COVER PAGE

Official Title:	A Phase 3, Open-Label, 1-Year Study of the Safety, Tolerability, and Need for Re-Treatment with SAGE-217 in Adult Subjects with Major Depressive Disorder
NCT Number:	NCT03864614
Document Date:	Protocol Version 7.0: 10 May 2021

A PHASE 3, OPEN-LABEL, 1-YEAR STUDY OF THE SAFETY, TOLERABILITY, AND NEED FOR RE-TREATMENT WITH SAGE-217 IN ADULT SUBJECTS WITH MAJOR DEPRESSIVE DISORDER

PROTOCOL NUMBER: 217-MDD-303

Study Drug	SAGE-217
Clinical Phase	Phase 3
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Tel: [redacted] E-mail: [redacted]
Sponsor Medical Monitor	[redacted] MD Tel: [redacted] E-mail: [redacted]
Date of Original Protocol	Version 1.0, 18 October 2018
Date of Amendment 1	Version 2.0, 09 January 2019
Date of Amendment 2	Version 3.0, 25 April 2019
Date of Amendment 3	Version 4.0, 06 February 2020
Date of Amendment 4	Version 5.0, 19 March 2020
Date of Amendment 5	Version 6.0, 24 November 2020
Date of Amendment 6	Version 7.0, 10 May 2021

Protocol Number:	217-MDD-303
Study Drug:	SAGE-217
Study Phase:	Phase 3
Sponsor:	Sage Therapeutics, Inc.
Protocol Date:	Version 7.0, 10 May 2021

Sponsor Approval

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 10-May-2021 | 15:12 EDT
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10-May-2021 | 15:12 EDT

[redacted] MD, MBA

Date (DD MMM YYYY)

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DocuSigned by:
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Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 10-May-2021 | 20:08 EDT
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10-May-2021 | 20:08 EDT

[redacted] RAC

Date (DD MMM YYYY)

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DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 10-May-2021 | 15:19 EDT
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[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 10-May-2021 | 15:15 EDT
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10-May-2021 | 15:15 EDT

[redacted] PhD

Date (DD MMM YYYY)

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DocuSigned by:
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Signer Name: [redacted]
Signing Reason: I approve this document
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10-May-2021 | 15:07 EDT

[redacted] MBBS (MD)

Date (DD MMM YYYY)

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Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 10-May-2021 | 15:03 EDT
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10-May-2021 | 15:03 EDT

[redacted] PhD

Date (DD MMM YYYY)

[redacted]

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-MDD-303 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 MMM YYYY)

CONTACT INFORMATION

Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician	[redacted] MD [redacted]	Email: [redacted] Tel: [redacted]
Syneos Medical Monitor	[redacted] MD [redacted]	Email: [redacted] Tel: [redacted]
24-Hour Serious Adverse Event reporting	IQVIA Lifecycle Safety	Email: Sage.Safety@iqvia.com SAE Hotline Tel: 855-564-2229 Fax: 855-638-1674
Product Complaint Contact	Sage Therapeutics	Email: productcomplaints@sagerx.com Phone: 1-833-554-7243

2. SYNOPSIS

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

Name of Study Drug: SAGE-217 Capsules

Name of Active Ingredient: SAGE-217

Title of Study:
A Phase 3, Open-label, 1-year Study of the Safety, Tolerability, and Need for Re-treatment with SAGE-217 in Adult Subjects with Major Depressive Disorder

Number of Sites and Study Location: This study will take place at approximately 75 sites in the United States; non-US sites may be included as needed.

Phase of Development: 3

Planned Duration of Subject Participation:
For Part A de novo subjects, the planned duration of participation is approximately 56 weeks: Screening Period (28 days), Initial Treatment Period (14 days), Follow-up Period (14 days), and Observational Period (48 weeks). In Part B, rollover subjects will enter the study during the Observational Period, therefore the planned duration of participation is approximately 46 weeks. Additional 14-day treatment periods with SAGE-217 may occur during the Observational Period.

The following objectives and endpoints will be evaluated in 2 separate study parts: Part A (de novo subjects who have their initial treatment cycle in the current study) and Part B (rollover subjects who have their initial treatment cycle in the parent study).

Objectives:

Primary:

- To determine the safety and tolerability of initial treatment and/or re-treatment(s) with SAGE-217 in adults with Major Depressive Disorder (MDD) experiencing a major depressive episode (MDE) at study entry for de novo subjects or at entry in the parent study for rollover subjects over a 1-year period

Secondary:

- To assess the need for re-treatment with SAGE-217 following initial treatment in adults with MDD experiencing an MDE at study entry for de novo subjects or at entry in the parent study for rollover subjects over a 1-year period
- To assess the response of initial treatment and/or re-treatment(s) with SAGE-217 following an initial 2-week treatment period in adults with MDD experiencing an MDE at study entry for de novo subjects or at entry in the parent study for rollover subjects over a 1-year period

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Endpoints:

Primary:

- The safety and tolerability of the initial treatment with SAGE-217 and/or re-treatment with SAGE-217, as assessed by the incidence and severity of adverse events/serious adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); and suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS).

Secondary:

- The need for re-treatment with SAGE-217 as assessed by:
  - Time to first re-treatment (Kaplan-Meier curves)
  - Number of subjects achieving the requirements for re-treatment
  - Number of re-treatment cycles for each subject
- The response of initial treatment and/or re-treatment as assessed by:
  - Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at the end of each 14-day treatment (initial and/or re-treatment) period
  - HAM-D response at the end of each 14-day treatment (initial and/or re-treatment) period, defined as a ≥50% reduction in HAM-D score from baseline;
  - HAM-D remission at the end of each 14-day treatment (initial and/or re-treatment) period, defined as HAM-D total score ≤7
  - Clinical Global Impression - Improvement (CGI-I) response, defined as "much improved" or "very much improved", at the end of each 14-day treatment (initial and/or re-treatment) period
  - Change from baseline in Clinical Global Impression - Severity (CGI-S) score at the end of each 14-day treatment (initial and/or re-treatment) period

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Study Description:

This is an open-label, long-term, longitudinal study in adult subjects with MDD. With protocol amendment 5, this study will be conducted in 2 parts - Part A and Part B. Each part will enroll unique subjects and may be enrolled concurrently. Each study part is described below.

Part A – de novo subjects

In Part A, de novo subjects currently experiencing an MDE will complete a Screening Period of up to 28 days, an Initial Treatment Period (14 days) and Follow-Up Period (14 days). Subjects achieving response or remission with SAGE-217 will be followed for 48 weeks (Observational Period).

The Screening Period for de novo subjects begins with the signature of the informed consent form (ICF); 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).

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

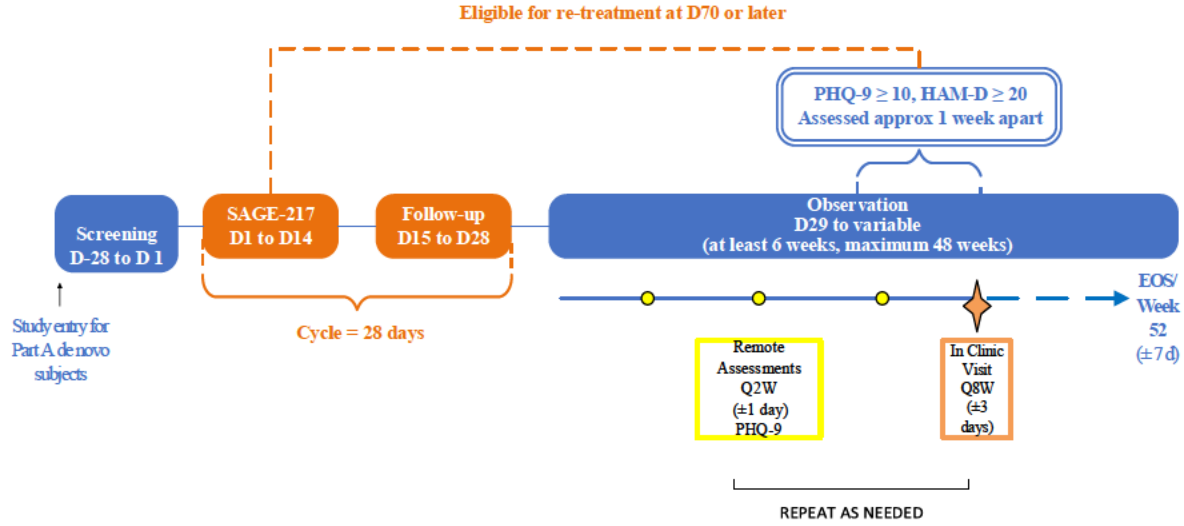
Beginning on Day 1, qualified subjects will self-administer study drug once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat or with a fat-containing snack) on an outpatient basis for 14 days.

During the initial treatment, antidepressants are permitted provided a subject is on a stable dose for at least 60 days prior to Day 1 and agrees to continue on the stable dose through at least the initial treatment and follow-up period. After the initial treatment period, subjects who respond (defined as a ≥50% reduction in HAM-D score from baseline) by Day 15 will be followed naturalistically for 48 weeks (see Part A study schematic below).

If a subject does not exhibit a response to SAGE-217 by Day 15 of the initial treatment, the subject will be terminated from the study upon completion of the 14-day follow-up period.

Qualified subjects (ie, HAM-D Responders at Day 15) will return to the site every 8 weeks during the 48-week observational period for clinical assessments. A follow-up visit to collect any AEs and any concomitant medications and/or procedures, and to remind subjects to complete remote assessment(s) during the observational period will be conducted 14 days (±1 day) after the completion of the treatment period.

A Part A study schematic is shown in the figure below.



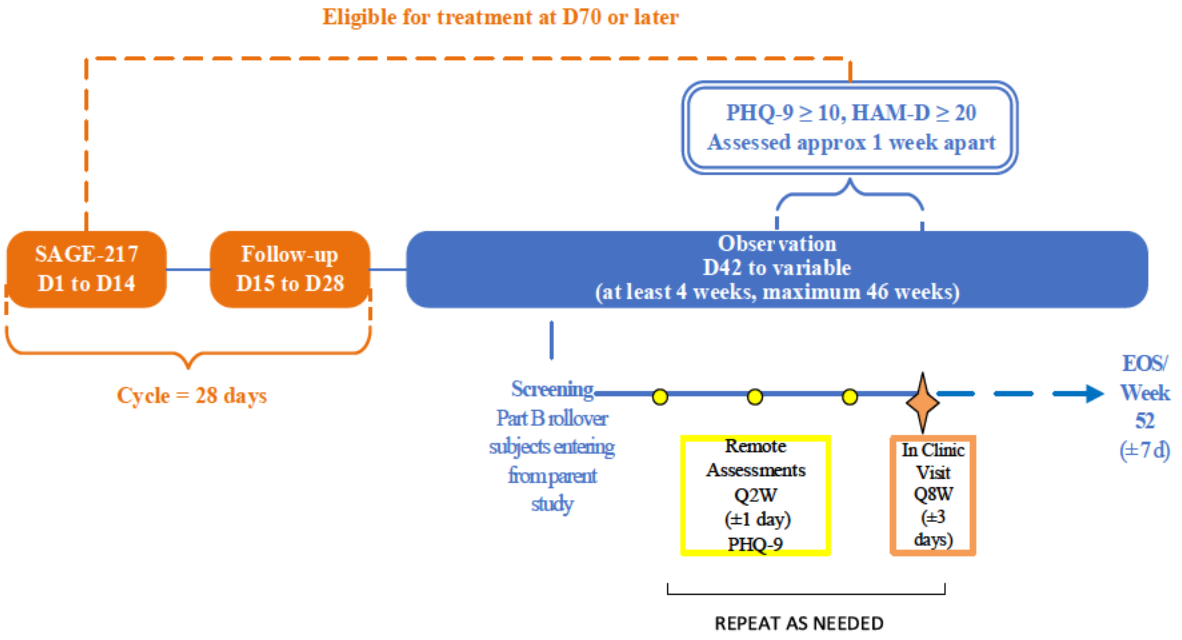
Note: For de novo subjects, the Observational Period only applies to those subjects that exhibit a HAM-D response by Day 15 with the initial treatment, defined as a ≥50% reduction in HAM-D score from baseline. De novo subjects who do not exhibit a HAM-D response by Day 15 of Cycle 1 will be terminated from the study upon completion of the Day 28 follow-up visit. De novo subjects who exhibit a HAM-D response by Day 15 of Cycle 1 will be eligible for re-treatment at Day 70 or later.

