solution
PCS	Potentially clinically significant
PHQ-9	9-item Patient Health Questionnaire
[redacted]	[redacted]
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

This study is being conducted in 2 parts – Part A and Part B. Unless otherwise specified, text in the following sections applies to both study parts.

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 suicide attempts in adults 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).

5.2. SAGE-217

SAGE-217 is a synthetic positive allosteric modulator of $GABA_A$ 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 $GABA_A$ receptors, and, consistent with the actions of other $GABA_A$ receptor potentiators (Rudolph 2011), exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo.

Unlike other neurotropic medications that target $GABA_A$ receptors, SAGE-217 is an allosteric modulator of both synaptic as well as extrasynaptic $GABA_A$ receptors (Martinez Botella 2017).

As such, SAGE-217 may represent a therapeutic advantage in the treatment of depressive disorders by resetting the GABAergic imbalance in depression by affecting both phasic and tonic inhibition.

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 (Gunduz-Bruce 2019). 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. The most common adverse events (AEs) associated with SAGE-217 are somnolence, dizziness, and sedation; most AEs were reported as mild or moderate in intensity. Refer to the Investigator's Brochure for a detailed description of the chemistry, pharmacology, efficacy, and safety of SAGE-217.

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

Part A

There will be 2 dose levels of SAGE-217 in Part A 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 (MTD) for the oral solution formulation 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 Part A.

Part B

To date, the current capsule utilized in clinical studies is not associated with an MTD. Initial MTD assessments were performed using SAGE-217 in an oral solution (OS) at steady-state in healthy subjects, which provided an MTD with a C_{max} of 125 ng/mL at 30 mg OS. While re-identification of the MTD using the capsule formulations was not conducted, steady-state 30 mg

capsules provide a model-derived C_{max} approximately 50% lower (64 ng/mL) than the concentration associated with the MTD of 30 mg OS (125 ng/mL).

Studies 217-MDD-201 and 217-PPD-201, employing 30 mg capsules administered each evening for 14 days, demonstrated significant reduction in symptoms of depression, anxiety and insomnia. The safety profile in these studies is consistent with the $GABA_A$ neurosteroid mechanism, including adverse drug reactions (ADRs) of somnolence, sedation, and dizziness at rates of 4 to 15%; the majority with mild intensity. Phase 3 studies in a broader patient population demonstrate activity of SAGE-217 associated with improvement in depressive symptoms, however, both the efficacy and safety findings support investigation of a higher dose, with predictable ADRs expected to be within an acceptable range.

Preliminary data through Day 42 of the double-blind period in Part A of this study demonstrated significant anti-depressant effects compared to placebo at Day 3, 8, and 12 but not Day 15 (primary endpoint) for the 30 mg dose. The 20 mg dose did not separate from placebo at any timepoint. The rates of expected ADRs of somnolence, sedation and dizziness in the 30 mg arm were each less than 10%; rates of discontinuation for AEs were lower with SAGE-217 30 mg (2.1%) than with placebo (3.2%). No clinically relevant changes in vital signs, laboratories, electrocardiogram measures, or suicidal thinking were observed in either Part A of the current study or across the full SAGE-217 program, now with over 2000 subjects exposed to treatment. In addition, approximately 112 additional subjects have received blinded study drug (SAGE-217 or placebo) in ongoing blinded clinical studies. Relevant results from Part A of this study are available in the SAGE-217 Investigator's Brochure.

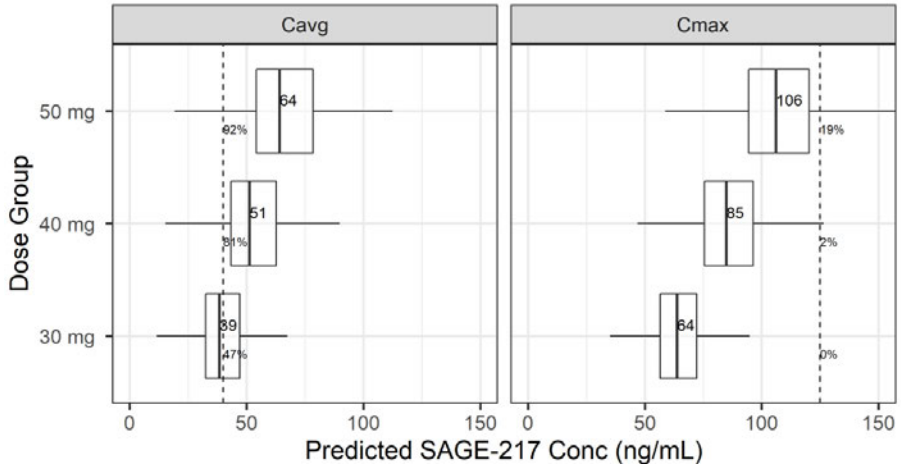
Direct and modeled data from completed studies to date (including efficacy studies 217-MDD-201 and 217-PPD-201) in addition to Part A (through Day 42 of the double-blind period) of the current study, have been used to assess and predict the efficacy and safety outcomes at SAGE-217 concentrations expected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

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

Direct evidence related to efficacy and safety outcomes following administration of SAGE-217 capsules at doses above 30 mg is further provided by results from a Phase 1, placebo-controlled study in healthy subjects using a 5-hour phase advance model of insomnia (Study 217-EXM-101). Administration of single doses of SAGE-217 up to 45 mg improved sleep efficiency, duration, maintenance and sleep quality compared with placebo. Evening administration of SAGE-217 was generally well tolerated, with an acceptable safety and tolerability profile. All reported TEAEs were mild and all resolved. Additional data from Study 217-EXM-101 are provided in the Investigator's Brochure.

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

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



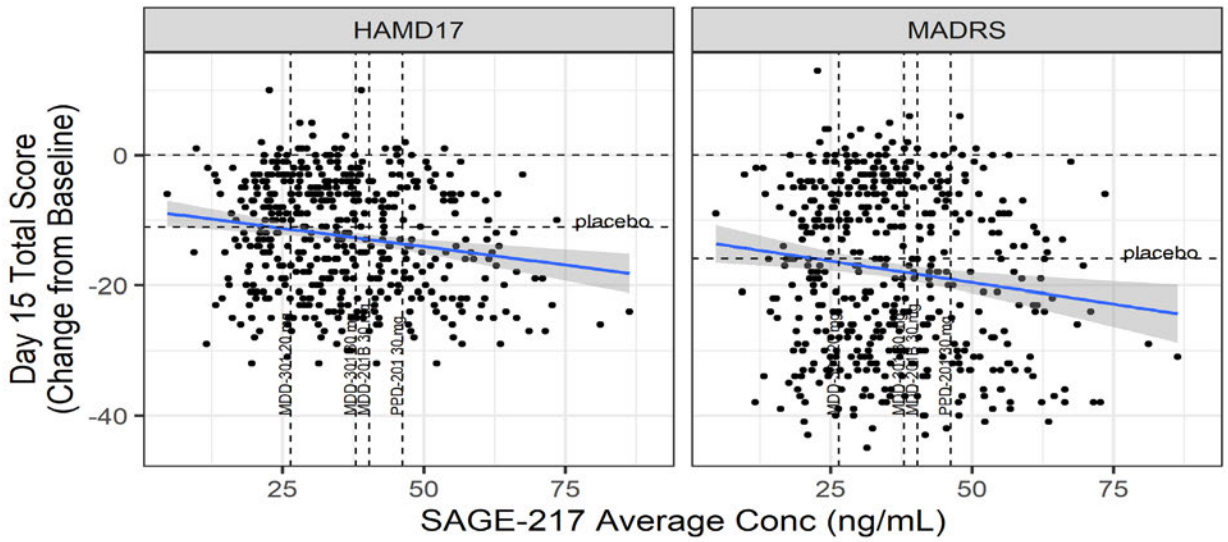
Dashed vertical lines represent target concentrations for efficacy (C_{avg} >40 ng/mL) and safety (C_{max}<125 ng/mL). Percentage next to dashed lines indicate the percentages with C_{avg}>40 ng/mL or with C_{max}>124 ng.

