Official Title: A Phase 3, Randomized, Double-Blind, Placebo-controlled Study of The Efficacy And Safety Of Sage-217 With a Fixed, Repeated Treatment Regimen on Relapse Prevention in Adults With Major Depressive Disorder

NCT Number: NCT04007367

Document Date: Protocol Amendment 1, Version 2.0, 29 August 2019

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF SAGE-217 WITH A FIXED, REPEATED TREATMENT REGIMEN ON RELAPSE PREVENTION IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

PROTOCOL 217-MDD-302

EUDRACT NUMBER: 2019-002640-25

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, PhD, MSc Tel: [redacted] E-mail: [redacted]
Date of Original Protocol	Version 1.0, 24 June 2019
Date of Amendment 1	Version 2.0, 27 August 2019

Confidentiality Statement

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

Protocol Number:	217-MDD-302
Study Drug:	SAGE-217
Study Phase:	Phase 3
Sponsor:	Sage Therapeutics, Inc.
Protocol Date:	Version 2.0, 27 August 2019

Sponsor Approval

[redacted]

28 Aug 2019
[redacted], MD, PhD, MSc — Date (DD MMM YYYY)

28 Aug 2019
[redacted] RAC — Date (DD MMM YYYY)

for 28 Aug 2019
[redacted] — Date (DD MMM YYYY)

for 29 Aug 2019
[redacted], PhD — Date (DD MMM YYYY)

29-AUG-2019
[redacted] DVM, MS, MPH — Date (DD MMM YYYY)

27AUG2019
[redacted] — Date (DD MMM YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-MDD-302 clinical protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed name of Investigator

_____

Signature of Investigator

_____

Date (DD Month YYYY)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Syneos Health Medical Monitor – North America	[redacted], MD	Email: [redacted] Office: [redacted] Cell: [redacted]
Syneos Health Medical Monitor – Europe	[redacted], MD, MPH	Email: [redacted] Office: [redacted]
Sage Study Physician	[redacted], MD, PhD, MSc	Email: [redacted] Tel: [redacted]
24-Hour Serious Adverse Event Reporting	IQVIA Lifecycle Safety	Email: Sage.Safety@iqvia.com Telephone Fax North America, United Kingdom, Germany: [redacted] alt: [redacted] Pause [redacted] alt: [redacted] Pause [redacted] France, Spain, Denmark: [redacted]
Product Complaint Reporting	Sage Therapeutics, Inc.	Email: productcomplaints@sagerx.com Tel: [redacted]

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, Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of SAGE-217 with a Fixed, Repeated Treatment Regimen on Relapse Prevention in Adults with Major Depressive Disorder

Number of Sites and Study Location: This is a global study that will take place at approximately 70 sites in the United States, Canada, and Europe.

Phase of Development: 3

Planned Duration of Subject Participation:
The planned duration of subject participation is up to 52 weeks, including a Screening Period (up to 4 weeks), an Open-label (OL) Phase (8 weeks), and a Double-blind (DB) Phase (40 weeks)

Objectives:
Primary:

- To evaluate the efficacy of SAGE-217 with a fixed, repeated treatment regimen in the prevention of relapse in subjects with major depressive disorder (MDD) who have responded to OL treatment with SAGE-217

Secondary:

- To evaluate the long-term safety and tolerability of a fixed, repeated treatment regimen of SAGE-217 up to 1 year
- [redacted]
- [redacted]
- [redacted]

Endpoints:
Primary:

- Time to relapse during the DB Phase (days; from first dose of study drug in the DB Phase to relapse [date] during the DB Phase)

Secondary:

- Percentage of subjects who relapse during the DB Phase
- Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at the end of each 14-day treatment period in the DB Phase.
- HAM-D response at the end of each 14-day treatment period in the DB Phase, defined as a ≥50% reduction in HAM-D score from baseline
- HAM-D remission at the end of each 14-day treatment period in the DB Phase, 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 period in the DB Phase
- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at the end of each 14-day treatment period in the DB Phase
- Change from baseline in 9-item Patient Health Questionnaire (PHQ-9) score at the end of each 14-day treatment period in the DB Phase
- Time to relapse during the DB phase (days; from first dose of study drug in DB Phase to relapse [date] during the DB Phase) for subjects who achieved HAM-D remission in the OL Phase
- Incidence of treatment-emergent adverse events (TEAEs)

[redacted]

Study Description:

This is a study with an OL phase followed by a randomized, DB, placebo-controlled phase to assess the effect of SAGE-217 monotherapy in a fixed, repeated treatment regimen versus placebo on relapse prevention in adult subjects with MDD (Montgomery-Åsberg Depression Rating Scale [MADRS] ≥32, HAM-D ≥22) who are not currently taking antidepressants. See Figure 1 for a schematic of the study design.

The Screening Period (Table 2) begins with the signature of the informed consent form (ICF); the ICF must be signed prior to beginning any screening activities. The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the MADRS, HAM-D, and CGI-S.

Beginning on Day 1 of the OL Phase, eligible subjects will self-administer a single dose of study drug once daily in the evening with food, on an outpatient basis, for 14 consecutive days. Practical options include taking SAGE-217 within 1 hour of dinner or taking SAGE-217 later in the evening with solid food. Subjects will return to the study center during the OL treatment and follow-up periods as outlined in Table 3.

Subjects who complete the OL Phase (through Day 56) with no significant tolerability issues as judged by the Investigator and who exhibited a HAM-D response, defined as a ≥50% reduction from baseline in HAM-D total score, at Visits 4, 6, 7, and 8 (see Table 3) will be eligible for the DB Phase. One excursion of <50% reduction from baseline (but total score ≤21) in HAM-D total score or one missing HAM-D total score at Visit 6 or 7, will be permitted for eligibility to the DB Phase.