Part B – rollover subjects

In Part B, adults with MDD who have completed a Sage-sponsored randomized, double-blind, placebo-controlled study with a provision for rollover (parent study) will sign the ICF and be screened to determine eligibility to enter the study at the Day 42 visit during the Observational Period (see Table 3).

The Screening Visit may occur on the same calendar day as the End of Study Visit in the parent study; therefore, no assessments conducted for the final, End of Study Visit in the parent study will need to be repeated. If subjects do not enroll in the current study at the final, End of Study Visit in the parent study, but complete the Screening Visit for the current study within 5 calendar days, the drug and alcohol screen and pregnancy test (female subjects only) should be repeated. Additional assessments may be conducted at the Screening Visit if necessary.

Subjects will return to the site every 8 weeks during the observational period for clinical assessments and be followed through the End of Study/Week 52 Visit. Rollover subjects may be eligible for treatment with SAGE-217 no sooner than Day 70. A Part B study schematic is shown in the figure below.



Note: Part B rollover subjects enter the study at Day 42 during the Observational Period.

SAGE-217 treatment cycles (all subjects in Part A and Part B)

Each 14-day treatment period and corresponding 14-day follow-up period is considered a cycle (28 days).

For de novo subjects, the initial treatment is Cycle 1 and re-treatments will be numbered sequentially. Rollover subjects complete a double-blind treatment cycle in the parent study and enter the study during the Observational Period and therefore, do not complete Cycle 1 in the current study. If rollover subjects meet the criteria to receive SAGE-217 in the current study, they will start at Cycle 2. The dose of SAGE-217 administered during each new treatment cycle (initial or re-treatment) in all subjects will be 50 mg or reduced dose of 40 mg, per criteria described in Section 7.4. Each cycle will begin with Day 1 (eg, the first day of the first re-treatment period will be Day 1 of Cycle 2). A maximum of 5 treatment cycles is permitted for de novo subjects; for rollover subjects, a maximum of 4 treatment cycles within Part B is permitted (ie, 4 cycles in the current study *plus* the initial double-blinded cycle in the parent study). A new re-treatment cycle cannot start after Week 48; subjects starting a new SAGE-217 treatment cycle between Weeks 45 and 48 will be followed through the end of the treatment cycle (Day 28, end of Follow-up period of treatment cycle). If a subject does not tolerate the 50 mg dose, and has been reduced to 40 mg, the subject may continue to receive the reduced dose of 40 mg for subsequent re-treatment cycles, as determined by the investigator.

The need for re-treatment will be assessed every 14 days via remote assessments during the 48-week observational period based on the results of the subject-reported PHQ-9; if the PHQ-9 score is ≥10, the subject will return to the site in approximately one week to be assessed by the clinician-administered HAM-D. New SAGE-217 cycles may be initiated for subjects with a HAM-D score ≥20. In all subjects, the End of Study/Week 52 Visit is mandatory if another scheduled on site visit does not fall in the Week 52 window.

A minimum period of 8 weeks (56 days) is required between SAGE-217 treatment periods. This is based on the period of 8 weeks establishing 'full remission' of a depressive episode (DSM-5) and is aligned with the treatment period which would be required for any available antidepressant (ADT) to

exhibit maximal efficacy. Rollover subjects, therefore, will not be eligible to begin their first SAGE-217 treatment period until 56 days has elapsed from the date of last dose of blinded study drug (SAGE-217 or placebo) administered in the parent study.

As this is the first study in which longitudinal re-treatment with SAGE-217 will be examined, and based on known withdrawal symptoms with other GABAergic drugs and non-clinical findings in a 9-month study of SAGE-217 in dogs (Investigator's Brochure), the potential for withdrawal-related events, including seizure, will be monitored following the guidelines outlined in Section 8.5.1, which include study drug discontinuation or dose reduction.

If a subject exhibits suicidality at any time, they will return to the site as soon as possible for assessment by the Investigator. The assessments for the Screening Period and Treatment and Follow-up Periods in Part A – de novo subjects are summarized in Table 1; the assessments for the Observational Period in Part A - de novo subjects are summarized in Table 2. The assessments for Screening and Observational Period in Part B - rollover subjects are summarized in Table 3; the assessments for the Treatment and Follow-Up Periods in Part B – rollover subjects are summarized in Table 4.

Number of Subjects (Planned): In Part A, approximately 1200 de novo subjects will be dosed, with the expectation to achieve follow-up of 675 subjects for 6 months and 235 subjects for 1 year. In Part B, approximately 350 rollover subjects may be enrolled.

Eligibility Criteria:

Part A – de novo subjects

Inclusion Criteria:

Qualified de novo 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 75 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 during any 14-day treatment period.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a MADRS total score of ≥28 and a HAM-D total score of ≥20 at Screening and Day 1 (prior to dosing).
7. Subjects taking antidepressants indicated for the treatment of major depressive disorder 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 must have done so for at least 60 days prior to Day 1. Subjects receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1.
8. Female subject agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicular stimulation hormone [FSH] >40

mIU/mL), and/or surgically sterile (hysterectomy or bilateral oophorectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy.

9. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
10. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
11. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

Exclusion Criteria:

De novo 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 has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study. A body mass index (BMI) ≤18 or ≥45 kg/m^2 at Screening is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical co-morbidities (such as sleep apnea, chronic obstructive pulmonary disease [COPD]), concomitant medications, and prior tolerability of sedating agents.
3. 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 will be used for this purpose.
4. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine (including esketamine) within the current major depressive episode.
5. Subject is taking any of the following:
    a. benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, zolpidem, brexanolone) at Day -28,
    b. benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, zolpidem, brexanolone) daily or near-daily (≥4 days per week) for 1 year, in the year prior to first dose of study drug,
    c. benzodiazepine or $GABA_A$ modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1
6. Subject is taking non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia, over-the-counter sleep aids, melatonin) first generation (typical) antipsychotics (eg, haloperidol, perphenazine), and/or second generation (atypical)

antipsychotics (eg, aripiprazole, quetiapine) at Day -14. Note that antihistamines used during the day solely for indication(s) other than insomnia are permitted.

7. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
8. Subject has a positive pregnancy test at Screening or on Day 1 prior to the start of study drug administration for any treatment cycle.
9. Subject that is breastfeeding at Screening or on Day 1 (prior to administration of study drug) 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 in each treatment cycle.
10. Subject has detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at Screening.
11. 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.
12. Subject has active psychosis per Investigator assessment.
13. Subject has a medical history of seizures.
14. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
15. 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.
16. Subject has been taking chronic or as-needed psychostimulants (eg, methylphenidate, amphetamine) or opioids at Day -28.
17. Subject has had exposure to another investigational medication or device within 30 days prior to Screening.
18. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
19. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 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 for any SAGE-217 treatment cycle.
20. Use of strong CYP3A inducers within 28 days prior to the first dose of study drug for any SAGE-217 treatment cycle or planned use during any treatment cycle. Examples include: rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, and St John's Wort.
21. Subject has a positive drug and/or alcohol screen at Screening or on Day 1 prior to dosing of the initial treatment cycle.
22. Subject plans to undergo elective surgery during the initial treatment and follow-up period.
23. Subject has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) within the past year prior to Screening.

24. Subject has a history of sleep apnea.
25. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
26. Subject ≥65 years of age has a history of cognitive impairment, increased risk for falls (including but not limited to impaired balance and/or gait) or is already taking ≥2 CNS active drugs as per the American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.

Part B – rollover subjects

Inclusion Criteria:

Qualified rollover 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 in good physical health and has no clinically significant findings, as determined by the investigator.
3. Subject has completed treatment with double-blind study drug and has completed the final (end-of-study) visit in the parent study.
4. Subject agrees to adhere to the study requirements, including not participating in night shift work during any 14-day treatment period.
5. Female subject agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicular stimulation hormone [FSH] >40 mIU/mL), and/or surgically sterile (hysterectomy or bilateral oophorectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy.
6. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4
7. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
8. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

Exclusion Criteria:

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

1. Experienced major protocol deviations or adverse events in the parent study which could potentially compromise subject safety, in the investigator's opinion.
2. Subject is currently at significant risk of suicide, as judged by the Investigator, or has attempted suicide since enrolling in the parent study

3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
4. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine (including esketamine) since enrolling in the parent study
5. Subject is taking first generation (typical) antipsychotics (eg, haloperidol, perphenazine), and/or second generation (atypical) antipsychotics (eg, aripiprazole, quetiapine) at Screening or within the time period between completion of the parent study and Screening.
6. Subject has taken an antidepressant other than sertraline, escitalopram, citalopram, duloxetine or desvenlafaxine within 60 days prior to screening, including within the time period between completion of the parent study and Screening.
7. Subject has a known allergy to SAGE-217, brexanolone, allopregnanolone, or related compounds.
8. Subject has a positive pregnancy test at Screening.
9. Subject that is breastfeeding at Screening 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 in each treatment cycle, if applicable.
10. Subject has active psychosis per Investigator assessment.
11. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
12. Subject has a new history of mild, moderate, or severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria from the time of enrollment in the parent study or within the time period between completion of the parent study and Screening.
13. Subject has taken psychostimulants (eg, methylphenidate, amphetamine) or opioids during the parent study or within the time period between completion of the parent study and Screening.
14. Subject has had exposure to another investigational medication (other than SAGE-217) or device during the parent study or within the time period between completion of the parent study and Screening.
15. Subject has a positive drug and/or alcohol screen at Screening.
16. Subject has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) during the parent study or within the time period between completion of the parent study and Screening.
17. History of poor compliance with the study drug and/or procedures in the parent study as determined by the Investigator

SAGE-217 Dosage and Mode of administration:

SAGE-217 is available as hard gelatin capsules for oral administration. Available dose strengths are as 30-mg or 20-mg capsules, with single or multiple capsules administered as appropriate to achieve the total daily dose of 50 mg or 40 mg specified per all treatment cycles (initial or re-treatment).

Reference Therapy, Dosage and Mode of Administration:

Not applicable

Duration of Treatment:

In Part A, all de novo subjects will receive a daily oral dose of SAGE-217 from Day 1 through Day 14 of the first treatment cycle.

In Part B, rollover subjects will enter the current study after completing a 14-day double-blind treatment period and 4-week follow-up in the parent study.

According to the re-emergence of depressive symptoms, SAGE-217 may be administered to both de novo and rollover subjects in subsequent 14-day treatment periods.

Statistical Methods:

Separate statistical analysis plans (SAP) will be generated for each part of the study and will provide a detailed description of the analyses to be performed in the study. For Part B- rollover subjects, the parent study database will be used in analysis.

The SAP for each study part will be finalized and approved prior to database lock for respective parts. The data for Part A – de novo subjects may be analyzed and reported prior to database lock for Part B – rollover subjects. Any deviations from or changes to the SAPs following database lock will be described in detail in the clinical study report.

General Considerations

For the purpose of all analyses where applicable, baseline will be defined as the latest value before the first dose of SAGE-217 Cycle 1 for de novo subjects. A period-specific baseline will be defined as the latest value before the first dose of SAGE-217 in each 14-day treatment cycle.

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.

Analysis Sets

The Safety Set for both Part A and Part B is defined as all subjects administered study drug.

The Full Analysis Set for de novo subjects is defined as all subjects in the Safety Set who completed Treatment Cycle 1 and moved on to Observational Period 1 (ie, these subjects had HAM-D response by Day 15 and did not discontinue the study for any reason within Treatment Cycle 1).

The Full Analysis Set for rollover subjects is defined as all subjects in the Safety Set who have at least one HAM-D total score available after the first dose of study drug within this protocol.