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

Increased granularity of the exposure-efficacy relationship is provided in Figure 2. Across Studies 217-MDD-201B, 217-PPD-201, and Part A of the current study, increased concentrations of SAGE-217 were associated with a larger reduction in depressive symptoms (Figure 2). Based on linear regression modeling, effect sizes for HAM-D were dose dependent, with a 50 mg dose administered once daily for 14 days predicted to provide greater therapeutic

benefit compared to daily doses of 40 and 30 mg. Based on preliminary results from Part A of this study, a dose of 30 mg may be considered the minimally effective dose.

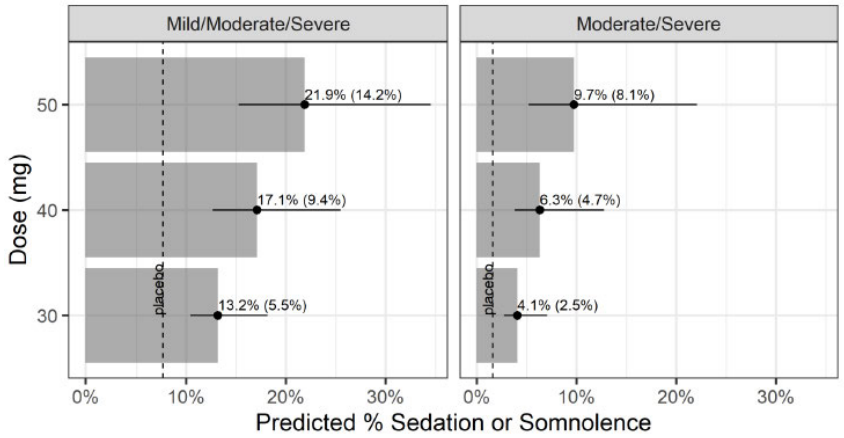
Figure 2: Total score change on Day 15 (Studies 217-MDD-201B, 217-PPD-201, Part A of the current study)



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

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

Figure 3: Predicted incidence of sedation or somnolence by dose



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

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

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

Sedation, an extension of the pharmacologic mechanism of SAGE-217, was the primary dose-limiting effect in toxicity studies in rats and dogs. In dogs, the toxicologic 'effect dose' levels of 2.5 mg/kg/day (9-month study, episodic dosing study) or 2 mg/kg/day (3-month study) associated with a low incidence of convulsion and/or early mortality during or following the dosing phase, were associated with exposures 7- to 11-fold above clinically relevant C_{max} following administration of 30 mg capsules. Similar margin calculations for adverse effect levels in dogs to potential higher SAGE-217 dose levels (40 or 50 mg/day) remain at or above 4.5x for both C_{max} and AUC. All non-clinical findings are provided in the SAGE-217 Investigator's Brochure. The totality of the nonclinical safety data supports the use of SAGE-217 for the

treatment of patients at the higher clinical dose regimen, particularly in the context of the current safety database of greater than 2000 subjects exposed to SAGE-217 treatment.

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

6. STUDY OBJECTIVES AND 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:

- Part A only: 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. Part A - Secondary Endpoints

- 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 ≥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 ≤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. Part B – Key Secondary Endpoints

- Change from baseline in CGI-S at Day 15
- Change from baseline in HAM-D total score at Day 8, Day 3, and Day 42

6.2.4. Part B – Other Secondary Endpoints

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as “much improved” or “very much improved”, at Day 15
- Change from baseline in MADRS total score at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline in PRO measures of health-related quality of life, as assessed by responses to the SF-36v2, and of depressive symptoms as assessed by the PHQ-9

6.2.5. 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]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD. This study will be conducted in 2 parts – Part A and Part B. Bart B will commence after all subjects in Part A have completed the Day 42 visit. Part A and Part B will enroll unique subjects. For both study parts, 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. Each study part is described below.

Part A

Part A 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) with the intent of identifying subjects who may meet exclusion criteria due to participation in another clinical study (Section 8.2). 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 ≥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 2.

Part B

Part B will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, and a 28-day double-blind follow-up period. Part B of the study may run concurrently with the extended follow-up period in Part A.

The Screening Period begins with the signing of the 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) with the intent of identifying subjects who may meet

exclusion criteria due to participation in another clinical study (Section 8.2). 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 ≥60 days) and randomized within each stratum to one of 2 treatment groups (SAGE-217 50 mg or matching placebo) in a 1:1 ratio. Subjects will self-administer study drug once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat or with a fat-containing snack), on an outpatient basis, for 14 days. See Section 10.5 for examples of fat-containing snacks. Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 3.

During the treatment period, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the Investigator, subjects who cannot tolerate the 40-mg dose may be discontinued from study drug.

Subjects who discontinue treatment early should return to the site for an 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 ET visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and decides to terminate the study on the same day during a clinic visit; in this case, all EOT visit assessments should be conducted in addition to an abbreviated physical exam.

7.2. Number of Subjects

In Part A, approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects (see Section 13.8). In Part B, approximately 370 subjects will be randomized and dosed to obtain sufficient evaluable subjects for all analyses.

7.3. Treatment Assignment

For both study parts, subjects will be randomly assigned to a treatment group on Day 1 and will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥60 days) at baseline. In Part A, randomization will be performed within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo. In Part B, randomization will be performed within each stratum in a 1:1 ratio to receive SAGE-217 50 mg or matching placebo.

7.4. Dose Adjustment Criteria

In Part A, dose adjustments are not permitted and subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated (see Section 8.3).

During the treatment period in Part B, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the Investigator, subjects who cannot tolerate the 40-mg dose may be discontinued from study drug (refer to Section 8.3 for procedures for early study drug discontinuation). If dose adjustment is deemed necessary by the Investigator at any time during the treatment period, the subject will return to the site to return any remaining study drug and for the adjusted dose to be dispensed.

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 64 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. For Part A, subject has a MADRS total score of ≥32 and a HAM-D total score ≥22 at screening and Day 1 (prior to dosing). For Part B, subject has a HAM-D total score ≥24 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 who have stopped taking antidepressants within 60 days must have stopped for longer than 5 half-lives of the antidepressant 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 or without 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 is currently at significant risk of suicide, as judged by the Investigator, or 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. For Part A, a body mass index (BMI) $\leq$18 or $\geq$50 kg/m^2 at Screening is exclusionary; a BMI of 40 to 49 kg/m^2, 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. For Part B, a BMI $\leq$18 or $\geq$45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
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 $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Subject is taking any benzodiazepine or GABA modulator with a half-life of ≥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, including suicidality, at the discretion of the Investigator

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 may withdraw the subject from the study at his/her discretion. 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.

In Part A, 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.

In Part B, subjects who discontinue study drug early should return to the site for an 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. If necessary, 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 EOT visit assessments should be conducted in addition to an abbreviated physical exam.

For both study parts, 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

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

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

9.2. Prior Medications, Concomitant Medications, 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, $GABA_A$ 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 ≥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 who are feeling sedated, somnolent, and/or dizzy are to refrain from driving or engaging in any activity requiring alertness.

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 10.5, Table 2, and Table 3).

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 2 and Table 3, 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. For both study parts, 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 ≥60 days) at baseline.

In Part A, 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. In Part B, randomization will be done within each stratum in a 1:1 ratio to receive SAGE-217 50 mg or matched placebo.

In both study parts, 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 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 Part A, 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 Part B, the Sponsor, site personnel and subjects will remain blinded until the database lock when all subjects complete the Day 42 visit.