Beginning on Day 1 of the DB Phase, eligible subjects will be randomized to receive SAGE-217 30 mg or matching placebo in a 1:1 ratio. The 40-week DB Phase consists of five 14-day treatment periods, each separated by a 6-week follow-up period; the end of each follow-up period coincides with the first visit of the next treatment period. During the 14-day treatment periods, subjects will self-administer a single dose of study drug once daily in the evening with food, on an outpatient basis. Subjects will return to the study center during the DB treatment and follow-up periods as outlined in Table 3.

During the follow-up periods of the DB Phase, depressive symptoms will be monitored every 7 (+3) days via remote PHQ-9; if the PHQ-9 score is ≥10, the subject will return to the site as soon as possible to be assessed by the clinician-administered HAM-D (Table 4). If the HAM-D is ≥18 at this visit, the subject will return to the site in 7 to 14 days to be reassessed by the HAM-D (Table 4); if the HAM-D remains ≥18, the subject will be considered to have relapsed at this visit. A summary of all events for which a subject may be considered to have relapsed is presented in the table below. Final determination of relapse will be made by an Independent Relapse Adjudication Committee (IRAC) for events other than 2 consecutive HAM-D scores ≥18 assessed 7 to 14 days apart.

Summary of Events Which May Result in Relapse

Event	Requires Review by IRAC?
2 consecutive HAM-D scores ≥18 assessed 7 to 14 days apart	No
Any worsening of depression requiring hospitalization	Yes
Any Investigator-determined risk of suicide	Yes
Worsening of overall depressive symptoms as measured by CGI-S ≥4 and an increase from baseline in CGI-S score of ≥ 2points	Yes
PHQ-9 score ≥10 and subsequent subject withdrawal from study	Yes
Single PHQ-9-triggered HAM-D score ≥18 and subsequent subject withdrawal from study	Yes

Subjects that have 2 consecutive HAM-D total scores ≥18 during a treatment period are encouraged to complete the treatment period. Subjects who experience any of the first 4 events described in the table above will not be eligible for further randomized treatment periods; these subjects may receive treatment as clinically indicated by their physician and should return to the site for follow-up visits as outlined in Table 5.

If at any time during the study, 30 mg SAGE-217 is not tolerated, as assessed by the occurrence of a severe AE judged by the Investigator to be related to study drug, the dose will be reduced to 20 mg and continued for the remainder of the treatment period. Dose adjustments related to moderate AEs will be at the discretion of the Investigator. Subsequent treatment periods will begin with the 30-mg dose, regardless of whether a subject required a dose adjustment in a previous treatment period. Subjects who cannot tolerate the 20-mg dose at any time will be terminated from the study upon completion of an end of treatment (EOT) visit as soon as possible, and an ET visit 7 days later.

Number of Subjects (Planned): Approximately 546 subjects are planned to be dosed in the OL Phase to ensure at least 300 subjects are dosed in the DB Phase.

Eligibility Criteria:

Inclusion Criteria:

Qualified subjects will meet all of the following criteria:

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is a male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements. Subject agrees and understands how to use a smartphone for purposes of the study.
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 had at least 1 prior major depressive episode (MDE) in the 5 years prior to Screening (not including the current episode) as determined by the SCID-5-CT.
7. Subject has a MADRS total score of ≥32 and a HAM-D total score of ≥22 at Screening and Day 1 (prior to dosing) of the OL Phase.
8. Subject is willing to delay start of any antidepressant, anxiolytic, insomnia, psychostimulant, prescription opioid regimens, and new psychotherapy (including Cognitive Behavioral Therapy for Insomnia [CBT-I]) until after study completion.
9. Subjects receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1.
10. Female subject agrees to use one of the following methods of highly effective contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicular stimulation hormone [FSH] >40 mIU/mL), surgically sterile (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence):
    - Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation.
    - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
    - Intrauterine device.
    - Intrauterine hormone-releasing system.
    - Bilateral tubal ligation/occlusion.
    - Vasectomized partner.
11. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence). Acceptable methods of effective contraception for males includes vasectomy or a condom with spermicide used together with highly effective female contraception methods if the female

partner(s) is of child-bearing potential (see Inclusion Criteria #10 for acceptable contraception methods).

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

Exclusion Criteria:

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

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject 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.
3. Subject has a body mass index (BMI) ≤18 or ≥50 kg/m2 at Screening. Note that a BMI of 40 to 49 kg/m2, inclusive, at Screening is subject to a broader evaluation of medical co-morbidities (such as sleep apnea, COPD), concomitant medications, prior tolerability of sedating agents.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from two different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.
5. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine (including esketamine) within the current major depressive episode.
6. Subject has taken antidepressants within 60 days prior to Day 1.
7. Subject is taking or has taken 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) daily or near-daily (≥4 days per week) for 1 year, in the last year prior to the 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
8. Subject is taking non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids), or first generation or second generation (typical/atypical) antipsychotics at Day -14. Note that non-sedating anti-histamines are permitted.
9. Subject is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as-needed, at Day -28.
10. Subject is participating in cognitive behavioral therapy for insomnia (CBT-I) within 28 days prior to Day 1.

11. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
12. Subject has a positive pregnancy test at screening or on Day 1 prior to dosing.
13. Subject is breastfeeding at Screening or on Day 1 (prior to administration of study drug) and does not agree to temporarily cease giving breast milk to 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 period.
14. 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.
15. Subject has a clinically significant abnormal 12-lead ECG at the screening or on Day 1 of any treatment period. 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.
16. Subject has active psychosis per Investigator assessment.
17. Subject has a medical history of seizures.
18. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
19. 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.
20. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
21. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
22. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 half-lives (whichever is longer) prior to the first dose of study drug or plans to use these during any treatment period, 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 treatment period or plans to consume these products during any treatment period.
23. Subject has used any of the following strong CYP3A inducers within 28 days prior to the first dose of study drug for any SAGE-217 treatment period: rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, and St John's Wort.
24. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing in the Open-label Phase.
25. Subject plans to undergo elective surgery or procedure requiring general anesthesia at any time from Screening through the duration of the study. Procedures requiring conscious sedation and ambulatory procedures performed under local anesthesia may be scheduled under the following guidelines:
    a. Procedures requiring conscious sedation (eg, colonoscopy) no later than 7 days prior to the start of the first dose of each treatment period and no earlier than 7 days after the last dose of each treatment period from screening throughout the duration of the study.
    b. Elective ambulatory procedures performed under local anesthesia are allowed at any time during the study.

26. Subject has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
27. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
28. Subject regularly participates in night shift work or expects to perform night shift work during any 14-day treatment period (occasional night shift work during follow-up periods is permitted).

SAGE-217 Dosage and Mode of administration:

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

Reference Therapy, Dosage and Mode of Administration:

In the DB Phase, placebo will be provided as hard gelatin capsules for oral administration in the evening with food.

Duration of Treatment:

All subjects will receive a daily dose of SAGE-217 from Day 1 through Day 14 in the OL Phase. Subjects that exhibit a HAM-D response to SAGE-217 in the OL Phase will be randomized to receive either daily doses of SAGE-217 or placebo in 14-day treatment periods, separated by 6-week follow-up periods, for 40 weeks in the DB Phase (for a total of six 14-day treatment periods during the 52-week study).

Statistical Methods:

Detailed description of the statistical analyses to be performed for this study will be provided in a statistical analysis plan (SAP). The SAP will be finalized and approved prior to treatment unblinding. Any deviations from or changes to the SAP following database lock will be described in detail in the clinical study report.

General Considerations

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.

Continuous endpoints will be summarized descriptively with n, mean, standard deviation, median, minimum, and maximum. For categorical endpoints, descriptive summaries will include counts and percentages.

Analysis Sets

The Enrolled Set is defined as all subjects who receive a dose of study drug in the OL phase.

The Randomized Set is defined as all subjects who are randomized in the DB phase.

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

The Full Analysis Set is defined as all randomized subjects in the Safety Set with a valid baseline and at least 1 post-baseline HAM-D total score,

[redacted]

Determination of Sample Size

The randomization in the DB phase is 1:1, with 150 subjects randomized in each treatment arm – placebo and SAGE-217. Assuming a relapse rate of 34% in the placebo arm (Borges 2014) and 17% in the SAGE-217 arm for a fixed 40-week repeated treatment regimen (Hazard ratio = 0.448), this sample size will provide a 90% power with 0.05 level of significance in comparing time to relapse (through comparison of survival curves) by Log-Rank test. Further, assuming that only 55% of the subjects dosed in the OL phase will qualify as responders to be randomized in the DB phase, 546 subjects will need to be dosed in the OL phase.

An interim analysis is planned when about 50% of expected relapse events occur (ie, 34 of 67 expected relapse events happen) to estimate the hazard ratio with a view to re-estimate the sample size. This unblinded interim analysis will be performed by an independent third party, external to the Sponsor, with specific directions on how to conclude depending on the range of hazard ratio observed. The decision will be communicated to the Sponsor only in terms of "no change in sample size necessary" or "increase the sample size to XXX"; hence the Sponsor will remain blinded. The final analysis will be complete when the last subject completes (or ET) the study. The methods to control the type I error rate will be provided in the SAP.

Analysis of Primary Endpoint

The estimand is the time to relapse – number of days between the first dose in the first treatment period of the DB phase to the day of relapse. The analysis will use the FAS. Kaplan-Meier survival curves will be provided, along with the median time to relapse. Log-rank test will be used to compare the survival curves at the significance level of 0.05.

Analysis of Secondary Endpoints

Using FAS, the change from baseline will be summarized by randomized treatment group and each scheduled time point where the evaluation has been made. Baseline is defined as the last measurement prior to dosing in the DB Phase. A mixed effects model for repeated measures (MMRM) will be used for analysis; the model will include treatment, baseline value, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All post-baseline time points for the specific study period will be included in the model. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

For analysis of binary endpoints, the estimand is the Odds Ratio (OR). The generalized estimating equation (GEE) methods will be used for the analysis. GEE models will include terms for treatment, baseline value, assessment time point, and time point-by-treatment as explanatory variables. Model-based point estimates (ie, odds ratios), 95% confidence intervals, and p-values will be reported.

Time to relapse for remitters at the end of OL phase will be analyzed the same way as done for primary efficacy analysis.

Endpoints for the OL phase will be summarized by each scheduled timepoint, based on Enrolled Set.

[redacted]

Analysis of Safety Endpoints

Safety and tolerability of SAGE-217 will be evaluated by incidence of adverse events/serious adverse events, and [redacted]. Safety Set will be used for safety analyses.

The [redacted] measurements comparison between SAGE-217 and placebo will be assessed longitudinally (at baseline and the end of every other active treatment course, and the end of every other no-treatment follow up period) as specified in the Schedule of Events. The data will be analyzed using an MMRM with the change from baseline as the response variable.

Safety and tolerability will be summarized for the OL phase using the Enrolled Set.