In addition, the cohorts of subjects who started with the 30-mg dose versus the 50-mg dose may be analyzed separately for de novo subjects.

Determination of Sample Size

The sample size is not based on a formal sample size calculation. The sample size of 1200 de novo subjects in Part A was chosen in order to have at least 675 subjects complete 24 weeks of the study and at least 235 subjects complete through 56 weeks, consistent with the objective of assessing SAGE-217

long-term safety. Approximately 350 subjects are expected to roll over from the parent study and enroll in Part B.

Analysis of Primary Endpoint

Safety and tolerability of SAGE-217 will be evaluated by incidence and severity of adverse events/serious adverse events, concomitant medication usage, vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. In addition to overall study results, the results from each treatment cycle will be provided separately whenever applicable. Safety analyses will use the Safety Set for overall safety.

A study period is defined as a treatment cycle and its subsequent observation period; the Safety Set for a given study period includes subjects in the Safety Set who are dosed in the respective study period. Safety analyses will be provided based on the Safety Set for each study period when appropriate.

Analysis of Secondary Endpoints

Using the Full Analysis Set, Kaplan-Meier (KM) survival curve will be provided for time to first re-treatment; the estimand is the median time to first re-treatment, and it will be estimated from KM analysis.

Number and percentage of subjects needing at least one re-treatment (ie, meeting the criteria for re-treatment, but not necessarily retreated) will be provided. Number of re-treatment cycles per subject will be summarized.

Change from baseline and/or from period-specific baseline, when appropriate, in HAM-D total score and subscale scores will be summarized by each treatment cycle. 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) will be summarized for each treatment cycle. Change from baseline and/or from period-specific baseline, when appropriate, in CGI-S will be summarized for each treatment period. CGI-I will be summarized for each treatment cycle.

[redacted]

Table 1: Schedule of Events (Screening, Treatment, and Follow-up Periods) – Part A (de novo subjects)

	Screening Period[a, b]	Cycle[c]			
		Open-label Treatment Period (Initial and Re-treatments)			Follow-up
Days	**D-28 to D-1**	**D1**	**D8 (+1d)**	**D15 (±1d)/ EOT[d]**	**D28 (±1d) and/or ET**
Study Procedure					
Informed Consent	X				
Duplicate Subject Check[e]	X				
Inclusion/Exclusion	X	X			
Demographics	X				
Medical/Family History	X				
SCID-5	X				
ICD-10	X				
MGH ATRQ	X				
Serum FSH test[f]	X				
Physical Examination[g]	X	X			
Body Weight/Height	X			X (wt only)	
Clinical Laboratory Assessments[h]	X	X	X	X	
Drug & Alcohol Screen[i]	X	X	X	X	
Pregnancy Test[j]	X	X		X	
Hepatitis & HIV Screen	X				
[redacted]					
Vital Signs[m]	X	X	X	X	X
12-Lead ECG[n]	X	X		X	
C-SSRS[o]	X	X	X	X	X
MADRS	X	X			
HAM-D[p, q]	X	X	X	X	X[r]
CGI-S	X	X	X	X	X
CGI-I			X	X	X
PHQ-9		X	X	X	X
[redacted]					

[redacted]					
Study Drug Dispensation		X	X		
Study Drug Administration		X (Day 1 through Day 14)			
Study Drug Accountability/Return			X	X	
[redacted]					
Adverse Events/SAEs[t]	X				
Prior/Concomitant Medications[u]	X				

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ET = early termination; ECG = electrocardiogram; EOT = end of treatment; FSH = follicle stimulating hormone; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; ICD-10 = International Statistical Classification of Diseases and Related Health Problems version 10; [redacted] MADRS = Montgomery-Åsberg Depression Rating Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; O = Optional; SCID-5 = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PHQ-9 = 9-item Patient Health Questionnaire; [redacted] SAE = serious adverse event; [redacted] wt = weight

[a] Screening procedures are to be conducted before initial (Cycle 1) treatment period only.

[redacted]

[c] Each cycle is 28 days (±1 day) and is comprised of a 14-day treatment period and a 14-day follow-up period. The initial treatment is considered Cycle 1 and re-treatments will be numbered sequentially. Each re-treatment cycle will begin with Day 1 (eg, the first day of the first re-treatment will be Day 1 of Cycle 2).

[d] 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. The follow-up visit should occur 14 days after the last dose of treatment. Subjects who discontinue treatment due to tolerability should be followed without any further administration of study drug in any subsequent cycle. 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 EOT visit will be conducted.

[e] 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.

[f] A serum FSH test will be conducted at Screening for female subjects who 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.

[g] 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).

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

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

[j] Serum pregnancy test at Screening and urine pregnancy test thereafter.

[redacted]

[m] 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. When vital signs are scheduled at the same time as blood draws, vital signs should be obtained first.

[n] Triplicate ECGs will be collected. When ECG and blood draws are scheduled at the same time, ECG should be performed before blood draws.

[o] 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.

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

[q] The assessment timeframe for the HAM-D scale will refer to the past 7 days (1 week).

[r] Subjects that do not exhibit a response to SAGE-217 by Day 15 of the initial treatment, defined as a ≥50% reduction in HAM-D score from baseline, will be terminated from the study upon completion of the follow-up visit.

[redacted]

[t] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.

[u] Prior medications will be collected at Screening and concomitant medications will be collected at each subsequent visit.

Table 2: Schedule of Events (Observational Period) – Part A (de novo subjects)

	Observational Period[a] (Day 29 through Week 52)			EOS/Week 52 (±7 d)
	Remote Assessment Q2W (±1 d)	**Visit Q8W/ET (± 3 d)**	**Unscheduled Visit (as needed)[b]**	
Study Procedure				
PHQ-9[c]	X[d]	X	X	X
Abbreviated Physical Examination		X		X
Body Weight		X		X
Clinical Laboratory Assessments		X		X
Drug & Alcohol Screen		X		X
Pregnancy Test		X		X
Vital Signs		X		X
12-Lead ECG		X		X
C-SSRS		X		X
HAM-D[e]		X	X	X
CGI-S		X		X
CGI-I		X		X
[redacted]				
Concomitant Medications[f]		X	X	X
[redacted]				
Adverse Events/SAEs[h]	X			

ECG = electrocardiogram; ET = early termination; d = days; EOS = end of study;
HAM-D = Hamilton Rating Scale for Depression, 17-item; [redacted]
O = optional; PHQ-9 = 9-item Patient Health Questionnaire; Q2W = once every 2 weeks; Q8W = once every 8 weeks; [redacted] SAE = serious adverse event

[a] Within an Observational Period, the Q2W remote assessments will begin on Day 42 (±1 day) and occur every 2 weeks (14 days) thereafter. The Q8W visits will begin on Day 70 (±3 days) and occur every 8 weeks (56 days) thereafter.

[b] A subject will return to the site outside of the Q8W visit schedule if the PHQ-9 score is ≥10 and/or upon any suicidal thoughts or behaviors.

[c] All PHQ-9 assessments will be performed via a [redacted].

[d] The subject will take the PHQ-9 every 14 days; if the PHQ-9 score is ≥10, then the subject will return to the site to be assessed by the clinician-administered HAM-D in approximately one week. If the HAM-D score is <20, the subject will take the PHQ-9 on a weekly basis: the subject will return to the site to be assessed by the HAM-D

each week that the PHQ-9 score remains ≥10; if the PHQ-9 score is <10, the subject will take the PHQ-9 every 2 weeks thereafter.

[e] If the HAM-D score is ≥20 (assessed approximately one week from having a PHQ-9 score ≥10) and it has been at least 8 weeks since the last treatment day of the previous SAGE-217 treatment cycle (ie, Day 70 or later), the subject will begin a 14-day re-treatment period with a 14-day follow-up visit (see Table 1). If the HAM-D score is ≥20 but it has been less than 8 weeks since the last treatment day of the previous SAGE-217 treatment cycle (ie, Day 69 or earlier), see Section 9.2.1 for guidance on allowable interventions; the subject will take the PHQ-9 on a weekly basis until the 8-week period has lapsed, at which time the subject may begin a re-treatment period with SAGE-217 (see Table 1), or until the PHQ-9 score is <10.

[f] Concomitant medications will be collected at each in-clinic visit.

[redacted]

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

Table 3: Schedule of Events (Screening and Observational Period) – Part B (rollover subjects)

	Screening[a] (within 5 days of completing the final, end-of-study visit in the parent study)	Observational Period[b] (Day 56 through Week 52)			EOS/Week 52 (±7 d)
		Remote Assessment Q2W (±1 d)	Visit Q8W/ ET (±3 d)	Unscheduled Visit (as needed)[c]	
Study Procedure					
Informed Consent	X				
Interim Medical History [d]	X				
[redacted]					
PHQ-9 [e]		X[f]	X	X	X
Inclusion/Exclusion	X				
Abbreviated Physical Examination			X		X
Body Weight			X		X
Clinical Laboratory Assessments			X		X
Drug & Alcohol Screen	X [g]		X		X
Pregnancy Test (urine)	X [g]		X		X
Vital Signs			X		X
12-Lead ECG			X		X
C-SSRS			X		X
HAM-D [h]			X	X	X
CGI-S			X		X
CGI-I			X		X
[redacted]					
Prior/Concomitant Medications [i]	X		X	X	X
Adverse Events/SAEs [j]	X				

ECG = electrocardiogram; ET = early termination; d = days; EOS = end of study; HAM-D = Hamilton Rating Scale for Depression, 17-item; [redacted]O = optional; PHQ-9 = 9-item Patient Health Questionnaire; Q2W = once every 2 weeks; Q8W = once every 8 weeks; [redacted]
SAE = serious adverse event

[a] Rollover subjects will enter the study for screening at the Day 42 visit during the Observational Period. This visit may occur on the same day as the final, end-of-study visit in the parent study. If conducted on the same day, the assessments listed at this visit do not need to be repeated; in this case, the informed consent and

inclusion/exclusion criteria only will be documented. If the Screening Visit is not conducted on the same day as the final, end-of-study visit in the parent study, the pregnancy test and drug and alcohol screen are to be conducted. Additional assessments may be conducted if necessary.

[b] Within an Observational Period, the Q2W remote assessments will begin on Day 56 (±1 day) and occur every 2 weeks (14 days) thereafter. The Q8W visits will begin on Day 70 (±3 days) and occur every 8 weeks (56 days) thereafter.

[c] A subject will return to the site outside of the Q8W visit schedule if the PHQ-9 score is ≥10 and/or upon any suicidal thoughts or behaviors.

[d] Any new medical conditions or procedures with onset/start date after completion of the parent study and prior to signing informed consent in the current study will be recorded as interim medical history.

[e] All PHQ-9 assessments will be performed via a [redacted].

[f] The subject will take the PHQ-9 every 14 days; if the PHQ-9 score is ≥10, then the subject will return to the site to be assessed by the clinician-administered HAM-D in approximately one week. If the HAM-D score is <20, the subject will take the PHQ-9 on a weekly basis: the subject will return to the site to be assessed by the HAM-D each week that the PHQ-9 score remains ≥10; if the PHQ-9 score is <10, the subject will take the PHQ-9 every 2 weeks thereafter.

[g] To be assessed if the visit is not conducted on the same calendar day as the final (end-of-study) visit in the parent study.

[h] If the HAM-D score is ≥20 (assessed approximately one week from having a PHQ-9 score ≥10) and it has been at least 8 weeks since the last dose of double-blind treatment in the parent study (ie, Day 70 or later), the subject will begin a 14-day SAGE-217 treatment period with a 14-day follow-up visit (see Table 4). If the HAM-D score is ≥20 but it has been less than 8 weeks since the last dose of double-blind treatment in the parent study (ie, Day 69 or earlier), see Section 9.2.1 for guidance on allowable interventions; the subject will take the PHQ-9 on a weekly basis until the 8-week period has lapsed, at which time the subject may begin a treatment period with SAGE-217 (see Table 4), or until the PHQ-9 score is <10.

[i] See Section 9.2.1.

[j] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study. Ongoing adverse events from the parent study will be recorded at the Screening Visit.