9.4.1. Emergency Identification of Study Drug

During the study, the blind is to be broken 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 should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a subject. Requests from the Investigator about the treatment administered to study subjects should be discussed with the Sage Medical Monitor. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the 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. At the of withdrawal from the study/stopping participation, if possible, an EOT and/or ET visit should be conducted.

If a subject(s) or study personnel become unblinded to subject's treatment assignment before database lock, the subject(s) will be excluded from the Per Protocol Set, but included in Full Analysis Set, as detailed further in the statistical analysis plan.

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. 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. For Part A, each unit dose consists of 1 capsule. For Part B, each unit dose consists of 2 capsules (see Section 9.1). 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

In Part A, 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.

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

In both study parts, 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 2 and Table 3.

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.

10.8. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness or performance (applicable for approved marketed products) of a drug product after it is released for distribution. In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in Table 1. Where possible, personnel should segregate any product, materials, or packaging associated with the product complaint.

11. ASSESSMENT OF EFFICACY [redacted]

All assessments will be conducted according to the schedule of assessments (Table 2 and Table 3). 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 past 7 days (1 week) will be used at Screening and during the extended Follow-up Period (Part A only), 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 ≤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: 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; Part A Only)

The ISI will be assessed in Part A only. 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 (Part A Only)

The Core Consensus Sleep Diary will be assessed in Part A only. This instrument 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]

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

All assessments will be conducted according to the schedule of assessments (Table 2 and Table 3).

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, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, bipolar disorder, persistent depressive disorder, postpartum depression, substance use disorder, alcohol use disorder, major depressive disorder with seasonal pattern, major depressive disorder with psychotic features, premenstrual dysphoric disorder, major depressive disorder with atypical features, schizophrenia; or schizoaffective disorder will be documented. The 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 10th 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. COVID-19 Questions

Information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of Medical History, AE collection, and prior/concomitant medication/procedure collection at Screening and throughout the study.

Questions to be asked are as follows:

- Were you diagnosed with COVID-19 by a healthcare professional?
  - If the answer is “no”, no further questions.
  - If the answer is “yes”, the following questions are asked:
    - Did you have a test? If yes, was the result positive, negative or inconclusive?
    - Were you isolated? If yes, what were the dates of isolation?
    - Were you hospitalized? If yes, what were the dates of hospitalization?

12.1.3. Weight and Height

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

12.1.4. 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. An abbreviated physical exam includes a brief medical history followed by a targeted physical exam. 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.

12.1.5. 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.

12.1.6. 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. When ECG [redacted] sample collection occur during the same visit, the ECGs will be conducted first.

12.1.7. 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 5.

Table 5: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Coagulation
Red blood cell count Hemoglobin Hematocrit White blood cell count with differential Platelet count	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin	pH Specific gravity Protein Glucose Red blood cell Nitrite	Activated partial thromboplastin time Prothrombin time International normalized ratio

Red Blood Cell Indices (MCV, MCH, MCHC) Reflex to Red blood cell morphology if indices are abnormal	Indirect bilirubin Total protein Creatinine Blood urea nitrogen 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	Leukocyte esterase Ketones Bilirubin Urobilinogen	
Diagnostic			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C Reflex HCV RNA HIV-1 and -2 Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: serum hCG Female subjects, if menopause is suspected and not surgically sterile: FSH	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine 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).

12.1.7.1. Drugs of Abuse and Alcohol

Urine toxicology tests will be performed for selected drugs of abuse (see Table 5). A breath test for alcohol will be performed.

12.1.7.2. 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.

12.1.8. 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 2 and Table 3).

12.1.9. 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 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.

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 6: Relationship to Study Drug

Relationship	Definition
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. 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. 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. Any complication during pregnancy (eg, anemia, infections, pre-eclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, 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. Overdose

An overdose is defined as more than 2 capsules of study drug taken by a subject in an 18-hour period or more than 4 capsules taken by a subject in a 36-hour period.

Overdoses, regardless of presence of associated clinical manifestation(s) (eg, headache, abnormal laboratory value) will be considered an AE and recorded as such on the eCRF. Any clinical manifestation(s) of overdose must also be recorded as an AE on the eCRF. In addition,

all overdoses must be recorded on an Overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose.

13. STATISTICS

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. Separate SAPs will be generated for each part of the study. The SAP for each study part will be finalized and approved prior to treatment unblinding of each respective part.

In Part A, 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. Data from Part A may be analyzed and reported following final database lock and before Part B is complete. For Part B, the final database lock will occur when all subjects complete the study; treatment unblinding and analyses will follow the database lock.

Separate clinical study reports will be produced for each part of the study.

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.

[redacted]

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 ≥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, 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 diary endpoints in Part A only (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score in Part A only, 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 ≥50% reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of ≤7.0). GEE models will include terms for treatment, baseline score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 and matching placebo at 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]

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

For Part A, 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%.

For Part B, assuming a two-sided alpha level of 0.05, a sample size of 216 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 a standard deviation (SD) of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 240 total randomized subjects will be required to obtain 216 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 postbaseline HAM-D assessment. To ensure sufficient power for subgroup analyses, approximately 370 subjects will be randomized for Part B (see SAP for details).

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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Protocol 217-MDD-301, Amendment 6

Date of Amendment: 14 September 2020

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 increase the sample size of Part B from 240 to 370 participants to ensure sufficient power for all subgroup analyses. Additional changes are outlined below:

Objectives and Endpoints (Part B):

- Revised timepoints for the key secondary endpoint, change from baseline in HAM-D total score, to coincide with those defined in the statistical analysis plan
- Specified terminology of secondary endpoints

Schedule of Assessments (Part B):

- Added COVID-19 questions

Statistical Analysis:

- Revised to specify that, in the event of unblinding of a subject's treatment assignment before database lock, the subject will be excluded from the Per Protocol Set, to coincide with the process defined in the statistical analysis plan
- Removed compound symmetry as a method to achieve convergence in the event of a convergence issue
- Specified that the sandwich estimator for the variance covariance matrix will be derived when the covariance structure is not UN

Other:

- Removed score of '0 (not assessed)' as a choice for the Clinical Global Impression Scale
- [redacted]
- Added 'post-traumatic stress disorder' and 'bipolar disorder' to the list of disorders for which full medical history will be documented

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. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Tel: [redacted] email: [redacted]
Sponsor Medical Monitor	[redacted], MD, MBA Tel: [redacted] 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 MAR 2019
Date of Amendment 4	Version 5.0, 25 MAR 2019
Date of Amendment 5	Version 6.0, 02 MAR 2020
Date of Amendment 6	Version 7.0, 14 SEP 2020
Date of Amendment 7	Version 8.0, 14 DEC 2020

SPONSOR APPROVAL

Protocol Number:	217-MDD-301
Study Drug:	SAGE-217
Study Phase:	Phase 3
Sponsor:	Sage Therapeutics, Inc.
Protocol Date:	Version 8.0, 14 December 2020

Sponsor Approval

DocuSigned by:
[redacted]
15-Dec-2020 | 13:52 EST
Signer Name: [redacted]
[redacted]
Date
Sage Therapeutics

DocuSigned by:
[redacted]
15-Dec-2020 | 12:33 EST
Signer Name: [redacted]
[redacted]
Date
Sage Therapeutics

DocuSigned by:
[redacted]
14-Dec-2020 | 16:03 EST
Signer Name: [redacted]
[redacted]
Date
Sage Therapeutics

DocuSigned by:
[redacted]
14-Dec-2020 | 15:45 EST
Signer Name: [redacted]
[redacted]
Date
Sage Therapeutics

DocuSigned by:
[redacted]
14-Dec-2020 | 15:56 EST
Signer Name: [redacted]
[redacted]
Date
Sage Therapeutics

DocuSigned by:
[redacted]
14-Dec-2020 | 15:53 EST
Signer Name: [redacted]
[redacted]
Date
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)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Syneos Health Medical Monitor	[redacted], MD [redacted]	Email: [redacted] Office: [redacted] Cell: [redacted]
Sage Study Physician	[redacted], MD, MBA [redacted]	Email: [redacted] Tel: [redacted]
24-Hour Serious Adverse Event Reporting	IQVIA Lifecycle Safety	Email: Sage.Safety@iqvia.com Telephone: +1 855-564-2229 Fax: +1 855-638-1674
Product Complaint Reporting	Sage Therapeutics, Inc.	Email: productcomplaints@sagerx.com Tel: +1 833-554-7243

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics

Name of Investigational Product:
SAGE-217 Capsules

Name of Active Ingredient:
SAGE-217

Title of Study: 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

Number of Sites and Study Location: Part A: Approximately 55 sites in the United States

Part B: Approximately 40 sites in the United States

Phase of development: 3

Planned Duration of Subject Participation:

Part A: 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)

Part B: up to 70 days (up to 28-day Screening Period, 14-day Double-blind Treatment Period, and a 28-day double-blind Follow-up Period)

Objectives:

Primary:

- To evaluate the efficacy of SAGE-217 in the treatment of major depressive disorder (MDD) compared to placebo.