Table 2: Schedule of Events (Screening Period)

	Screening Period
Study Day	**-28 to -1**
Visit	**1**
Study Procedure	
Informed Consent	X
Duplicate Subject Check (US only)[a]	X
Inclusion/Exclusion	X
Demographics	X
Medical/Family History	X
SCID-5	X
ICD-10[b]	X
MGH-ATRQ	X
Serum FSH test[c]	X
Full Physical Examination[d]	X
Body Weight/Height	X
[redacted]	
Drug & Alcohol Screen[f]	X
Serum Pregnancy Test (all female subjects)	X
Hepatitis & HIV Screen	X
Subject training[g]	X
[redacted]	
HAM-D[j]	X
MADRS	X
CGI-S	X
Adverse Events/SAEs[k]	X

	Screening Period
Study Day	**-28 to -1**
Visit	**1**
Prior Medications	X

CGI-S – Clinical Global Impression - Severity; [redacted];
ECG = electrocardiogram; 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; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; SCID-5 = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; SAE = serious adverse event; US = United States

[a] Subjects at US sites will be asked to authorize that their unique subject identifiers be entered into a registry with the intent of identifying subjects who may meet exclusion criteria for participation in another clinical study.

[b] ICD-10 code(s) for the diagnosis of the current major depressive episode to be collected if available.

[c] A serum FSH test will be conducted at Screening for female subjects that are not surgically sterile to confirm whether a female subject with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being post-menopausal.

[d] A full physical examination will be conducted, including assessment of body systems (eg, head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities), as well as [redacted] and neurological examinations and mental status examinations.

[redacted]
Urine toxicology for selected drugs of abuse (see Table 8) and breath test for alcohol.

[g] Subjects will be trained on use of study drug adherence monitoring and PHQ-9 software applications and devices by site personnel.

[redacted]

[j] The HAM-D is to be completed as early during the visit as possible. The assessment timeframe for HAM-D will refer to the past 7 days (1 week).

[k] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study (Section 12.2).

Table 3: Schedule of Events (Open-label and Double-blind Phases)

	Open-Label						Double-blind Treatment & FU 1				Double-blind Treatment & FU 2				Double-blind Treatment & FU 3				Double-blind Treatment & FU 4				Double-blind Treatment & FU 5				EOS
Study Day	**1**	**8 (+1)**	**15 (+1)**	**21 (±1)**	**28 (±1)**	**42 (±1)**	**56 (±1)**	**63 (+1)**	**70 (+1)**	**76 (±3)**	**111 (+3)**	**118 (+1)**	**125 (+1)**	**131 (±3)**	**166 (+3)**	**173 (+1)**	**180 (+1)**	**186 (±3)**	**221 (+3)**	**228 (+1)**	**235 (+1)**	**241 (±3)**	**276 (+3)**	**283 (+1)**	**290 (+1)**	**296 (±3)**	**331 (±3)**
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Treatment Period Day	**1**	**8**	**15/ EOT[a]**	**21**	**28**	**42**	**56/ 1[b]**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ ET[a]**
Study Procedure																											
Inclusion/ Exclusion	X																										
MADRS	X																										
Subject training[c]	X																										
Randomization							X																				
Abbreviated Physical Examination[d]	X			X			X			X	X			X	X			X	X			X	X			X	X
Body Weight	X		X				X		X		X		X		X		X		X		X		X		X		X
[redacted]																											
Drug & Alcohol Screen[f]	X						X				X				X				X				X				
Urine Pregnancy Test[g]	X		X				X		X		X		X		X		X		X		X		X		X		X
[redacted]																											

	Open-Label						Double-blind Treatment & FU 1				Double-blind Treatment & FU 2				Double-blind Treatment & FU 3				Double-blind Treatment & FU 4				Double-blind Treatment & FU 5				EOS
Study Day	**1**	**8 (+1)**	**15 (+1)**	**21 (±1)**	**28 (±1)**	**42 (±1)**	**56 (±1)**	**63 (+1)**	**70 (+1)**	**76 (±3)**	**111 (+3)**	**118 (+1)**	**125 (+1)**	**131 (±3)**	**166 (+3)**	**173 (+1)**	**180 (+1)**	**186 (±3)**	**221 (+3)**	**228 (+1)**	**235 (+1)**	**241 (±3)**	**276 (+3)**	**283 (+1)**	**290 (+1)**	**296 (±3)**	**331 (±3)**
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Treatment Period Day	**1**	**8**	**15/ EOT[a]**	**21**	**28**	**42**	**56/ 1[b]**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ ET[a]**
[redacted]																											
HAM-D[k]	X	X	X		X	X	X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
CGI-S	X	X	X		X	X	X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
CGI-I		X	X		X	X	X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
[redacted]																											
Study Drug Dispensation	X	X					X	X			X	X			X	X			X	X			X	X			
Study Drug Administration	X (daily for 14 days)						X (daily for 14 days)				X (daily for 14 days)				X (daily for 14 days)				X (daily for 14 days)				X (daily for 14 days)				
Study Drug Accountability/ Return		X	X					X	X			X	X			X	X			X	X			X	X		
PHQ-9[m]	X (every 7 [+3] days)																										