Table 4: Schedule of Events (Treatment and Follow-Up Periods) – Part B (rollover subjects)

	Cycle[a]			
	Open-label Treatment Period (Re-treatments)			Follow-up
Days	**D1**	**D8 (+1d)**	**D15 (±1d)/ EOT[b]**	**D28 (±1d)**
Study Procedure				
Abbreviated Physical Examination	X			
Body Weight			X	
Clinical Laboratory Assessments[c]	X	X	X	
Drug & Alcohol Screen[d]	X	X	X	
Pregnancy Test[e]	X		X	
[redacted]				
Vital Signs[g]	X	X	X	X
12-Lead ECG[h]	X		X	
C-SSRS[i]	X	X	X	X
MADRS	X			
HAM-D [j,k]	X	X	X	X
CGI-S	X	X	X	X
CGI-I		X	X	X
PHQ-9	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	
Adverse Events/SAEs[l]	X			
Prior/Concomitant Medications[m]	X			

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ET = early termination; ECG = electrocardiogram; EOT = end of treatment; FSH = follicle stimulating hormone; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; MADRS = Montgomery-Åsberg Depression Rating Scale; O = Optional; PHQ-9 = 9-item Patient Health Questionnaire; [redacted] SAE = serious adverse event; [redacted] wt = weight

[a] Each cycle is 28 days (±1 day) and is comprised of a 14-day treatment period and a 14-day follow-up period. Rollover subjects may be eligible for re-treatment beginning on Day 1 of Cycle 2; any subsequent re-treatments will be numbered sequentially.

[b] 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. The follow-up visit should occur 14 days after the last dose of treatment. Subjects who discontinue treatment due to tolerability should be followed without any further administration of study drug in any subsequent cycle. 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 EOT visit will be conducted.

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

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

[e] Urine pregnancy test.

[redacted]

[g] 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. When vital signs are scheduled at the same time as blood draws, vital signs should be obtained first.

[h] Triplicate ECGs will be collected. When ECG and blood draws are scheduled at the same time, ECG should be performed before blood draws.

[i] The "Since Last Visit" C-SSRS form will be completed at any time of day.

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

[k] The assessment timeframe for the HAM-D scale will refer to the past 7 days (1 week).

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

[m] See Section 9.2.1.

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

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or specialist term	Explanation
ADT	Antidepressant therapy
AE	adverse event
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CS	clinically significant
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ET	early termination
FSH	follicle stimulating hormone
GABA	γ-aminobutyric acid
HAM-D	Hamilton Rating Scale for Depression
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
IRB	institutional review board
IRT	interactive response technology
[redacted]	
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
NCS	not clinically significant
PHQ-9	9-item Patient Health Questionnaire
PK	pharmacokinetic(s)
[redacted]	
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event

Abbreviation or specialist term	Explanation
SAP	statistical analysis plan
SCID-5-CT	Structured Clinical Interview for Diagnostic and DSM-5 Clinical Trial Version
SD	standard deviation
[redacted]	
SUSAR	suspected, unexpected, serious adverse reactions
TEAE	treatment-emergent adverse event
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Major Depressive Disorder and Unmet Medical Need

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

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

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association 2013), 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, 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).

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.

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) associated with SAGE-217 (overall) were sedation, somnolence, and dizziness; 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.

5.3. Potential Risks and Benefits

The apparent risks of SAGE-217 are based on clinical data reports of adverse events in completed and ongoing studies and the known pharmacology of the drug. Sedation, somnolence, and dizziness were identified as adverse drug reactions. Most AEs were reported as mild or moderate in intensity and reversible.

SAGE-217 may present a treatment option for MDD that has more rapid onset of action (days instead of weeks), when compared to available therapies.

Based on nonclinical findings, embryo-fetal toxicity and withdrawal effects are considered important potential risk for SAGE-217. Risk mitigation measures in this study include monitoring for adverse effects, monitoring for potential withdrawal effects, requiring highly effective contraceptive measures for study participants, and inclusion of dose adjustment criteria and individual subject stopping criteria (Section 8.5.1). Finally, due to the sedation/somnolence observed, SAGE-217 is administered in the evening in this study.

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

5.4. Dose Justification

To date, the current capsule utilized in clinical studies is not associated with a maximum tolerated dose (MTD). Initial MTD assessments were performed using SAGE-217 in an oral solution (OS) at steady-state in healthy 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.

Study 217-MDD-301A, a randomized, multi-center, 3-arm study examining SAGE-217 20 and 30 mg capsules compared to placebo, found significant anti-depressant effects compared to placebo at Days 3, 8, and 12 but not Day 15 (primary endpoint) for the 30 mg dose. The 20 mg dose did not separate from placebo at any 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 adverse events were lower with SAGE-217 30 mg (2.1%) than with placebo (3.2%). No clinically relevant changes in vital signs, laboratory results, electrocardiogram measures, or suicidal thinking were observed in either 217-MDD-301A or across the full SAGE-217 program, now with over 2000 subjects exposed to treatment. Relevant results from 217-MDD-301A are available in the SAGE-217 Investigator's Brochure.

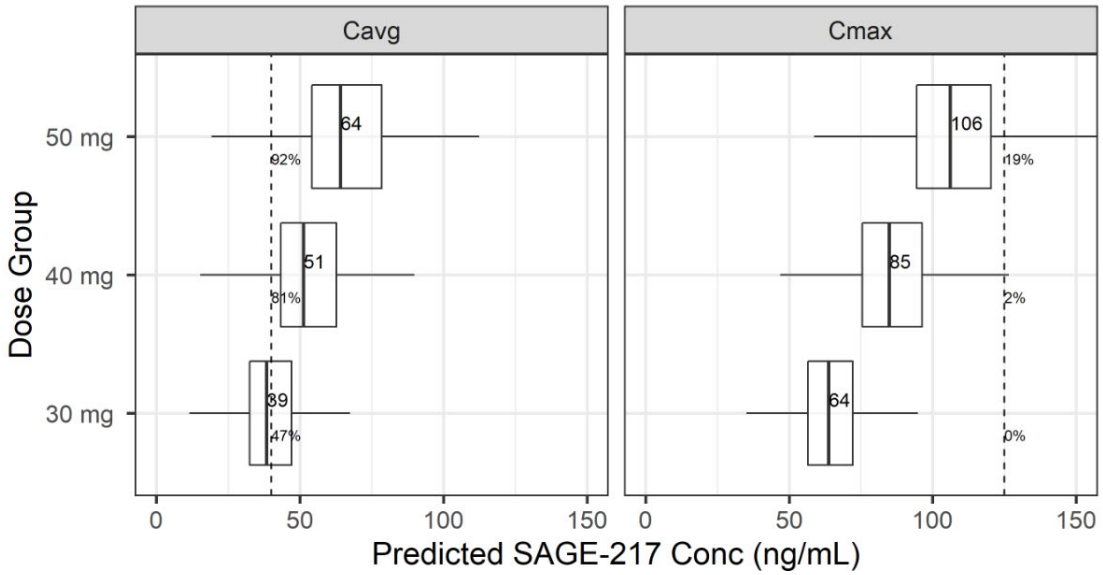
Direct and modeled data from completed studies to date (including efficacy studies 217-MDD-201 and 217-PPD-201) in addition to 217-MDD-301A (through Day 42 of the double-blind period), have been used to assess and predict the efficacy and safety outcomes at SAGE-217 concentrations expected with higher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

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

Direct evidence related to efficacy and safety outcomes following administration of SAGE-217 capsules at doses above 30 mg is further provided by results from a Phase 1, placebo-controlled study in healthy 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 maximally tolerated dose of the oral solution (125 ng/mL).

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

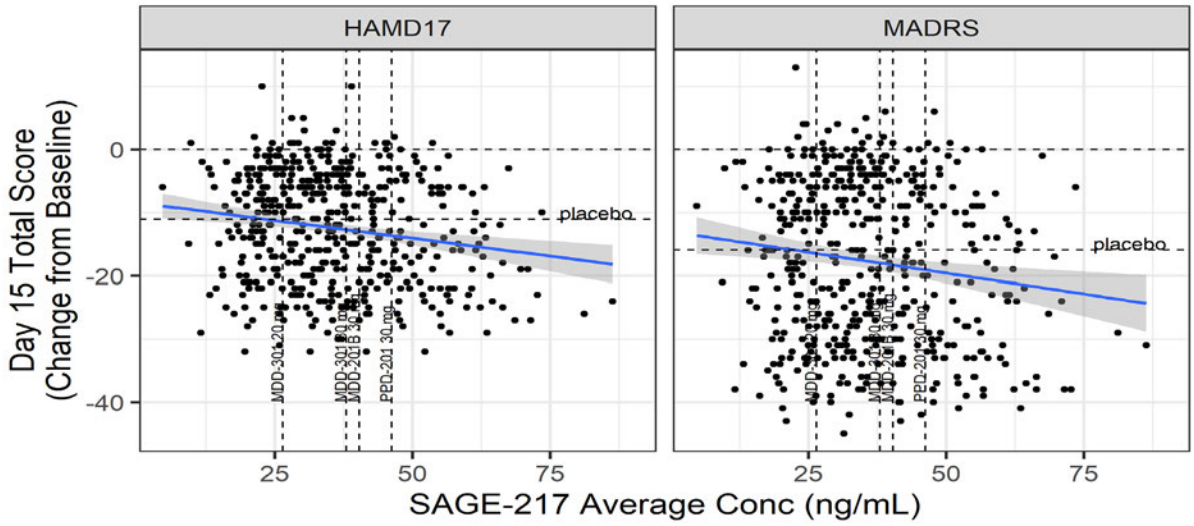


Dashed vertical lines represent target concentrations for efficacy (C_{avg} >40 ng/mL) and safety (C_{max}<125 ng/mL). Percentage next to dashed lines indicate the percentages with C_{avg}>40 ng/mL or with C_{max}>124 ng.

The selection of 50 mg dosed daily was based first on efficacy, enabling the largest number of 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-MDD-301A, and 217-PPD-201, increased concentrations of SAGE-217 were associated with a larger reduction in depressive symptoms (Figure 2). Based on linear regression modeling, effect sizes for HAM-D were dose dependent, with a 50 mg dose administered once daily for 14 days predicted to provide greater therapeutic benefit compared to daily doses of 40 and 30 mg. Based on the 217-MDD-301A results, a dose of 30 mg may be considered the minimally effective dose.

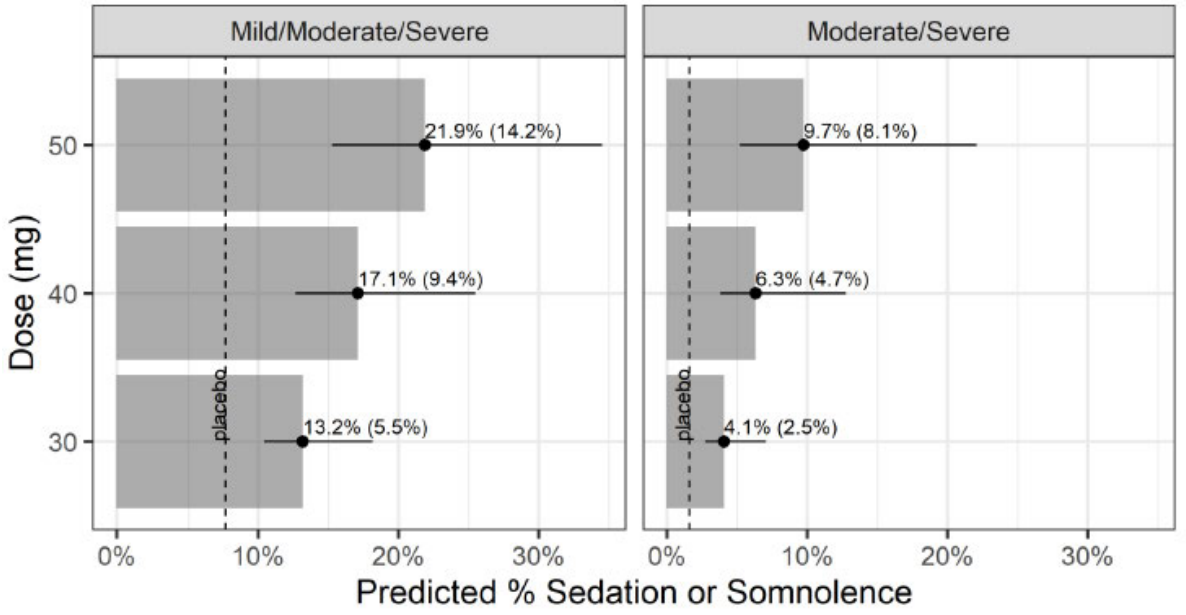
Figure 2: Total score change on Day 15 (Studies 217-MDD-201B, 217-MDD-301A, 217-PPD-201)



Solid blue line= linear regression line; shaded area=95% CI around the regression; horizontal dashed line=mean placebo response; Vertical dashed lines from left to right are average concentrations for 20 mg capsules 217-MDD-301A, 30 mg capsules MDD-301A, 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-301A, 217-MDD-201, and 217-PPD-201. The safety endpoint for modeling was selected as the incidence of sedation or somnolence during SAGE-217 treatment, as they represent on-target effects at the $GABA_A$ receptor and are the most commonly occurring adverse events with SAGE-217 when considering all doses and formulations. Logistic regression modeling indicated higher C_{max} values were associated with an increased incidence of sedation or somnolence across mild, moderate and severe intensities. Based on this observed relationship, the predicted incidence rates of sedation or somnolence were simulated at SAGE-217 doses of 30, 40 or 50 mg administered once daily (Figure 3).