Secondary:

- Part A only: 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.

Safety:

- To evaluate the safety and tolerability of SAGE-217.

[redacted]

Endpoints:

Primary:

- 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.

Part A - Secondary:

- Change from baseline in the 17-item HAM-D total score at other timepoints
- HAM-D response at Day 15 and all other time points, defined as a ≥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 ≤7
- Clinical Global Impression - Improvement (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 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)

Part B - Key Secondary:

- Change from baseline in CGI-S at Day 15
- Change from baseline in HAM-D total score at Day 8, Day 3, and Day 42

Part B – Other Secondary:

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as "much improved" or "very much improved", at Day 15
- Change from baseline in MADRS total score at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline in PRO measures of health-related quality of life, as assessed by responses to SF-36v2, and of depressive symptoms, as assessed by the 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]

[redacted]

Study Description:

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD. This study will be conducted in 2 parts – Part A and Part B. Part B will commence after all subjects in Part A have completed the Day 42 visit. Parts A and B will enroll unique subjects. For both study parts, 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. Each study part is described below.

Part A

Part A 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. 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 ≥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 2.

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.

Part B

Part B will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day follow-up period. Part B of the study may run concurrently with the extended follow-up period in Part A.

The Screening Period begins with the signing of the ICF at the Screening Visit; the ICF must be signed prior to beginning any screening activities. 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 ≥60 days) and randomized within each stratum to one of 2 treatment groups (SAGE-217 50 mg or matching placebo) in a 1:1 ratio. Subjects will self-administer study drug once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 3.

During the treatment period, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the Investigator, subjects who cannot tolerate the 40-mg dose may be discontinued from study drug.

Subjects who discontinue treatment early should return to the site for an 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 ET visit. If necessary, 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 EOT visit assessments should be conducted in addition to an abbreviated physical exam.

Number of Subjects (planned):

Part A: approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects.

Part B: up to 575 subjects will be randomized and dosed to obtain sufficient evaluable subjects for all analyses.

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 64 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. For Part A, subject has a MADRS total score of ≥32 and a HAM-D total score ≥22 at screening and Day 1 (prior to dosing). For Part B, subject has a HAM-D total score ≥24 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 who have stopped taking antidepressants within 60 days must have stopped for longer than 5 half-lives of the antidepressant 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 or without 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 is currently at significant risk of suicide, as judged by the Investigator, or 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. For Part A, a body mass index (BMI) ≤18 or ≥50 kg/m^2 at Screening is exclusionary; a BMI of 40 to 49 kg/m^2, 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. For Part B, a BMI ≤18 or ≥45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
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 $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Subject is taking any benzodiazepine or GABA modulator with a half-life of ≥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.

SAGE-217 Dosage and Mode of Administration:
SAGE-217 is available as hard gelatin capsules for oral administration. Available dose strengths are:

- Part A: a 30-mg or 20-mg dose
- Part B: a 50-mg dose, with the option to reduce to 40 mg for intolerable AEs

Reference Therapy, Dosage, and Mode of Administration:
Placebo will be provided as hard gelatin capsules for oral administration.

Duration of Treatment: 14 days

Statistical methods:

A detailed description of the statistical analyses to be performed in the study will be provided in the Statistical Analysis Plan (SAP). Separate SAPs will be generated for each part of the study. The SAP for each study part will be finalized and approved prior to treatment unblinding of each respective part.

For Part A, 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.

Part B will not include an extended follow-up period, and the database lock will occur at the end of the study after all subjects have completed the Day 42 visit.

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.

The Modified Full Analysis Set (mFAS) is defined as all participants in the FAS with a total HAM-D score ≥ 26 at baseline.

[redacted]

Determination of Sample Size

For Part A, 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%.

For Part B, assuming a two-sided alpha level of 0.05, a sample size of 216 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 a standard deviation (SD) of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 240 total randomized subjects will be required to obtain 216 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. To provide more power for analyses of key secondary endpoints, up to 575 subjects will be randomized for Part B.

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, 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 in Part A only (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score in Part A only, 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 ≥50% reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of ≤7.0). GEE models will include terms for treatment, baseline score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 and matching placebo at 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, 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 2: Schedule of Events (Part A)

Visits	Screening Period	Double-Blind, Placebo-Controlled Treatment Period					Follow-up Period					Extended Follow-Up
Visit Days	**D-28 to D-1**	**D1**	**D3 (±1d)**	**D8 (+1d)**	**D12 (±1d)**	**D15 (+1d) and/or EOT[a]**	**D18 (±1d)**	**D21 (±1d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d) or ET**	**D70, D126, D182 (±7d)**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12, V13, V14**
Study Procedure												
Informed Consent	X											
Duplicate Subject Check[b]	X											
Inclusion/Exclusion	X	X										
Serum FSH test[c]	X											
SCID-5-CT	X											
MGH ATRQ	X											
Demographics	X											
Medical/Family History	X											
Subject training[d]	X	X										
Randomization		X										
Physical Examination[e]	X	X									X	
Body Weight/Height	X					X (wt only)					X (wt only)	
Clinical Laboratory Assessments[f]	X	X		X		X		X	X		X	X
Drug & Alcohol Screen[g]	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[h]	X	X				X			X		X	
Hepatitis & HIV Screen	X											
[redacted]												

Visits	Screening Period	Double-Blind, Placebo-Controlled Treatment Period					Follow-up Period					Extended Follow-Up
Visit Days	D-28 to D-1	D1	D3 (±1d)	D8 (+1d)	D12 (±1d)	D15 (+1d) and/or EOT[a]	D18 (±1d)	D21 (±1d)	D28 (±3d)	D35 (±3d)	D42 (±3d) or ET	D70, D126, D182 (±7d)
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12, V13, V14
Study Procedure												
[redacted]												
Vital Signs[k]	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[l]	X	X				X					X	X (Day 182 only)
C-SSRS[m]	X	X	X	X	X	X	X	X	X	X	X	X
HAM-D[n, o]	X	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[o]		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
[redacted]												
ISI		X		X		X	X	X	X		X	X
PWC-20		X				X	X	X				
Sleep diary[p]	X											
[redacted]												
Study Drug Dispensation		X		X								
Study Drug Administration		X (Day 1 through Day 14)										

Visits	**Screening Period**	**Double-Blind, Placebo-Controlled Treatment Period**					**Follow-up Period**					**Extended Follow-Up**
Visit Days	**D-28 to D-1**	**D1**	**D3 (±1d)**	**D8 (+1d)**	**D12 (±1d)**	**D15 (+1d) and/or EOT[a]**	**D18 (±1d)**	**D21 (±1d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d) or ET**	**D70, D126, D182 (±7d)**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12, V13, V14**
Study Procedure												
Study Drug Accountability/Return				X		X					X[r]	
Adverse Events/SAEs[s]	X											
Prior/Concomitant Medications/Procedures[t]	X											

CGI-I = Clinical Global Impression – Improvement; CGI-S – Clinical Global Impression – Severity; [redacted] 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; PHQ-9 = 9-item Patient Health Questionnaire; PWC-20 = 20-item Physician Withdrawal Checklist; 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

[a] 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. 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.