	Open-Label						Double-blind Treatment & FU 1				Double-blind Treatment & FU 2				Double-blind Treatment & FU 3				Double-blind Treatment & FU 4				Double-blind Treatment & FU 5				EOS
Study Day	**1**	**8 (+1)**	**15 (+1)**	**21 (±1)**	**28 (±1)**	**42 (±1)**	**56 (±1)**	**63 (+1)**	**70 (+1)**	**76 (±3)**	**111 (+3)**	**118 (+1)**	**125 (+1)**	**131 (±3)**	**166 (+3)**	**173 (+1)**	**180 (+1)**	**186 (±3)**	**221 (+3)**	**228 (+1)**	**235 (+1)**	**241 (±3)**	**276 (+3)**	**283 (+1)**	**290 (+1)**	**296 (±3)**	**331 (±3)**
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Treatment Period Day	**1**	**8**	**15/ EOT[a]**	**21**	**28**	**42**	**56/ 1[b]**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ ET[a]**
Adverse Events/SAEs[n]	X																										
Concomitant Medications	X																										

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; [redacted];
ECG = electrocardiogram; EOT = end of treatment; [redacted]; EOS = End of study; EOT = end of treatment; ET = early termination; FU = follow-up; HAM-D = Hamilton Rating Scale for Depression, 17-item; PHQ-9 = 9-item Patient Health Questionnaire; [redacted]; SAE = serious adverse event; [redacted]

[a] Subjects who discontinue treatment early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. The follow-up visits should occur as scheduled relative to the last day of treatment. Subjects who discontinue treatment early will be terminated from the study upon completion of their final follow-up visit. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for the ET visit will be conducted.

[b] The completion of the Open-label Phase for all subjects coincides with the first day of the Double-Blind Phase (Study Day 56, Visit 8). Subjects that do not exhibit a response to SAGE-217 in the Open-label Phase (Section 7.1.2) will be terminated from the study on this day upon completion of all assessments.

[c] Subjects will be trained on use of study drug adherence monitoring and PHQ-9 software applications and devices by site personnel.

[d] An abbreviated physical examination will include assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems.

[redacted]

[f] Urine toxicology for selected drugs of abuse (Table 8) and breath test for alcohol.

[g] Urine pregnancy test for female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal.

[redacted]

[k] The HAM-D is to be completed as early during the visit as possible. The assessment timeframe for HAM-D will refer to the past 7 days (1 week) at Days 28 and 42 of the OL Phase and at each Day 56/1 of the DB Phase; “Since Last Visit” will be used for all other visits.

[redacted]

[m] All PHQ-9 assessments will be performed via web browser. The subject will take the first PHQ-9 on Day 1 and then every 7 days thereafter; if the PHQ-9 score is ≥10, the subject will return to the site as soon as possible to be assessed by the clinician-administered HAM-D. If the HAM D is ≥18 at this visit, the subject will return to the site in 7 to 14 days to be reassessed by the HAM-D. See Table 4 for the assessments to be conducted at these visits.

[n] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study (Section 12.2).

Table 4: Schedule of Events (Visits for Assessment of Relapse)

Study Procedure	
Abbreviated Physical Examination[a]	X
[redacted]	
Urine Pregnancy Test[c]	X
[redacted]	
HAM-D[f]	X
CGI-S	X
[redacted]	
EQ-5D-5L	X
Adverse Events/SAEs[g]	X
Concomitant Medications	X
CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; [redacted]; ECG = electrocardiogram; [redacted]; HAM-D = Hamilton Rating Scale for Depression, 17-item; SAE = serious adverse event; [redacted]	

[a] An abbreviated physical examination will include assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems.

[redacted]

[c] Urine pregnancy test for female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal.

[redacted]

[f] The HAM-D is to be completed as early during the visit as possible. The assessment timeframe for HAM-D will refer to the past 7 days (1 week).

[g] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study (Section 12.2).

Table 5: Schedule of Events (Follow-up for Subjects that Meet Relapse Criteria)

Study Day	**111, 166, 221, 276, 331/EOS (+3)**
Treatment Period Day	**56/1/ET**
Study Procedure	
[redacted]	
Drug & Alcohol Screen	X
[redacted]	
HAM-D	X
CGI-S	X
CGI-I	X
[redacted]	
PHQ-9[a]	X
Adverse Events/SAEs	X
Concomitant Medications	X

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; [redacted]; EOS = End of study; ET = early termination; HAM-D = Hamilton Rating Scale for Depression, 17-item; PHQ-9 = 9-item Patient Health Questionnaire; SAE = serious adverse event; [redacted]

[a] The PHQ-9 will be completed by the subject during the visit at the site.

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

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 6: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
AE	adverse event
AR(1)	Autoregressive (1)
BMI	body mass index
CBT-I	cognitive behavioral therapy for insomnia
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
COPD	chronic obstructive pulmonary disease
CRT	choice reaction time
CS	clinically significant
[redacted]	
CYP	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	ethics committee
[redacted]	
eCRF	electronic case report form
[redacted]	
EOS	end of study
EOT	end of treatment
[redacted]	
ET	early termination
FAS	Full Analysis Set
FSH	follicle stimulating hormone
GABA	γ-aminobutyric acid
GEE	generalized estimating equation
HAM-D	Hamilton Rating Scale for Depression
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICD-10	International Statistical Classification of Diseases and Related Health Problems version 10
ICF	informed consent form

Abbreviation or specialist term	Explanation
ID	identification
IRAC	Independent Relapse Adjudication Committee
IRB	institutional review board
IRT	interactive response technology
ISI	Insomnia Severity Index
LS	Least squares
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
MGH ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MMRM	mixed effects model for repeated measures
NCS	not clinically significant
OL	open label
OR	Odds Ratio
PHQ-9	9-item Patient Health Questionnaire
[redacted]	
PPD	postpartum depression
[redacted]	
SAE	serious adverse event
SAP	statistical analysis plan
SCID-5-CT	Structured Clinical Interview for Diagnostic and DSM-5 Clinical Trial Version
SD	standard deviation
SDS	Sheehan Disability Scale
SMCC	silicified microcrystalline cellulose
SRT	simple reaction time
SUSAR	suspected, unexpected, serious adverse reactions
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TSH	thyroid stimulating hormone

Abbreviation or specialist term	Explanation
US	United States
VAS	visual analogue scale
WHO	World Health Organization
[redacted]	

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 (US), 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).