Figure 3: Predicted incidence of sedation or somnolence by dose



Circle and solid line=point estimate and 95% prediction interval. Percentage on the right of 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 antidepressants. As with usual clinical practice, all 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 Study 217-CLP-113 exposed to 30 mg daily for 4 days, followed by a single dose of 60 mg achieved a mean plasma concentration of 97 ng/mL at 8.5 hours after dosing, suggesting the C_{max} experienced by these 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 over 2000 subjects exposed to SAGE-217 treatment.

In summary, recent results from a large, multicenter trial of SAGE-217 in MDD (217-MDD-301A) 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 over 2000 subjects exposed across different doses/concentrations. In addition, higher doses offer the potential for improved therapeutic benefit over the short 14-day treatment course.

According to the DSM-5, a period of 8 weeks is required to establish 'full remission' of a depressive episode (American Psychiatric Association 2013). Further, available antidepressant therapies (ADT) often take up to 8 weeks to exhibit maximal efficacy. Thus, a minimum period of 8 weeks (56 days) is required between the end of a 14-day treatment period and the beginning of a new SAGE-217 treatment cycle.

6. STUDY OBJECTIVES AND PURPOSE

The following objectives and endpoints will be evaluated in 2 separate study parts: Part A (de novo subjects who have their initial treatment cycle in the current study) and Part B (rollover subjects who have their initial treatment cycle in the parent study).

6.1. Study Objective

6.1.1. Primary Objective

The primary objective of this study is to determine the safety and tolerability of initial treatment and/or re-treatment(s) with SAGE-217 in adults with MDD experiencing a major depressive episode (MDE) at study entry for de novo subjects or at entry in the parent study for rollover subjects over a 1-year period.

6.1.2. Secondary Objectives

Secondary objectives of this study are:

- To assess the need for re-treatment with SAGE-217 following initial treatment in adults with MDD experiencing an MDE at study entry for de novo subjects or at entry in the parent study for rollover subjects over a 1-year period
- To assess the response of initial treatment and/or re-treatment(s) with SAGE-217 following an initial 2-week treatment period in adults with MDD experiencing an MDE at study entry for de novo subjects or at entry in the parent study for rollover subjects over a 1-year period

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6.2. Endpoints

6.2.1. Primary Endpoint

The primary endpoint of this study is the safety and tolerability of the initial treatment with SAGE-217 and re-treatment with SAGE-217, as assessed by measures including the incidence and severity of AEs/SAEs; changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); and suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS).

6.2.2. Secondary Endpoints

Secondary endpoints of this study are:

- The need for re-treatment with SAGE-217 as assessed by:
  - Time to first re-treatment (Kaplan-Meier curves)
  - Number of subjects achieving the requirements for re-treatment
  - Number of re-treatment cycles for each subject
- The response of initial treatment and/or re-treatment as assessed by:
  - Change from baseline in the 17-item HAM-D total score at the end of each 14-day treatment (initial and/or re-treatment) period
  - HAM-D response at the end of each 14-day treatment (initial and/or re-treatment) period, defined as a ≥50% reduction in HAM-D score from baseline
  - HAM-D remission at the end of each 14-day treatment (initial and/or re-treatment) period, defined as HAM-D total score ≤7
  - CGI-I response, defined as "much improved" or "very much improved", at the end of each 14-day treatment (initial and/or re-treatment) period
  - Change from baseline in Clinical Global Impression - Severity (CGI-S) score at the end of each 14-day treatment (initial and/or re-treatment) period.

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7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label, long-term, longitudinal study in adult subjects with MDD. With protocol amendment 5, this study will be conducted in 2 parts – Part A and Part B. Each part will enroll unique subjects and may be enrolled concurrently. Each study part is described below and schematics of the study designs are shown in Figure 4 and Figure 5.

Part A – de novo subjects

In Part A, de novo subjects currently experiencing an MDE will complete a Screening Period of up to 28 days, an Initial Treatment Period (14 days) and Follow-Up Period (14 days). Subjects achieving response or remission with SAGE-217 will be followed for 48 weeks (Observational Period).

The Screening Period for de novo subjects begins with the signature of the informed consent form (ICF); 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 (see Section 8.2).

The diagnosis of MDD must be made according to Structured Clinical Interview for 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.

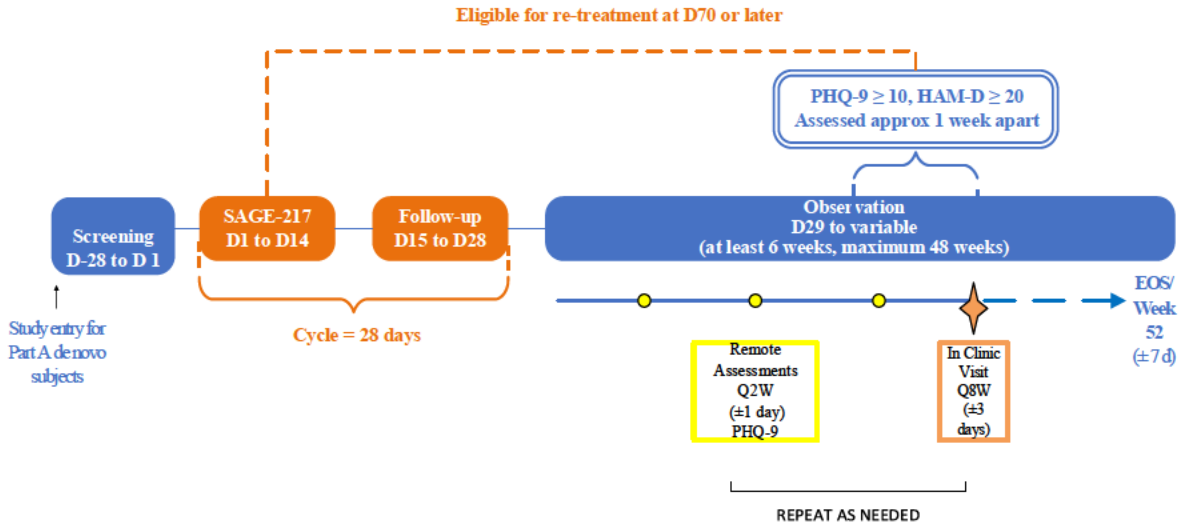
Beginning on Day 1, qualified subjects will self-administer study drug once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat or with a fat-containing snack) on an outpatient basis for 14 days.

During the initial treatment, antidepressants are permitted provided a subject is on a stable dose for at least 60 days prior to Day 1 and agrees to continue on the stable dose through at least the initial treatment and follow-up period. After the initial treatment period, subjects who respond (defined as a ≥50% reduction in HAM-D score from baseline) by Day 15 will be followed naturalistically for 48 weeks (see Figure 4 below).

If a subject does not exhibit a response to SAGE-217 by Day 15 of the initial treatment, the subject will be terminated from the study upon completion of the 14-day follow-up period.

Qualified subjects (ie, HAM-D Responders at Day 15) will return to the site every 8 weeks during the 48-week observational period for clinical assessments. A follow-up visit to collect any AEs and any concomitant medications and/or procedures, and to remind subjects to complete remote assessment(s) during the observational period will be conducted 14 days (±1 day) after the completion of the treatment period.

Figure 4: Part A Study Design Schematic



Note: For de novo subjects, the Observational Period only applies to those subjects who exhibit a HAM-D response by Day 15 with the initial treatment, defined as a ≥50% reduction in HAM-D score from baseline. De novo subjects who do not exhibit a HAM-D response by Day 15 of Cycle 1 will be terminated from the study upon completion of the Day 28 follow-up visit. De novo subjects who exhibit a HAM-D response by Day 15 of Cycle 1 will be eligible for re-treatment at Day 70 or later.

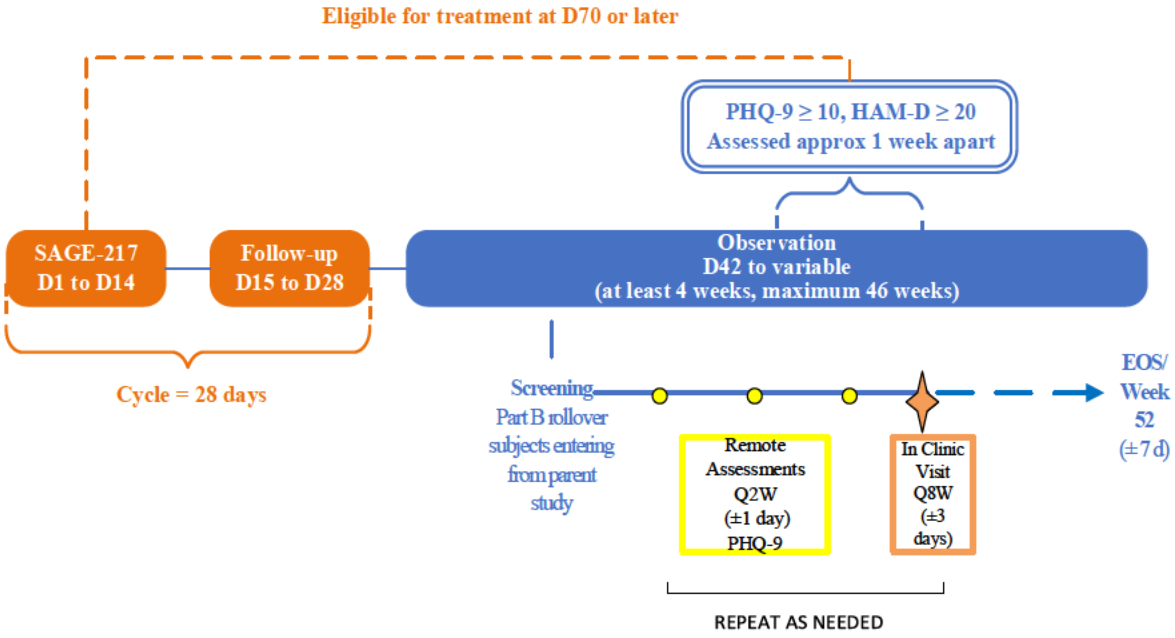
Part B – rollover subjects

In Part B, adults with MDD who have completed a Sage-sponsored randomized, double-blind, placebo-controlled study with a provision for rollover (parent study) will sign the ICF and be screened to determine eligibility to enter the study at the Day 42 visit during the Observational Period (see Table 3).