[b] 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.

[c] 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.

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

[e] A full physical examination will be conducted at Screening and abbreviated physical examinations will be conducted thereafter. A full physical examination includes assessment of body systems (eg, head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities).

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

[g] Urine toxicology for selected drugs of abuse (as per the lab manual) and breath test for alcohol.

[h] 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]

[k] 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.

[l] Triplicate ECGs will be collected. When ECGs [redacted] collection occur on the same day, the 12-lead ECGs will be performed [redacted] sample collection.

[m] 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.

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

[o] The assessment timeframe for HAM-D scales will refer to the past 7 days (1 week) at Screening and during the extended follow-up period 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.

[p] 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]

To be performed at the ET visit only.

[s] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.

[t] Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.

Table 3: Schedule of Events (Part B)

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 [a]**	**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**
Study Procedure											
Informed Consent	X										
Duplicate Participant Check [b]	X										
Inclusion/Exclusion	X	X									
Serum FSH test [c]	X										
SCID-5-CT	X										
MGH ATRQ	X										
Demographics	X										
Medical/Family History[d]	X										
Subject training [e]	X	X									
Randomization		X									
Physical Examination [f]	X	X									X
Body Weight/Height	X					X (weight only)					X (weight only)
Clinical Laboratory Assessments [g]	X	X		X		X		X	X		X
Drug & Alcohol Screen [h]	X	X	X	X	X	X	X	X	X	X	X

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** [a]	**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**
Study Procedure											
Pregnancy Test [i]	X	X				X			X		X
Hepatitis & HIV Screen	X										
[redacted]											
Vital Signs [l]	X	X	X	X	X	X	X		X		X
12-Lead ECG [m]	X	X				X					X
C-SSRS [n]	X	X	X	X	X	X	X	X	X	X	X
HAM-D [o, p]	X	X	X	X	X	X		X	X	X	X
MADRS		X		X		X			X		X
HAM-A [p]		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
SF-36v2	X	X		X		X			X		X
PHQ-9		X		X		X			X		X
PWC-20		X				X	X	X			
[redacted]											
Study Drug Dispensation		X		X							
Study Drug Administration		X (Day 1 through Day 14)									

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 [a]	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
Study Procedure											
Study Drug Accountability/Return				X		X					X [r]
Adverse Events/SAEs[d, s]	X										
Prior/Concomitant Medications/Procedures[d, t]	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; 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; [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.

[a] 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. If necessary, 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 EOT visit assessments should be conducted in addition to an abbreviated physical exam.

[b] 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.

[c] A serum follicle stimulating hormone test will be conducted at Screening for female participants 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.

[d] Information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of Medical History, AE collection, and prior/concomitant medication/procedure collection at Screening and throughout the study.

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

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

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

[h] Urine toxicology for selected drugs of abuse (as per the lab manual) and breath test for alcohol.

[i] Serum pregnancy test at screening and urine pregnancy test thereafter for female subjects who are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal.

[redacted]

[l] 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 participant has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Vital signs may be repeated at the discretion of the Investigator as clinically indicated.

[m] Triplicate ECGs will be collected. When ECGs [redacted] sample collection occur on the same day, the 12-lead ECGs will be performed [redacted] collection.

[n] 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.

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

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

[redacted]

[r] To be performed at the ET visit only.

[s] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.

[t] Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.

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

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 4: Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
ADR	adverse drug reaction
AE	adverse event
AUC	area under the curve
C_{avg}	average plasma concentration
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
C_{max}	maximum plasma concentration
CRF	case report form
CS	clinically significant
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ET	early termination
[redacted]	[redacted]
FSH	follicle stimulating hormone
GABA	γ-aminobutyric acid
GEE	generalized estimating equation
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Rating Scale for Depression
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ID	identification

Abbreviation or specialist term	Explanation
IRB	institutional review board
IRT	interactive response technology
ISI	Insomnia Severity Index
MADRS	Montgomery Åsberg Depression Rating Scale
MDD	major depressive disorder
mFAS	Modified Full Analysis Set
MGH ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MMRM	mixed effects model for repeated measures
MTD	maximum tolerated dose
NCS	not clinically significant
NOAEL	no-observed-adverse-effect-level
OS	oral solution
PCS	Potentially clinically significant
PHQ-9	9-item Patient Health Questionnaire
[redacted]	[redacted]
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

This study is being conducted in 2 parts – Part A and Part B. Unless otherwise specified, text in the following sections applies to both study parts.

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 suicide attempts in adults 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).

5.2. SAGE-217

SAGE-217 is a synthetic positive allosteric modulator of $GABA_A$ 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 $GABA_A$ receptors, and, consistent with the actions of other $GABA_A$ receptor potentiators (Rudolph 2011), exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo.

Unlike other neurotropic medications that target $GABA_A$ receptors, SAGE-217 is an allosteric modulator of both synaptic as well as extrasynaptic $GABA_A$ receptors (Martinez Botella 2017).

As such, SAGE-217 may represent a therapeutic advantage in the treatment of depressive disorders by resetting the GABAergic imbalance in depression by affecting both phasic and tonic inhibition.

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 (Gunduz-Bruce 2019). 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. The most common adverse events (AEs) associated with SAGE-217 are somnolence, dizziness, and sedation; most AEs were reported as mild or moderate in intensity. Refer to the Investigator's Brochure for a detailed description of the chemistry, pharmacology, efficacy, and safety of SAGE-217.

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

Part A

There will be 2 dose levels of SAGE-217 in Part A 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 (MTD) for the oral solution formulation 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 Part A.

Part B

To date, the current capsule utilized in clinical studies is not associated with an MTD. Initial MTD assessments were performed using SAGE-217 in an oral solution (OS) at steady-state in healthy subjects, which provided an MTD with a C_{max} of 125 ng/mL at 30 mg OS. While re-identification of the MTD using the capsule formulations was not conducted, steady-state 30 mg

capsules provide a model-derived C_{max} approximately 50% lower (64 ng/mL) than the concentration associated with the MTD of 30 mg OS (125 ng/mL).

Studies 217-MDD-201 and 217-PPD-201, employing 30 mg capsules administered each evening for 14 days, demonstrated significant reduction in symptoms of depression, anxiety and insomnia. The safety profile in these studies is consistent with the $GABA_A$ neurosteroid mechanism, including adverse drug reactions (ADRs) of somnolence, sedation, and dizziness at rates of 4 to 15%; the majority with mild intensity. Phase 3 studies in a broader patient population demonstrate activity of SAGE-217 associated with improvement in depressive symptoms, however, both the efficacy and safety findings support investigation of a higher dose, with predictable ADRs expected to be within an acceptable range.

Preliminary data through Day 42 of the double-blind period in Part A of this study demonstrated significant anti-depressant effects compared to placebo at Day 3, 8, and 12 but not Day 15 (primary endpoint) for the 30 mg dose. The 20 mg dose did not separate from placebo at any timepoint. The rates of expected ADRs of somnolence, sedation and dizziness in the 30 mg arm were each less than 10%; rates of discontinuation for AEs were lower with SAGE-217 30 mg (2.1%) than with placebo (3.2%). No clinically relevant changes in vital signs, laboratories, electrocardiogram measures, or suicidal thinking were observed in either Part A of the current study or across the full SAGE-217 program, now with over 2000 subjects exposed to treatment. In addition, approximately 112 additional subjects have received blinded study drug (SAGE-217 or placebo) in ongoing blinded clinical studies. Relevant results from Part A of this study are available in the SAGE-217 Investigator's Brochure.