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

5.2. SAGE-217

SAGE-217 is a synthetic positive allosteric modulator of $GABA_A$ receptors, the major class of inhibitory neurotransmitter receptors in the brain. In pharmacokinetic (PK) studies in mice and rats, SAGE-217 demonstrated rapid penetration and equilibrium across the blood brain barrier and is generally expected to have good extravascular exposure. In exploratory in vitro receptor and ion channel assays and in vivo safety pharmacology studies, SAGE-217 was highly selective

for $GABA_A$ receptors, and exhibits activity consistent with the actions of other $GABA_A$ receptor potentiators (Rudolph 2011) when administered in vivo.

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

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, dizziness, headache, upper respiratory tract infection, diarrhea, and nausea. Among these sedation, somnolence and dizziness are considered adverse drug reactions with SAGE-217. Most adverse events (AEs) were reported as mild or moderate in intensity and reversible. In completed studies, 2 SAEs have been reported in subjects administered SAGE-217 and 1 SAE was reported in a subject administered placebo. These include one subject with Essential Tremor who experienced transient confusion leading to discontinuation of study drug (SAGE-217 oral solution, 30 mg). The second SAE of confusion was noted in a subject with postpartum depression (PPD) which resolved upon reduction of the study drug (SAGE-217 oral capsule) dose from 30 mg to 20 mg. One subject with PPD in the placebo group experienced obstructive pancreatitis which resolved with cholecystectomy. No deaths have been reported in any study of SAGE-217.

In a multiple-ascending dose study of SAGE-217 in healthy subjects (217-CLP-102), 1 cohort of subjects (n=9) was dosed with 30 mg SAGE-217 in the morning for 7 days, and after a washout period of 7 days, 7 of the subjects were re-treated with 30 mg SAGE-217 in the evening for 7 days. The most common TEAE in these 7 subjects after re-treatment with SAGE-217 was sedation (n=3, 42.9%), consistent with the pharmacology of the drug and with other clinical studies with SAGE-217. No evidence of withdrawal-related events, including seizure, were observed in these subjects.

Additional information on nonclinical and clinical data is provided in the Investigator's Brochure.

5.3. Potential Risks and Benefits

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

The dose level in this study of 30 mg per day is the dose level that was efficacious and well-tolerated in a Phase 2 study in subjects with MDD (217-MDD-201). Dose adjustments to 20 mg SAGE-217 are permitted; 20 mg SAGE-217 is anticipated to be well tolerated as it is lower than

the maximum tolerated dose level. Due to sedation/somnolence observed in previous clinical studies when administered in the morning, and improved tolerability when given in the evening, SAGE-217 will be administered in the evening in this study.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Study Objective

6.1.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of SAGE-217 with a fixed, repeated treatment regimen in the prevention of relapse in subjects with MDD who have responded to open-label (OL) treatment with SAGE-217.

6.1.2. Secondary Objective(s)

The secondary objective of this study is to evaluate the long-term safety and tolerability of a fixed, repeated treatment regimen of SAGE-217 up to 1 year.

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoint

The primary endpoint of this study is time to relapse during the double-blind (DB) Phase (days; from first dose of study drug in the DB Phase to relapse [date] during the DB Phase).

6.2.2. Secondary Endpoint(s)

Secondary endpoints of this study are:

- Percentage of subjects who relapse during the DB Phase
- Change from baseline in the 17-item HAM-D total score at the end of each 14-day treatment period in the DB Phase.
- HAM-D response at the end of each 14-day treatment period in the DB Phase, defined as a ≥50% reduction in HAM-D score from baseline
- HAM-D remission at the end of each 14-day treatment period in the DB Phase, 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 period in the DB Phase
- Change from baseline in Clinical Global Impression - Severity (CGI-S) score at the end of each 14-day treatment period in the DB Phase

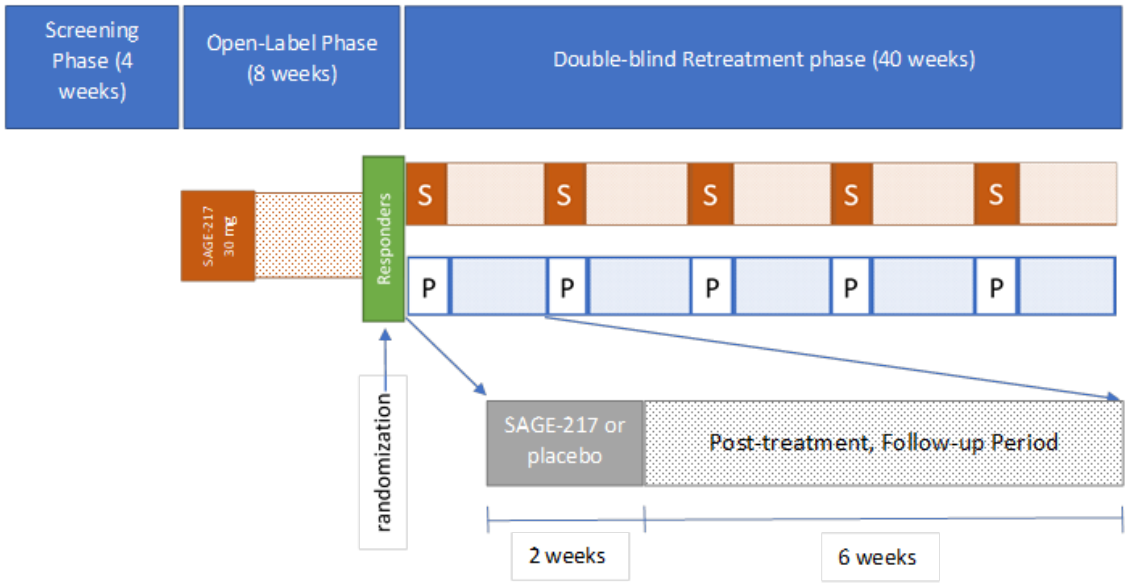
- Change from baseline in 9-item Patient Health Questionnaire (PHQ-9) score at the end of each 14-day treatment period in the DB Phase
- Time to relapse during the DB phase (days; from first dose of study drug in DB Phase to relapse [date] during the DB Phase) for subjects who achieved HAM-D remission in the OL Phase
- Incidence of TEAEs