The Screening Visit may occur on the same calendar day as the End of Study Visit in the parent study; therefore, no assessments conducted for the final, EndofStudy Visit in the parent study will need to be repeated. If subjects do not enroll in the current study at the final, End of Study visit in the parent study, but complete the Screening Visit for the current study within 5 calendar days, the drug and alcohol screen and pregnancy test (female subjects only) should be repeated. Additional assessments may be conducted at the Screening Visit if necessary.

Subjects will return to the site every 8 weeks during the observational period for clinical assessments and be followed through the End of Study/Week 52 Visit. Rollover subjects may be eligible for treatment with SAGE-217 no sooner than Day 70. A Part B study schematic is shown in Figure 5.

Figure 5: Part B Study Design Schematic



Note: Part B rollover subjects enter the study at Day 42 during the Observational Period.

SAGE-217 treatment cycles (all subjects in Part A and Part B)

Each 14-day treatment period of SAGE-217 and corresponding 14-day follow-up period is considered a cycle (Day 28). For de novo subjects, the initial treatment is Cycle 1 and re-treatments will be numbered sequentially. Rollover subjects complete a double-blind treatment cycle in the parent study and enter the study during the Observational Period and therefore, do not complete Cycle 1 in the current study. If rollover subjects meet the criteria to receive SAGE-217 in the current study, they will start at Cycle 2. The dose of SAGE-217 administered during each new treatment cycle (initial or re-treatment) will be 50 mg or reduced dose of 40 mg, per criteria described in Section 7.4. Each cycle will begin with Day 1 (eg, the first day of the first re-treatment period will be Day 1 of Cycle 2). A maximum of 5 treatment cycles is permitted for de novo subjects; for rollover subjects, a maximum of 4 treatment cycles within Part B is permitted (ie, 4 cycles in the current study plus the initial double-blinded cycle in the parent study). A new re-treatment cycle cannot start after Week 48; subjects starting a new SAGE-217 treatment cycle between Weeks 45 and 48 will be followed through the end of the treatment cycle (Day 28, end of Follow-up period of treatment cycle). If a subject does not tolerate the 50 mg dose, and has been reduced to 40 mg, the subject may continue to receive the reduced dose of 40 mg for subsequent re-treatment cycles, as determined by the investigator.

The need for re-treatment will be assessed every 14 days via remote assessments during the 48-week observational period based on the results of the subject-reported PHQ-9; if the PHQ-9 score is ≥10, the subject will return to the site to be assessed by the clinician-administered HAM-D. New SAGE-217 cycles may be initiated for subjects with a HAM-D score ≥20 assessed

approximately 1 week from the PHQ-9 score ≥10. In all subjects, the End of Study/Week 52 Visit is mandatory if another scheduled on site visit does not fall in the Week 52 window.

A minimum period of 8 weeks (56 days) is required between SAGE-217 treatment periods. This is based on the period of 8 weeks establishing 'full remission' of a depressive episode (American Psychiatric Association 2013) and is aligned with the treatment period which would be required for any available antidepressant (ADT) to exhibit maximal efficacy. Rollover subjects, therefore, will not be eligible to begin their first SAGE-217 treatment period until 56 days has elapsed from the date of last dose of blinded study drug (SAGE-217 or placebo) administered in the parent study.

Details guiding the use of as-needed benzodiazepines and GABA-modulators for insomnia (eg, eszopiclone, zopiclone, zaleplon, and zolpidem), new ADT use, or increases in concomitant medication ADT dose are provided in Section 9.2.1.

As this is the first study in which longitudinal re-treatment with SAGE-217 will be examined, and based on known withdrawal symptoms with other GABAergic drugs and non-clinical findings in a 9-month study of SAGE-217 in dogs (Investigator's Brochure), the potential for withdrawal-related events, including seizure, will be monitored following the guidelines outlined in Section 8.5.1, which include study drug discontinuation or dose reduction.

If a subject exhibits suicidality at any time, they will return to the site as soon as possible for assessment by the Investigator.

The assessments for the Screening Period and Treatment and Follow-up Periods in Part A – de novo subjects are summarized in Table 1; the assessments for the Observational Period in Part A - de novo subjects are summarized in Table 2. The assessments for Screening and Observational Period in Part B - rollover subjects are summarized in Table 3; the assessments for the Treatment and Follow-Up Periods in Part B – rollover subjects are summarized in Table 4.

7.2. Number of Subjects

In Part A, approximately 1200 de novo subjects will be dosed (Section 13.7). An estimated 25% will not exhibit response/remission during the first treatment exposure, leaving 900 to be followed for 1 year, expected to result in at least 675 subjects followed for 6 months and 235 subjects followed for 1 year. In Part B, approximately 350 rollover subjects may be enrolled.

7.3. Treatment Assignment

This is an open-label study in which all subjects will receive SAGE-217.

7.4. Dose Adjustment Criteria

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. If a subject has been shown to not tolerate the 50 mg dose, and has previously been dose reduced to 40 mg, they may be started at the 40 mg dose for any needed subsequent re-treatments, as determined by the investigator.

At the discretion of the investigator, subjects who cannot tolerate the 40-mg dose at any time may be discontinued from dosing upon completion of an end of treatment (EOT) visit as soon as

possible. These subjects should be followed without any further administration of study drug in any subsequent cycle, and complete assessments per the schedules of events (Table 1, Table 2 Table 3, and Table 4).

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 IRB and initiate withdrawal procedures for participating subjects.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria – Part A de novo subjects

Qualified de novo 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 75 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 during any 14-day treatment period.
5. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
6. Subject has a MADRS total score of ≥28 and a HAM-D total score of ≥20 at Screening and Day 1 (prior to dosing).
7. Subjects taking antidepressants used to treat major depressive disorder 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 must have done so for at least 60 days prior to Day 1. Subjects receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1.
8. Female subject agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicular stimulation hormone [FSH] >40 mIU/mL), and/or surgically sterile (hysterectomy or bilateral oophorectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy.
9. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
10. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
11. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

8.2. Subject Exclusion Criteria – Part A de novo subjects

De novo 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 has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological], urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study. A body mass index (BMI) ≤18 or ≥45 kg/m^2 at Screening is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical co-morbidities (such as sleep apnea, chronic obstructive pulmonary disease [COPD]), concomitant medications, and prior tolerability of sedating agents.
3. 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 will be used for this purpose.
4. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine (including esketamine) within the current major depressive episode.
5. Subject is taking any of the following:
    a. benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, zolpidem, brexanolone) at Day -28,
    b. benzodiazepines, barbiturates, or $GABA_A$ modulators daily or near-daily (≥4 days per week) for 1 year, in the year prior to first dose of study drug,
    c. benzodiazepine or $GABA_A$ modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1
6. Subject is taking non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia, over-the-counter sleep aids, melatonin), first generation (typical) antipsychotics (eg, haloperidol, perphenazine) and/or second generation (atypical) antipsychotics (eg, aripiprazole, quetiapine) at Day -14. Note that antihistamines used during the day solely for indication(s) other than insomnia are permitted.
7. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
8. Subject has a positive pregnancy test at Screening or on Day 1 prior to the start of study drug administration for any treatment cycle.
9. Subject that is breastfeeding at Screening or on Day 1 (prior to administration of study drug) 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 in each treatment cycle.
10. Subject has detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at Screening.

11. 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.
12. Subject has active psychosis per Investigator assessment.
13. Subject has a medical history of seizures.
14. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
15. 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.
16. Subject has been taking chronic or as-needed psychostimulants (eg, methylphenidate, amphetamine) or opioids at Day -28.
17. Subject has had exposure to another investigational medication or device within 30 days prior to Screening.
18. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
19. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 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 for any SAGE-217 treatment cycle.
20. Use of strong CYP3A4 inducers within 28 days prior to the first dose of study drug for any SAGE-217 treatment cycle or planned use during any treatment cycle. Examples include: rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, and St John's Wort.
21. Subject has a positive drug and/or alcohol screen at Screening or on Day 1 prior to dosing of the initial treatment cycle.
22. Subject plans to undergo elective surgery during the initial treatment and follow-up period.
23. Subject has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) within the past year prior to Screening.
24. Subject has a history of sleep apnea.
25. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
26. Subject ≥65 years of age has a history of cognitive impairment, increased risk for falls (including but not limited to impaired balance and/or gait), or is already taking ≥2 CNS active drugs as per the American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.

8.3. Subject Inclusion Criteria – Part B rollover subjects

Qualified rollover 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 in good physical health and has no clinically significant findings, as determined by the investigator.
3. Subject has completed treatment with double-blind study drug and has completed the final (end-of-study) visit in the parent study.
4. Subject agrees to adhere to the study requirements, including not participating in night shift work during any 14-day treatment period.
5. Female subject agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicular stimulation hormone [FSH] >40 mIU/mL), and/or surgically sterile (hysterectomy or bilateral oophorectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy.
6. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
7. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
8. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

8.4. Subject Exclusion Criteria – Part B rollover subjects

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

1. Experienced major protocol deviations or adverse events in the parent study which could potentially compromise subject safety, in the investigator's opinion.
2. Subject is currently at significant risk of suicide, as judged by the Investigator, or has attempted suicide since enrolling in the parent study
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
4. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine (including esketamine) since enrolling in the parent study

5. Subject is taking first generation (typical) antipsychotics (eg, haloperidol, perphenazine), and/or second generation (atypical) antipsychotics (eg, aripiprazole, quetiapine) at Screening or within the time period between completion of the parent study and Screening.
6. Subject has taken an antidepressant other than sertraline, escitalopram, citalopram, duloxetine or desvenlafaxine within 60 days prior to Screening, including within the time period between completion of the parent study and Screening.
7. Subject has a known allergy to SAGE-217, brexanolone, allopregnanolone, or related compounds.
8. Subject has a positive pregnancy test at Screening.
9. Subject that is breastfeeding at Screening 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 in each treatment cycle, if applicable.
10. Subject has active psychosis per Investigator assessment.
11. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
12. Subject has a new history of severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria within the 12 months prior to Screening or within the time period between completion of the parent study and Screening; or subject has a history of mild or moderate substance use disorder not in sustained remission for at least 6 months prior to Screening.
13. Subject has taken psychostimulants (eg, methylphenidate, amphetamine) or opioids during the parent study or within the time period between completion of the parent study and Screening.
14. Subject has had exposure to another investigational medication (other than SAGE-217) or device during the parent study or within the time period between completion of the parent study and Screening.
15. Subject has a positive drug and/or alcohol screen at Screening.
16. Subject has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) during the parent study or within the time period between completion of the parent study and Screening.
17. History of poor compliance with the study drug and/or procedures in the parent study as determined by the Investigator

8.5. 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.

Subjects who discontinue study drug early during a treatment period should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. The follow-up visit should take place 14 days after the last dose of treatment. Thereafter the subject should continue the observational period as scheduled (Table 2 or Table 3).

If at any time during a follow-up period or the observational period, a subject decides to terminate the study, the subject should contact the site and complete their remote assessments at an early termination (ET) visit. An ET visit may be on the same day as an EOT visit if a subject discontinues study drug and terminates the study on the same day during a treatment period; in this case, all events scheduled for the EOT visit will be conducted.

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

8.5.1. Individual Subject Stopping Criteria

This is the first study in which longitudinal re-treatment with SAGE-217 will be examined. Based on known withdrawal symptoms with other GABAergic drugs and non-clinical findings in a 9-month study of SAGE-217 in dogs (Investigator's Brochure), there is a potential for withdrawal-related events, including seizure. The following guidelines for study drug discontinuation or dose reduction are presented to support subject safety:

1. Any subject reporting a confirmed or suspected seizure at any time will be discontinued from treatment and will not be eligible for another treatment cycle but will continue to be followed in the study.
2. Following the first treatment period, the Investigator should monitor the course of CNS-based signs and symptoms suggestive of a seizure which are not accounted for by comorbid psychiatric or medical conditions. Examples of reported serious or severe

events which may reflect an oncoming and/or increased risk for seizure may include temporary confusion, tremors, involuntary muscle fasciculations or jerking movements of arms or legs, or paresthesia. Should such symptoms occur, the investigator should consider decreasing the dose of study drug to 40 mg, stopping treatment to assess the effect on the symptom(s) (eg, resolution, improvement, etc), or discontinuing the subject from treatment. A subject who discontinues treatment should remain in the study and continue protocol-required assessments until the end of the study.