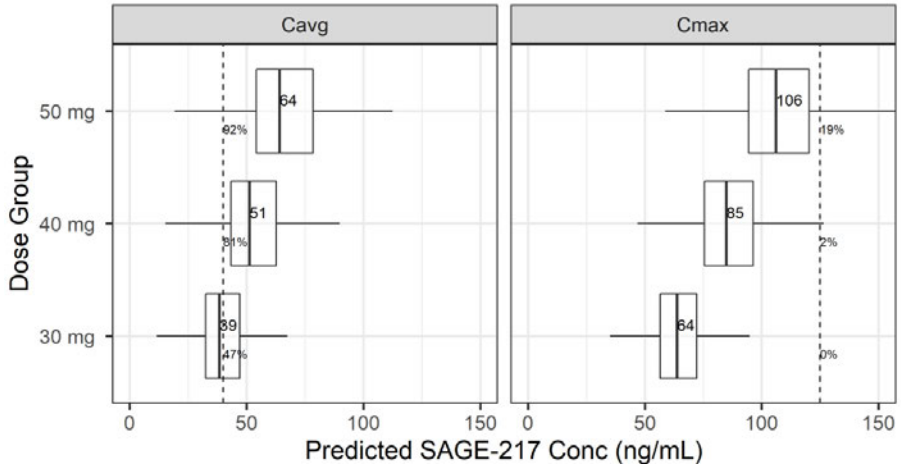
Direct and modeled data from completed studies to date (including efficacy studies 217-MDD-201 and 217-PPD-201) in addition to Part A (through Day 42 of the double-blind period) of the current study, have been used to assess and predict the efficacy and safety outcomes at SAGE-217 concentrations expected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

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

Direct evidence related to efficacy and safety outcomes following administration of SAGE-217 capsules at doses above 30 mg is further provided by results from a Phase 1, placebo-controlled study in healthy subjects using a 5-hour phase advance model of insomnia (Study 217-EXM-101). Administration of single doses of SAGE-217 up to 45 mg improved sleep efficiency, duration, maintenance and sleep quality compared with placebo. Evening administration of SAGE-217 was generally well tolerated, with an acceptable safety and tolerability profile. All reported TEAEs were mild and all resolved. Additional data from Study 217-EXM-101 are provided in the Investigator's Brochure.

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

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



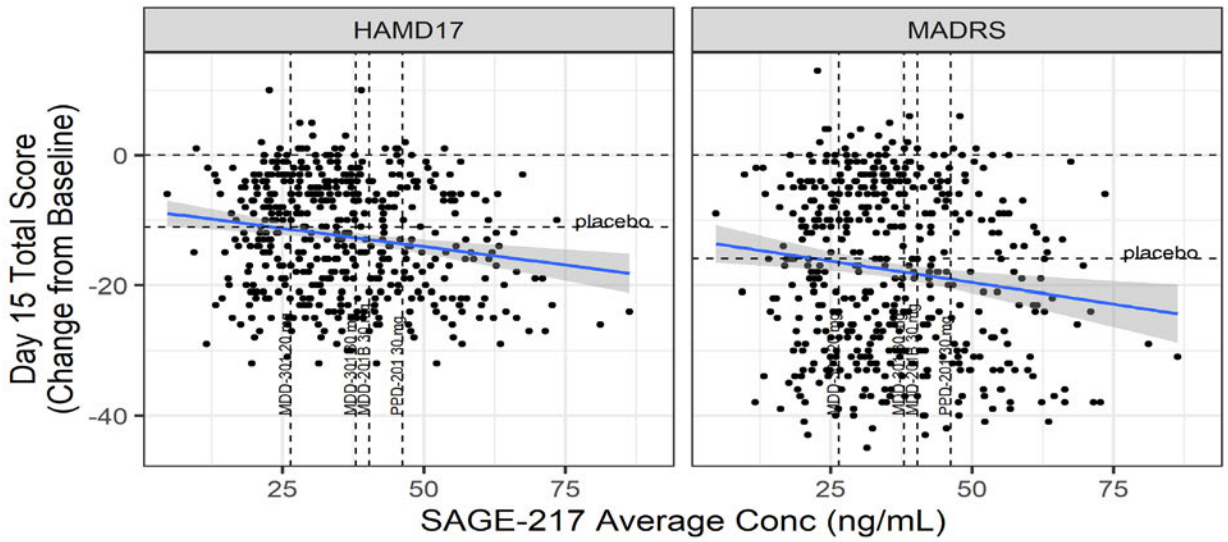
Dashed vertical lines represent target concentrations for efficacy (C_{avg} >40 ng/mL) and safety (C_{max}<125 ng/mL). Percentage next to dashed lines indicate the percentages with C_{avg}>40 ng/mL or with C_{max}>124 ng.

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

Increased granularity of the exposure-efficacy relationship is provided in Figure 2. Across Studies 217-MDD-201B, 217-PPD-201, and Part A of the current study, increased concentrations of SAGE-217 were associated with a larger reduction in depressive symptoms (Figure 2). Based on linear regression modeling, effect sizes for HAM-D were dose dependent, with a 50 mg dose administered once daily for 14 days predicted to provide greater therapeutic

benefit compared to daily doses of 40 and 30 mg. Based on preliminary results from Part A of this study, a dose of 30 mg may be considered the minimally effective dose.

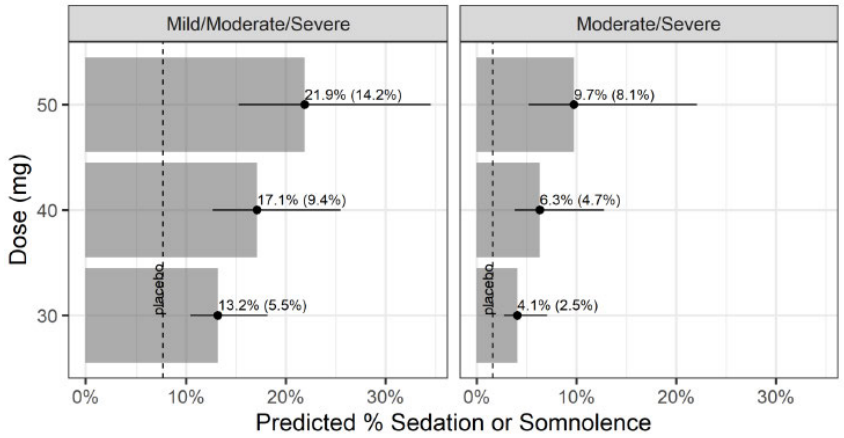
Figure 2: Total score change on Day 15 (Studies 217-MDD-201B, 217-PPD-201, Part A of the current study)



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

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

Figure 3: Predicted incidence of sedation or somnolence by dose



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

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

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

Sedation, an extension of the pharmacologic mechanism of SAGE-217, was the primary dose-limiting effect in toxicity studies in rats and dogs. In dogs, the toxicologic 'effect dose' levels of 2.5 mg/kg/day (9-month study, episodic dosing study) or 2 mg/kg/day (3-month study) associated with a low incidence of convulsion and/or early mortality during or following the dosing phase, were associated with exposures 7- to 11-fold above clinically relevant C_{max} following administration of 30 mg capsules. Similar margin calculations for adverse effect levels in dogs to potential higher SAGE-217 dose levels (40 or 50 mg/day) remain at or above 4.5x for both C_{max} and AUC. All non-clinical findings are provided in the SAGE-217 Investigator's Brochure. The totality of the nonclinical safety data supports the use of SAGE-217 for the

treatment of patients at the higher clinical dose regimen, particularly in the context of the current safety database of greater than 2000 subjects exposed to SAGE-217 treatment.