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a study with an OL phase followed by a randomized, DB, placebo-controlled phase to assess the effect of SAGE-217 monotherapy in a fixed, repeated treatment regimen versus placebo on relapse prevention in adult subjects with MDD (MADRS ≥32, HAM-D ≥22) who are not currently taking antidepressants. See Figure 1 for a schematic of the study design.

Figure 1: Study Design Schematic



S = SAGE-217; P = Placebo

7.1.1. Open-label Phase

The Screening Period (Table 2) begins with the signature of the informed consent form (ICF); the ICF must be signed prior to beginning any screening activities. 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 of the OL Phase, eligible subjects will self-administer a single dose of study drug once daily in the evening with food, on an outpatient basis, for 14 consecutive days. Subjects will return to the study center during the OL treatment and follow-up periods as outlined in Table 3.

7.1.2. Double-blind Phase

Subjects who complete the OL Phase (through Day 56) with no significant tolerability issues as judged by the Investigator and who exhibited a HAM-D response, defined as a ≥50% reduction from baseline in HAM-D total score, at Visits 4, 6, 7, and 8 (see Table 3) will be eligible for the DB Phase. One excursion of <50% reduction from baseline (but total score ≤21) in HAM-D total

score or one missing HAM-D total score at Visit 6 or 7 will be permitted for eligibility to the DB Phase.

Beginning on Day 1 of the DB Phase, eligible subjects will be randomized to receive SAGE-217 30 mg or matching placebo in a 1:1 ratio. The 40-week DB Phase consists of five 14-day treatment periods, each separated by a 6-week follow-up period; the end of each follow-up period coincides with the first visit of the next treatment period. During the 14-day treatment periods, subjects will self-administer a single dose of study drug once daily in the evening with food, on an outpatient basis. Subjects will return to the study center during the DB treatment and follow-up periods as outlined in Table 3.

7.1.2.1. Determination of Relapse

During the follow-up periods of the DB Phase, depressive symptoms will be monitored every 7 (+3) days via remote PHQ-9; if the PHQ-9 score is ≥10, the subject will return to the site as soon as possible to be assessed by the clinician-administered HAM-D (Table 4). If the HAM-D is ≥18 at this visit, the subject will return to the site in 7 to 14 days to be reassessed by the HAM-D (Table 4); if the HAM-D remains ≥18, the subject will be considered to have relapsed at this visit. A summary of all reasons a subject may be considered to have relapsed is presented in Table 7. Final determination of relapse will be made by an Independent Relapse Adjudication Committee (IRAC) for events other than 2 consecutive HAM-D scores ≥18 assessed 7 to 14 days apart. The IRAC Charter will include full details of membership and responsibilities.

Table 7: Summary of Events Which May Result in Relapse

Event	Requires Review by IRAC?
2 consecutive HAM-D scores ≥18 assessed 7 to 14 days apart	No
Any worsening of depression requiring hospitalization	Yes
Any Investigator-determined risk of suicide	Yes
Worsening of overall depressive symptoms as measured by CGI-S ≥4 and an increase from baseline in CGI-S score of ≥ 2 points	Yes
PHQ-9 score ≥10 and subsequent subject withdrawal from study	Yes
Single PHQ-9-triggered HAM-D score ≥18 and subsequent subject withdrawal from study	Yes

Subjects that have 2 consecutive HAM-D total scores ≥18 during a treatment period are encouraged to complete the treatment period. Subjects who experience any of the first 4 events described in the table above will not be eligible for further randomized treatment periods; these subjects may receive treatment as clinically indicated by their physician and should return to the site for follow-up visits as outlined in Table 5.

7.2. Number of Subjects

It is expected that approximately 546 subjects will need to be dosed in the OL Phase to ensure at least 300 subjects are dosed in the DB Phase. An independent interim analysis for sample size re-estimation will be conducted when approximately 50% of expected relapse events occur (Section 13.8).

7.3. Treatment Assignment

All subjects will receive SAGE-217 in the OL Phase. In the DB Phase, subjects will be randomly assigned in a 1:1 ratio to receive SAGE-217 or matching placebo.

7.4. Dose Adjustment Criteria

If at any time during the study, 30 mg SAGE-217 is not tolerated, as assessed by the occurrence of a severe AE judged by the Investigator to be related to study drug, the dose will be reduced to 20 mg and continued for the remainder of the treatment period. Dose adjustments related to moderate AEs will be at the discretion of the Investigator. Subsequent treatment periods will begin with the 30-mg dose, regardless of whether a subject required a dose adjustment in a previous treatment period. Subjects who cannot tolerate the 20-mg dose at any time will be terminated from the study upon completion of an end of treatment (EOT) visit as soon as possible, and an ET visit 7 days later.