As this is an open-label study, any severe or serious events, will be evaluated in an ongoing manner, including an evaluation of the benefit/risk profile of SAGE-217 in the context of the current study. As a result, the Sponsor may modify or discontinue the study.

8.5.2. Replacement of Subjects

Subjects will not be replaced.

9. TREATMENT OF SUBJECTS

9.1. Study Drug

In treatment cycles initiated prior to 217-MDD-303 Protocol Amendment 3, subjects were to self-administer SAGE-217 (30 mg or reduced dose of 20 mg, per criteria in Section 7.4) orally once daily in the evening with food for 14 days.

After 217-MDD-303 Protocol Amendment 4, in all treatment cycles all subjects will self-administer SAGE-217 50 mg (or reduced dose of 40 mg, per criteria in Section 7.4) orally once daily at approximately 8 PM with fat-containing food for 14 days. The 50-mg dose will be administered as 2 capsules per dose (one 30-mg capsule and one 20-mg capsule). If the dose is reduced to 40 mg, it will be administered as two 20-mg capsules.

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 (for subjects in Part A only) and throughout the duration of the study (for all subjects) will be recorded. In addition, antidepressant therapies taken in the 3 years prior to Screening will be recorded for subjects in Part A only.

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.

For Part A de novo subjects, 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 the initial treatment and follow-up period (through Day 28 of Cycle 1). De novo subjects who have stopped taking antidepressants must have done so for at least 60 days prior to Day 1.

For Part B rollover subjects, antidepressant use within 60 days prior to Screening other than sertraline, escitalopram, citalopram, duloxetine or desvenlafaxine is not permitted. Use of these antidepressants throughout the study is permitted.

See Table 5 for allowed concomitant psychotropic medications during each period of the study for both study parts.

9.2.1.1. Medication use for depressive symptom worsening following a SAGE-217 treatment cycle

Study 217-MDD-201, Part B, found that for subjects achieving remission or response at Day 15 (78.6%), 6.1% had a HAM-D ≥22 at Day 42; another 18.2% had a HAM-D score of 16 to 21 at Day 42 (Data on File, Sage Therapeutics). This indicates that most subjects who may experience a new MDE will have this experience after they reach the minimal required period (8 weeks or 56 days) before a new SAGE-217 treatment cycle. Because of this, most subjects will be eligible (ie, PHQ-9 ≥10 and HAM-D ≥20 confirmed over 2 weeks) for a SAGE-217 treatment cycle when needed; a 2-week period is required to establish a new MDE (DSM-5).

For de novo subjects who experience worsening depressive symptoms after Day 28 or for rollover subjects who experience worsening depressive symptoms after Screening and are not yet

eligible for a new SAGE-217 treatment cycle, there are 2 intervention options: as-needed medications (limited to a maximum of 4 days per week) and/or introduction of a new ADT or an increase in the dose of a current ADT (Table 5). To maintain equivalence in clinical status across all ADT use (ie, new SAGE-217, new ADT, or increase dose of current ADT), a requirement for PHQ-9 ≥10 and HAM-D ≥20 confirmed over 2 weeks will be required in all ADT use conditions. If a subject on a stable ADT is experiencing worsening depressive symptoms (PHQ-9 ≥10), it is recommended that only as-needed medications be used if the HAM-D score is <20; if the HAM-D score is ≥20, the current dose may be increased or a new ADT may be introduced. Furthermore, clinicians should consider an individual subject's initial experience with SAGE-217 when starting any new ADT, as it may substantially reduce the likelihood that the subject will be eligible for a new SAGE-217 treatment cycle once time allows (ie, HAM-D may be <20). There is no PHQ-9 or HAM-D score requirement for as-needed medication use.

Permitted as-needed medications for symptom management include benzodiazepines, GABA-modulators for insomnia (eg, eszopiclone, zopiclone, zaleplon, and zolpidem), and non-GABA treatments for insomnia; use of such treatments should be limited to a maximum of 4 days per week.

If as-needed medications and/or a new ADT was introduced or the dose of a current ADT was increased and the subject continues to exhibit a HAM-D ≥20, a new SAGE-217 treatment cycle can be initiated at Day 70 or later. After completion of a new SAGE-217 cycle, continued use of any intervention(s) used during the previous Observational Period will be at the investigator's discretion.

Any benzodiazepines and/or GABA-modulating medication use during the Observational Period must be stopped 7 days prior to any new SAGE-217 treatment cycle. As-needed non-GABA modulating medication use must be discontinued 1 day prior to any new SAGE-217 treatment cycle.

Medications intended for contraception are permitted for female subjects (see Section 8.1).

Table 5: Allowed Concomitant Psychotropic Medications During the Study (Part A and Part B)

Period	Timing (Part A)*	Timing (Part B)	Psychotropic medications allowed	Rationale
SAGE-217 Treatment	Day 1 to 14	Day 1 to 14	• SAGE-217 • Stable ADT • No as-needed medications[a] • No new ADT	Assess SAGE-217 response
SAGE-217 Follow-up	Day 15 to 28	Day 15 to 28	• Stable ADT • No as-needed medications[a] • No new ADT	Assess SAGE-217 safety in follow-up
Observation	Day 29 to 7 days prior to next SAGE-217 treatment cycle, if applicable	• At study entry (first observational period): Screening to 7 days prior to SAGE-217 treatment cycle, if applicable • For any subsequent observational period: Day 29 to 7 days prior to next SAGE-217 treatment cycle, if applicable	• Benzodiazepines ($t_{1/2}$ <48 hours; regular or as-needed) • As-needed GABA-modulators for insomnia ($t_{1/2}$ <48 hours)	• Establish 'full remission' • Assess symptom course over time
	Day 29 to 1 day prior to next SAGE-217 treatment cycle, if applicable	• At study entry (first observation period): Screening to 1 day prior to SAGE-217 treatment cycle, if applicable • For any subsequent observational period: Day 29 to 1 day prior to SAGE-217 treatment cycle, if applicable	• As-needed non-GABA-modulating treatments for insomnia	
	Day 29 through next SAGE-217 treatment cycle, if applicable	• At study entry (first observational period): Screening through SAGE-217 treatment cycle, if applicable • For any subsequent observation period: Day 29 through next SAGE-217 treatment cycle, if applicable	• Stable ADT • New ADT (except benzodiazepines)[b]	

[a] As-needed medications (benzodiazepines, GABA-modulators for insomnia [eg, eszopiclone, zopiclone, zaleplon, and zolpidem], and non-GABA treatments for insomnia [eg melatonin, over-the-counter sleep aids, trazodone, mirtazapine, etc]) should be limited to a maximum of 4 days per week.

[b] If a subject on a stable ADT is experiencing worsening depressive symptoms (PHQ-9 ≥10), it is recommended that only as-needed medications be used if the HAM-D score is <20; if the HAM D score is ≥20, the current ADT dose may be increased or a new ADT may be introduced.

*Timing relative to the initial/previous cycle of SAGE-217

ADT = antidepressant; Stable ADT = ADT started prior to study and continued at baseline or any new ADT started during an observation period and continued thereafter through a new SAGE-217 cycle; $t_{1/2}$ = half-life

9.2.2. Prohibited Medications

The following medications are prohibited at the specified times:

- See Table 5 for timing of psychotropic medications
- For Part A de novo subjects: benzodiazepines, barbiturates, $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, zolpidem, brexanolone), or GABA-containing 'over the counter' supplements in relationship to the first SAGE-217 treatment cycle: from 28 days prior to the first dose of SAGE-217 through the 14-day follow-up period; thereafter, these medications are prohibited in the 7 days prior to any new SAGE-217 treatment cycle and through the follow-up period of the cycle. For Part B rollover subjects, these agents are prohibited in the 7 days prior to any SAGE-217 treatment cycle and through the follow-up period of the cycle. For de novo subjects, any benzodiazepine or GABA modulator with a half-life of ≥48 hours is prohibited from 60 days prior to the first dose of SAGE-217 and throughout the duration of the study. For rollover subjects, these agents are prohibited at Screening and throughout the duration of the study.
- For Part A de novo subjects, first generation (typical) (eg, haloperidol, perphenazine) or second generation (atypical) antipsychotics (eg, aripiprazole, quetiapine)are prohibited from 14 days prior to the first treatment cycle and throughout the duration of the study; for Part B rollover subjects, these agents are prohibited at Screening and throughout the duration of the study.
- For Part A de novo subjects, non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia, over-the-counter sleep aids, melatonin) from 14 days prior to the first dose of SAGE-217 through the first 14-day treatment period; thereafter, these medications are prohibited 1 day prior to any new SAGE-217 treatment cycle and through the follow-up period of the cycle. For Part B rollover subjects, these agents are prohibited 1 day prior to any SAGE-217 treatment cycle and through the follow-up period of the cycle. Note that antihistamines used during the day solely for indication(s) other than insomnia are permitted for both de novo and rollover subjects.
- For Part A de novo subjects, the use of chronic or as-needed psychostimulants (eg, methylphenidate, amphetamine) or opioids from 28 days prior to the first treatment cycle and throughout the duration of the study; for Part B rollover subjects, these agents are prohibited during the parent study, within the time period between

completion of the parent study and Screening, and throughout the duration of the study.

- For Part A de novo subjects, exposure to another investigational medication or device from 30 days prior to Screening and throughout the duration of the study; for Part B rollover subjects, exposure to another investigational medication (other than SAGE-217) or device is prohibited during the parent study, within the time period between completion of the parent study and Screening, and throughout the duration of the study.
- Any known strong inhibitors of CYP3A4 within 28 days or 5 half-lives (whichever is longer) prior to a cycle of SAGE-217 and any time during a SAGE-217 treatment cycle.
- Use of strong CYP3A inducers such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, and St John's Wort within 28 days prior to a cycle of SAGE-217 and any time during a SAGE-217 treatment cycle.

9.2.3. Other Restrictions

The consumption of grapefruit juice, grapefruit, or Seville oranges, or products containing these is prohibited within 14 days prior to a cycle of SAGE-217 and at any time during a treatment cycle.

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

Female subjects that are lactating or actively breastfeeding must stop giving breast milk to the baby(ies) from just prior to receiving study drug until 7 days after the last dose of study drug following each treatment period, if applicable.

Elective surgeries are prohibited during the initial treatment and follow-up period (through Day 28 of Cycle 1; Part A de novo subjects only).

Subjects must not participate in night shift work during any 14-day treatment period.

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

De novo 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 therapy through at least the first 14-day follow-up period. Rollover subjects receiving psychotherapy on a regular schedule at Screening are permitted.

9.2.4. Acceptable Forms of Contraception

Acceptable forms of highly effective contraception for participants of childbearing potential or for partners of male participants who are of childbearing potential include:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation

- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Laparoscopic or abdominal occlusion procedure (including bilateral tubal ligation)
- Hysteroscopic bilateral tubal occlusion procedure performed at least 3 months prior to Screening
- Vasectomized partner (performed at least 3 months prior to Screening)

Acceptable forms of contraception for male participants include:

- Sexual abstinence (no sexual intercourse)
- History of vasectomy (performed at least 3 months prior to Screening)
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

9.3. Treatment Adherence

SAGE-217 will be self-administered by subjects once daily at approximately 8 PM with fat-containing food during the 14-day treatment periods (see Section 10.5). Sites will dispense study drug to the subjects to take at home with instructions for use (see Section 10.6, Table 1, and Table 4).

Subjects will be instructed to bring their dosing kit to the site as outlined in Table 1 and Table 4, 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 dosing instructions at clinic visits during any SAGE-217 treatment period. 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 an open-label study in which all subjects will receive SAGE-217.

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, colloidal silicon dioxide, and sodium stearyl fumarate as excipients. Capsules will be available in 20-mg and 30-mg dose strengths.