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

6. STUDY OBJECTIVES AND 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:

- Part A only: 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. Part A - Secondary Endpoints

- 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 ≥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 ≤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. Part B – Key Secondary Endpoints

- Change from baseline in CGI-S at Day 15
- Change from baseline in HAM-D total score at Day 8, Day 3, and Day 42

6.2.4. Part B – Other Secondary Endpoints

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as “much improved” or “very much improved”, at Day 15
- Change from baseline in MADRS total score at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline in PRO measures of health-related quality of life, as assessed by responses to the SF-36v2, and of depressive symptoms as assessed by the PHQ-9

6.2.5. 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]

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, parallel-group, placebo-controlled study in subjects with MDD. This study will be conducted in 2 parts – Part A and Part B. Bart B will commence after all subjects in Part A have completed the Day 42 visit. Part A and Part B will enroll unique subjects. For both study parts, 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. Each study part is described below.

Part A

Part A 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) with the intent of identifying subjects who may meet exclusion criteria due to participation in another clinical study (Section 8.2). 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 ≥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 2.

Part B

Part B will consist of a Screening Period of up to 28 days, a 14-day Treatment Period, and a 28-day double-blind follow-up period. Part B of the study may run concurrently with the extended follow-up period in Part A.

The Screening Period begins with the signing of the 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) with the intent of identifying subjects who may meet

exclusion criteria due to participation in another clinical study (Section 8.2). 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 ≥60 days) and randomized within each stratum to one of 2 treatment groups (SAGE-217 50 mg or matching placebo) in a 1:1 ratio. Subjects will self-administer study drug once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat or with a fat-containing snack), on an outpatient basis, for 14 days. See Section 10.5 for examples of fat-containing snacks. Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 3.

During the treatment period, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the Investigator, subjects who cannot tolerate the 40-mg dose may be discontinued from study drug.

Subjects who discontinue treatment early should return to the site for an 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 ET visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and decides to terminate the study on the same day during a clinic visit; in this case, all EOT visit assessments should be conducted in addition to an abbreviated physical exam.

7.2. Number of Subjects

In Part A, approximately 450 subjects will be randomized and dosed to obtain 399 evaluable subjects (see Section 13.8). In Part B, up to 575 subjects will be randomized and dosed to obtain sufficient evaluable subjects for all analyses.

7.3. Treatment Assignment

For both study parts, subjects will be randomly assigned to a treatment group on Day 1 and will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥60 days) at baseline. In Part A, randomization will be performed within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matching placebo. In Part B, randomization will be performed within each stratum in a 1:1 ratio to receive SAGE-217 50 mg or matching placebo.

7.4. Dose Adjustment Criteria

In Part A, dose adjustments are not permitted and subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated (see Section 8.3).

During the treatment period in Part B, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who cannot tolerate 50 mg will receive 40 mg for the remainder of the treatment period. At the discretion of the Investigator, subjects who cannot tolerate the 40-mg dose may be discontinued from study drug (refer to Section 8.3 for procedures for early study drug discontinuation). If dose adjustment is deemed necessary by the Investigator at any time during the treatment period, the subject will return to the site to return any remaining study drug and for the adjusted dose to be dispensed.

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 64 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. For Part A, subject has a MADRS total score of ≥32 and a HAM-D total score ≥22 at screening and Day 1 (prior to dosing). For Part B, subject has a HAM-D total score ≥24 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 who have stopped taking antidepressants within 60 days must have stopped for longer than 5 half-lives of the antidepressant 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 or without 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 is currently at significant risk of suicide, as judged by the Investigator, or 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. For Part A, a body mass index (BMI) $\leq$18 or $\geq$50 kg/m^2 at Screening is exclusionary; a BMI of 40 to 49 kg/m^2, 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. For Part B, a BMI $\leq$18 or $\geq$45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
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 $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Subject is taking any benzodiazepine or GABA modulator with a half-life of ≥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, including suicidality, at the discretion of the Investigator

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 may withdraw the subject from the study at his/her discretion. 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.

In Part A, 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.

In Part B, subjects who discontinue study drug early should return to the site for an 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. If necessary, 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 EOT visit assessments should be conducted in addition to an abbreviated physical exam.

For both study parts, 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

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

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

9.2. Prior Medications, Concomitant Medications, 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, $GABA_A$ 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 ≥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 who are feeling sedated, somnolent, and/or dizzy are to refrain from driving or engaging in any activity requiring alertness.

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 10.5, Table 2, and Table 3).

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 2 and Table 3, 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. For both study parts, 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 ≥60 days) at baseline.

In Part A, 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. In Part B, randomization will be done within each stratum in a 1:1 ratio to receive SAGE-217 50 mg or matched placebo.

In both study parts, 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 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 Part A, 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 Part B, the Sponsor, site personnel and subjects will remain blinded until the database lock when all subjects complete the Day 42 visit.

9.4.1. Emergency Identification of Study Drug

During the study, the blind is to be broken 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 should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a subject. Requests from the Investigator about the treatment administered to study subjects should be discussed with the Sage Medical Monitor. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the 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. At the of withdrawal from the study/stopping participation, if possible, an EOT and/or ET visit should be conducted.

If a subject(s) or study personnel become unblinded to subject's treatment assignment before database lock, the subject(s) will be excluded from the Per Protocol Set, but included in Full Analysis Set, as detailed further in the statistical analysis plan.

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. 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. For Part A, each unit dose consists of 1 capsule. For Part B, each unit dose consists of 2 capsules (see Section 9.1). 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

In Part A, 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.

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

In both study parts, 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 2 and Table 3.

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.

10.8. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness or performance (applicable for approved marketed products) of a drug product after it is released for distribution. In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in Table 1. Where possible, personnel should segregate any product, materials, or packaging associated with the product complaint.

11. ASSESSMENT OF EFFICACY [redacted]

All assessments will be conducted according to the schedule of assessments (Table 2 and Table 3). 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 past 7 days (1 week) will be used at Screening and during the extended Follow-up Period (Part A only), 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 ≤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: 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; Part A Only)

The ISI will be assessed in Part A only. 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 (Part A Only)

The Core Consensus Sleep Diary will be assessed in Part A only. This instrument 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]

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

All assessments will be conducted according to the schedule of assessments (Table 2 and Table 3).

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, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, bipolar disorder, persistent depressive disorder, postpartum depression, substance use disorder, alcohol use disorder, major depressive disorder with seasonal pattern, major depressive disorder with psychotic features, premenstrual dysphoric disorder, major depressive disorder with atypical features, schizophrenia; or schizoaffective disorder will be documented. The 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 10th 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. COVID-19 Questions

Information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of Medical History, AE collection, and prior/concomitant medication/procedure collection at Screening and throughout the study.

Questions to be asked are as follows:

- Were you diagnosed with COVID-19 by a healthcare professional?
  - If the answer is “no”, no further questions.
  - If the answer is “yes”, the following questions are asked:
    - Did you have a test? If yes, was the result positive, negative or inconclusive?
    - Were you isolated? If yes, what were the dates of isolation?
    - Were you hospitalized? If yes, what were the dates of hospitalization?

12.1.3. Weight and Height

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

12.1.4. 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. An abbreviated physical exam includes a brief medical history followed by a targeted physical exam. 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.

12.1.5. 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.

12.1.6. 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. When ECG [redacted] sample collection occur during the same visit, the ECGs will be conducted first.

12.1.7. 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 5.

Table 5: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Coagulation
Red blood cell count Hemoglobin Hematocrit White blood cell count with differential Platelet count	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin	pH Specific gravity Protein Glucose Red blood cell Nitrite	Activated partial thromboplastin time Prothrombin time International normalized ratio

Red Blood Cell Indices (MCV, MCH, MCHC) Reflex to Red blood cell morphology if indices are abnormal	Indirect bilirubin Total protein Creatinine Blood urea nitrogen 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	Leukocyte esterase Ketones Bilirubin Urobilinogen	
Diagnostic			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C Reflex HCV RNA HIV-1 and -2 Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: serum hCG Female subjects, if menopause is suspected and not surgically sterile: FSH	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine 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).