10.2. Study Drug Packaging and Labeling

SAGE-217 will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the study drug in appropriately labeled, subject-specific kits containing sealed unit doses. Each unit dose for 30-mg treatment cycles consists of 1 capsule, and each unit dose for 40-mg and 50-mg treatment cycles consists of 2 capsules. 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 is to be stored at room temperature (59 to 86°F; 15 to 30°C), safely and separately from other drugs.

10.4. Study Drug Preparation

Not applicable.

10.5. Study Drug Administration

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

If a 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 the next evening.

10.6. Study Drug Accountability

Upon receipt of study drug, the Investigator(s), or the responsible pharmacist or designee, will inspect the study drug and complete and follow the instructions regarding receipt in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the supplied subject-specific kits to subjects at the planned dispensation visit intervals outlined in Table 1 and Table 4.

Site staff will access the interactive response technology (IRT) at the Screening Visit to obtain a subject 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 enroll the eligible subject into the initial treatment cycle 1 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 visits for any other treatment cycles, 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 complain 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 the table on page 5. Where possible, personnel should segregate any product, materials or packaging associated with the product complaint.

11. ASSESSMENT OF EFFICACY

All assessments will be conducted according to the schedules of events (Table 1, Table 2 Table 3, and Table 4). 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. Every effort should be made for the same rater to perform the assessments at all visits for a particular subject. For rollover subjects, assessments in the current study should, if possible, be conducted by a different rater than the one who performed the assessments in the parent study.

11.1. Response Parameters

11.1.1. Hamilton Rating Scale for Depression

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. An assessment timeframe of 7 days will be used for all visits.

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

The HAM-D subscale scores will be calculated as the sum of the items comprising each subscale. A response will be defined as having a 50% or greater reduction from baseline in HAM-D total score. Remission will be defined as having a HAM-D total score of ≤7.

11.1.2. Clinical Global Impression

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."

[redacted]

11.1.4. 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 total 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.

[redacted]

[redacted]

[redacted]

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

All assessments will be conducted according to the schedules of events Table 1, Table 2, Table 3, and Table 4).

12.1.1. Demographic/Medical History

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including family psychiatric history, will be documented. For Part B rollover subjects, demographic characteristics and medical history will be obtained from the parent study. Interim medical history (ie, any new medical conditions or procedures with onset/start date after completion of the parent study and prior to signing informed consent in the current study) will also be documented for rollover subjects. For Part A de novo subjects only, 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 should be recorded.

For Part A de novo subjects only, the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire 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.

For Part A de novo subjects only, the severity of the depressive episode upon entry into the study will be evaluated using the MADRS, a 10-item diagnostic questionnaire. The MADRS total score will be calculated as the sum of the 10 individual item scores.

12.1.2. Weight and Height

Height (Screening only) and weight will be measured and documented. For Part B rollover subjects, height will be obtained from the parent study.

12.1.3. Physical Examination

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

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

12.1.4. 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 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?

12.1.5. 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

Supine 12-lead ECGs will be performed in triplicate at all scheduled time points. The standard parameters (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded.

Any abnormality in ECG intervals will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents. New or worsening abnormalities that are judged to be CS will be recorded as AEs, assessed according to Section 12.2.1.1.

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 6.

Table 6: 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 Thyroid stimulating hormone (TSH) Reflex to free T3/T4 if TSH is abnormal	pH Specific gravity Color Protein Glucose Red blood cell Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio
Diagnostic			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C Reflex HCV RNA HIV-1 and -2 Female subjects who 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 who 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 sub-investigator 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 NCS before proceeding with dosing.

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 CS will be recorded as AEs, assessed according to Section 12.2.1.1. A CS laboratory abnormality following dosing will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

For Part A de novo subjects only, a serum FSH 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). Postmenopausal status will be obtained as necessary from the parent study for Part B rollover subjects.

[redacted] These samples will be analyzed for effects on the kynurenine pathway and markers of inflammation, both previously implicated in depression. [redacted] Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (eg, CYP supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (eg, AKR1C4 [3a-hydroxysteroid dehydrogenase]), genes associated with the GABA receptor (eg, GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA. Additional unnamed biochemical biomarkers, genes, or gene categories as related to disease susceptibility and drug action may be analyzed, as future research may suggest novel candidates for influencing response to SAGE-217 and/or susceptibility to disorders for which SAGE-217 may be evaluated.

12.1.7.1. Drugs of Abuse and Alcohol

Urine toxicology tests will be performed for selected drugs of abuse (see Table 6). A breath test for alcohol will be performed.

12.1.7.2. Pregnancy Screen

In Part A, for de novo female subjects a serum pregnancy test will be performed at Screening; a urine pregnancy test will be performed in females who are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal at all other scheduled timepoints

thereafter, as outlined in Table 1 and Table 2, including the ET visit for subjects who prematurely discontinue.

In Part B, for rollover female subjects who complete the Screening Visit on the same day as the final, end-of-study visit in the parent study, a pregnancy test does not need to be repeated. If the Screening Visit is not conducted on the same day as the final, End of Study Visit in the parent study, a urine pregnancy test should be conducted. Urine pregnancy tests will be performed in females who are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal at all other scheduled timepoints, as outlined in Table 3 and Table 4 including the ET Visit for subjects who prematurely discontinue.

12.1.8. Columbia-Suicide Severity Rating Scale

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).

In Part A, 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 in Part A and in Part B, as outlined in Table 1, Table 2, Table 3, and Table 4.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

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 CS. Laboratory values and vital signs that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations that are clearly

attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

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

12.2.1.2. Serious Adverse Event

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). 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 7: 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. For subjects in Part B, ongoing adverse events with onset during the parent study will also be recorded at the Screening Visit. 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 on the Sage Therapeutics pregnancy outcome form, even if the subject was discontinued from the study. If the pregnancy ends for any reason before the anticipated date, the investigator should notify Sage.

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. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly/birth defects), the investigator should follow the procedures for reporting an SAE.

12.5. Reporting Serious Adverse Events

All SAEs must be reported to Sage, or designee, immediately. A written account of the SAE must be sent to Sage, or designee, within 24 hours of the first awareness of the event by the investigator and/or his staff. The Investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Sage, or designee.

Additional follow-up information, if required or available, should all be sent to Sage Therapeutics, or designee, within 24 hours of receipt on a follow-up SAE report form and placed with the original SAE information and kept with the appropriate section of the case report form 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 IRB 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. Institutional Review Boards will be notified of SAEs and/or SUSARs as required by local law.

12.6. Overdose

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, 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

Separate statistical analysis plans (SAP) will be generated for each part of the study and will provide a detailed description of the analyses to be performed in the study. For Part B rollover subjects, the parent study database will be used in analysis. The SAP for each study part will be finalized and approved prior to database lock for respective parts. The data for Part A de novo subjects may be analyzed and reported prior to database lock for Part B rollover subjects. Any deviations from or changes to the SAPs following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

Part A (de novo subjects)

The Safety Set is defined as all subjects administered study drug.

The Full Analysis Set (FAS) s is defined as all subjects in the Safety Set who completed Treatment Cycle 1 and moved on to Observational Period 1 (ie, these subjects had HAM-D response at Day 15 and did not discontinue the study for any reason within Treatment Cycle 1).

In addition, the cohorts of subjects who started with the 30-mg dose versus the 50-mg dose may be analyzed separately for de novo subjects.

Part B (rollover subjects)

The Safety Set is defined as all subjects administered study drug.

The FAS is defined as all subjects in the Safety Set who have at least one HAM-D total score available after the first dose of study drug within this protocol.

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.

13.3. General Considerations

For the purpose of all analyses where applicable, baseline will be defined as the latest value before the first dose of study drug in Cycle 1 for de novo subjects. A period-specific baseline will be defined as the latest value before the first dose of study drug in each treatment cycle.

For rollover subjects, the first cycle of treatment in this study will be marked in the database as Cycle 2. For purposes of analysis, the treatment cycles and study periods within this protocol will be renumbered as 1-4 for subjects who received placebo in the parent study.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), median, minimum, and maximum. In addition, change from baseline and/or period-specific 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, 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, including interim medical history for Part B rollover subjects (see Section 12.1.1), will be listed by subject.

13.5. Response Analyses

For de novo subjects, response analyses for the first treatment cycle will be provided based on the Safety Set. Subjects who do not achieve HAM-D response at Day 15 (at least 50% reduction from baseline HAM-D total score or missing Day 15 HAM-D) will be discontinued from the study after the 14-day follow-up period with treatment cycle 1.

Using the Full Analysis Set, Kaplan-Meier (KM) survival curve will be provided for time to first re-treatment; the estimand is the median time to first re-treatment -time from the last dose of study drug in Cycle 1 to first dose of study drug in Cycle 2- for de novo subjects and will be estimated from KM analysis. Number and percentage of subjects needing at least one re-treatment (ie, meeting the criteria for re-treatment, but not necessarily retreated) will be provided. Number of treatment cycles per subject will be summarized.

For rollover subjects, using the Full Analysis Set, KM survival curve will be provided for time to first re-treatment; the estimand is the median time to first re-treatment -time from the last dose of study drug in Cycle 1 to first dose of study drug in Cycle 2 - and will be estimated from KM analysis. Number and percentage of subjects needing at least one re-treatment (ie, meeting the criteria for re-treatment, but not necessarily retreated) will be provided. Number of treatment cycles per subject will be summarized.

Change from baseline, and/or from period-specific baseline when appropriate, in HAM-D total score and subscale scores will be summarized by each treatment cycle. 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) will be summarized for each treatment cycle. Change from baseline, and/or from period-specific baseline when applicable, in CGI-S will be summarized for each treatment cycle. CGI-I will be summarized for each treatment cycle.

[redacted]

13.6. Safety Analyses

The primary endpoint, the safety and tolerability of SAGE-217, will be evaluated by incidence and severity of AEs/SAEs, concomitant medication usage, vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. In addition to overall study results, the results from each treatment cycle will be provided separately whenever applicable. Safety analyses will use the Safety Set for overall safety.

A study period is defined as a treatment cycle and its subsequent observation period; the Safety Set for a given study period includes subjects in the Safety Set who are dosed in the respective

study period. Safety analyses will be provided based on the Safety Set for each study period within this protocol when appropriate.

13.6.1. Adverse Events

The analysis of adverse events will be based on the concept of TEAEs. The incidence of TEAEs will be summarized overall and by Medical Dictionary for Regulatory Activities Version 21.0 or higher, System Organ Class, 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 and/or modified baseline will be summarized in standard units for each treatment cycle. Normal range of each parameter is provided by the laboratory; shift from baseline (and/or period-specific baseline) to post-baseline values in abnormality of results will be provided. Potentially CS values will be summarized. 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

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 and/or period-specific baseline in vital signs will be summarized for each treatment cycle. Any abnormality deemed CS by the Investigator will be reported as an AE (see Section 12.2). Potentially CS values will be summarized. 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 CS abnormalities or changes in mean ECGs should be reported as an AE (see Section 12.2). Mean ECG data will be summarized by visit for each treatment cycle. Potentially CS values of QTcF will be summarized. Electrocardiogram findings will be listed by subject and visit for each treatment cycle.

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 September 2015, or later.

The medications taken prior to the initiation of the start of study drug within each part of the study 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.

Anxiolytics, anti-insomnia, and/or antidepressant drug use between treatment cycles will be summarized, and such use may be explored with respect to the need for re-treatment with SAGE-217, response to SAGE-217, and safety of SAGE-217. In particular, for de novo subjects only, the time to first anxiolytic or anti-insomnia use, and time to first antidepressant use will be provided with KM plots. .

13.6.7. Columbia Suicide Severity Rating Scale

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

13.7. Determination of Sample Size

The sample size is not based on a formal sample size calculation. The sample size of 1200 de novo subjects in Part A was chosen in order to have at least 675 subjects complete 24 weeks of the study and at least 235 subjects complete through 56 weeks, consistent with the objective of assessing SAGE-217 long-term safety. Approximately 350 subjects are expected to rollover from the parent study and enroll in 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 Institutional Review Board (IRB) 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

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB 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. 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 of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB 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 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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