12.1.7.1. Drugs of Abuse and Alcohol

Urine toxicology tests will be performed for selected drugs of abuse (see Table 5). A breath test for alcohol will be performed.

12.1.7.2. 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.

12.1.8. 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 2 and Table 3).

12.1.9. 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 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.

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 6: Relationship to Study Drug

Relationship	Definition
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. 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. 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. Any complication during pregnancy (eg, anemia, infections, pre-eclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, 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. Overdose

An overdose is defined as more than 2 capsules of study drug taken by a subject in an 18-hour period or more than 4 capsules taken by a subject in a 36-hour period.

Overdoses, regardless of presence of associated clinical manifestation(s) (eg, headache, abnormal laboratory value) will be considered an AE and recorded as such on the eCRF. Any clinical manifestation(s) of overdose must also be recorded as an AE on the eCRF. In addition,

all overdoses must be recorded on an Overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose.

13. STATISTICS

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. Separate SAPs will be generated for each part of the study. The SAP for each study part will be finalized and approved prior to treatment unblinding of each respective part.

In Part A, 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. Data from Part A may be analyzed and reported following final database lock and before Part B is complete. For Part B, the final database lock will occur when all subjects complete the study; treatment unblinding and analyses will follow the database lock.

Separate clinical study reports will be produced for each part of the study.

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.

The Modified Full Analysis Set (mFAS) is defined as all participants in the FAS with a total HAM-D score ≥ 26 at baseline.

[redacted]

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 ≥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 defined as follows:

1) The treatment regimen for participants is placebo or SAGE-217 for 14 days.
2) The target population is adult participants with a current diagnosis of MDD marked by baseline HAM-D total score ≥26.
3) The variable of interest is the change from baseline in HAM-D total score at Day 15.
4) The intercurrent events could be:
    a. The premature discontinuation of treatment for any reason, thus not having a Day 15 HAM-D total score available. This will be dealt with by a sensitivity analysis using multiple imputation technique (details will be provided in the SAP).
    b. Certain medications including, but not limited to, new antidepressants and benzodiazepines are prohibited until Day 42; however, the treatment policy strategy dictates that the results following prohibited medication use will not be manipulated but will be used ‘as is’ in analyses. (Note that no rescue medication is defined in this protocol; hence, there is no rescue medication to be considered).
5) The population summary level deals with the difference between SAGE-217 and placebo treatments in mean change from baseline in HAM-D total score at Day 15.

Data 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, 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 diary endpoints in Part A only (eg, sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO)), ISI score in Part A only, 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 ≥50% reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of ≤7.0). GEE models will include terms for treatment, baseline score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 and matching placebo at 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]

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

For Part A, 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%.

For Part B, assuming a two-sided alpha level of 0.05, a sample size of 216 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 a standard deviation (SD) of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each stratum (antidepressant use at baseline, yes or no), approximately 240 total randomized subjects will be required to obtain 216 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 postbaseline HAM-D assessment. To provide more power for analyses of key secondary endpoints, up to 575 subjects will be randomized for Part B.

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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Williams JBW. SIGH-A 24hr: V1.3 – 24 HR Version. 2013c.

Williams JBW. SIGH-A Past week: Past Week Version. 2013d.

Protocol 217-MDD-301, Amendment 7

Date of Amendment: 14 December 2020

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 increase the sample size of Part B (from approximately 370 to up to 575 participants) to provide more power for key secondary endpoints. In addition, a Modified Full Analysis Set has been added to the data analysis sets and details of the estimand for the primary efficacy analysis have been added.

The administrative changes outlined in Administrative Letter #4 from 14 October 2020 are also incorporated in this amendment, which are to correct footnotes in Table 3 ‘Schedule of Events (Part B)’.

Sage Therapeutics™

o (617) 949.4256 f (617) 299.8379
215 First Street, Cambridge, MA 02142
www.sagerx.com

October 14, 2020

217-MDD-301 Protocol Administrative Letter #4

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

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To Whom It May Concern:

This memo is to inform you of a clarification to 217-MDD-301 Protocol Version 7.0 (Amendment 6), dated 14Sep2020.

In **Table 3: Schedule of Events (Part B)**, footnotes o, p, q, r, s, and t were inadvertently shifted from the procedure(s) that they were intended to be associated with. The corrections are listed below, and a copy of the corrected **Table 3: Schedule of Events (Part B)** is included with this letter for reference.

Study Procedure	Incorrect Footnote(s)	Correct Footnote(s)
HAM-A	o	p
[redacted]		
Study Drug Accountability/Return (Day 42/ET Visit Column)	q	r
Adverse Events/SAEs	r	d, s
Prior/Concomitant Medications/Procedures	s	d, t

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.

Sincerely,

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 15-Oct-2020 | 14:27 EDT
18B637C692D5461B90CCB2CA3A540F5B
[redacted] MD
[redacted]

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 15-Oct-2020 | 15:07 EDT
104D24A153734DB69066E2ED46A7602E
[redacted]

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 15-Oct-2020 | 14:22 EDT
86C58AE751AD4A419C2948DD2DBABEA6
[redacted]

Table 3: Schedule of Events (Part B)

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 [a]**	**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**
Study Procedure											
Informed Consent	X										
Duplicate Participant Check [b]	X										
Inclusion/Exclusion	X	X									
Serum FSH test [c]	X										
SCID-5-CT	X										
MGH ATRQ	X										
Demographics	X										
Medical/Family History[d]	X										
Subject training [e]	X	X									
Randomization		X									
Physical Examination [f]	X	X									X
Body Weight/Height	X					X (weight only)					X (weight only)
Clinical Laboratory Assessments [g]	X	X		X		X		X	X		X
Drug & Alcohol Screen [h]	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test [i]	X	X				X			X		X

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 [a]**	**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**
Study Procedure											
Hepatitis & HIV Screen	X										
[redacted]											
Vital Signs [l]	X	X	X	X	X	X	X		X		X
12-Lead ECG [m]	X	X				X					X
C-SSRS [n]	X	X	X	X	X	X	X	X	X	X	X
HAM-D [o, p]	X	X	X	X	X	X		X	X	X	X
MADRS		X		X		X			X		X
HAM-A [p]		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
SF-36v2	X	X		X		X			X		X
PHQ-9		X		X		X			X		X
PWC-20		X				X	X	X			
[redacted]											
Study Drug Dispensation		X		X							
Study Drug Administration		X (Day 1 through Day 14)									
Study Drug Accountability/Return				X		X					X [r]

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** [a]	**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**
Study Procedure											
Adverse Events/SAEs[d, s]	X										
Prior/Concomitant Medications/Procedures[d, t]	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; 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; [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.

[a] 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. If necessary, 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 EOT visit assessments should be conducted in addition to an abbreviated physical exam.

[b] 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.

[c] A serum follicle stimulating hormone test will be conducted at Screening for female participants 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.

[d] Information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of Medical History, AE collection, and prior/concomitant medication/procedure collection at Screening and throughout the study.

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

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

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

[h] Urine toxicology for selected drugs of abuse (as per the lab manual) and breath test for alcohol.

[i] Serum pregnancy test at screening and urine pregnancy test thereafter for female subjects who are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal.

[redacted]

[l] 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 participant has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Vital signs may be repeated at the discretion of the Investigator as clinically indicated.

[m] Triplicate ECGs will be collected. When ECGs [redacted] sample collection occur on the same day, the 12-lead ECGs will be performed [redacted] sample collection.

[n] 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.

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

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

[redacted]

To be performed at the ET visit only.

[s] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.

[t] Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.