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 Institutional Review Board (IRB) or Ethics Committee and initiate withdrawal procedures for participating subjects.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Qualified subjects will meet all of the following criteria:

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is a male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements. Subject agrees and understands how to use a smartphone for purposes of the study.
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 had at least 1 prior major depressive episode (MDE) in the 5 years prior to Screening (not including the current episode) as determined by the SCID-5-CT.
7. Subject has a MADRS total score of ≥32 and a HAM-D total score of ≥22 at Screening and Day 1 (prior to dosing) of the Open-label Phase.
8. Subject is willing to delay start of any antidepressant, anxiolytic, insomnia, psychostimulant, prescription opioid regimens, and new psychotherapy (including Cognitive Behavioral Therapy for Insomnia [CBT-I]) until after study completion.
9. Subjects receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1.
10. Female subject agrees to use one of the following methods of highly effective contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicular stimulation hormone [FSH] >40 mIU/mL), surgically sterile (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence):
    - Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation.
    - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
    - Intrauterine device.
    - Intrauterine hormone-releasing system.
    - Bilateral tubal ligation/occlusion.
    - Vasectomized partner.

11. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence). Acceptable methods of effective contraception for males includes vasectomy or a condom with spermicide used together with highly effective female contraception methods if the female partner(s) is of child-bearing potential (see Inclusion Criteria #10 for acceptable contraception methods).
12. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
13. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

8.2. Subject Exclusion Criteria

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

1. Subject has attempted suicide associated with the current episode of MDD.
2. Subject 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.
3. Subject has a body mass index (BMI) ≤18 or ≥50 kg/m2 at Screening. Note that a BMI of 40 to 49 kg/m2, inclusive, at Screening is subject to a broader evaluation of medical co-morbidities (such as sleep apnea, COPD), concomitant medications, prior tolerability of sedating agents.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from two different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used for this purpose.
5. Subject has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine (including esketamine) within the current major depressive episode.
6. Subject has taken antidepressants within 60 days prior to Day 1.
7. Subject is taking or has taken 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) daily or near-daily (≥4 days per week) for 1 year, in the last year prior to the 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
8. Subject is taking non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids), or first generation or second

generation (typical/atypical) antipsychotics at Day -14. Note that non-sedating anti-histamines are permitted.

9. Subject is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as-needed, at Day -28.
10. Subject is participating in CBT-I within 28 days prior to Day 1.
11. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
12. Subject has a positive pregnancy test at screening or on Day 1 prior to dosing.
13. Subject is breastfeeding at Screening or on Day 1 (prior to administration of study drug) and does not agree to temporarily cease giving breast milk to 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 period.
14. 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.
15. Subject has a clinically significant abnormal 12-lead ECG at the Screening or on Day 1 of any treatment period. 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.
16. Subject has active psychosis per Investigator assessment.
17. Subject has a medical history of seizures.
18. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
19. 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.
20. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
21. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
22. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 half-lives (whichever is longer) prior to the first dose of study drug or plans to use these during any treatment period, 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 treatment period or plans to consume these products during any treatment period.
23. Subject has used any of the following strong CYP3A inducers within 28 days prior to the first dose of study drug for any SAGE-217 treatment period: rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, and St John's Wort.
24. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing in the Open-label Phase.

25. Subject plans to undergo elective surgery or procedure requiring general anesthesia at any time from Screening through the duration of the study. Procedures requiring conscious sedation and ambulatory procedures performed under local anesthesia may be scheduled under the following guidelines:
    a. Procedures requiring conscious sedation (eg, colonoscopy) no later than 7 days prior to the start of the first dose of each treatment period and no earlier than 7 days after the last dose of each treatment period from screening throughout the duration of the study.
    b. Elective ambulatory procedures performed under local anesthesia are allowed at any time during the study.
26. Subject has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
27. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
28. Subject regularly participates in night shift work or expects to perform night shift work during any 14-day treatment period (occasional night shift work during follow-up periods is permitted).

8.3. Subject Withdrawal Criteria

Subjects may discontinue from the study drug or terminate from the study at any time for any reason. Other than the events outlined in Table 7, the Investigator may withdraw the subject from the study drug or from the study for any of the following reasons:

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

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

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

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

Subjects who discontinue treatment early should return to the site for an EOT visit (Table 3) as soon as possible, preferably the day after treatment is discontinued. The follow-up visits should occur as scheduled relative to the last day of treatment. Subjects who discontinue treatment early will be terminated from the study upon completion of the final follow-up visit in the current period. If at any time after the EOT visit, a subject decides to terminate the study, the subject

should return for an ET visit. The EOT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for the ET visit will be conducted.

8.3.1. Subjects that Meet Relapse Criteria

Subjects that meet relapse criteria (Table 7) will not be eligible for further randomized treatment periods and should return for follow-up visits as outlined in Table 5. Subjects that meet relapse criteria during a treatment period and discontinue treatment early should return to the site for an EOT visit (Table 3) as soon as possible, preferably the day after treatment is discontinued, and thereafter, should return for follow-up visits as outlined in Table 5.

If at any time after a subject meets relapse criteria, the subject decides to terminate the study, the subject should return for an ET visit (Table 5). An EOT visit and an ET visit 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.

8.3.2. Individual Subject Stopping Criteria

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 period but will continue to be followed in the study for safety (Section 12.2.1).
2. Following the first treatment period, the Investigator should monitor the course of central nervous system-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, in consultation with the Sage Medical Monitor, should consider decreasing the dose of study drug to 20 mg, stopping treatment to assess the effect on the symptom(s) (eg, resolution, improvement, etc), or discontinuing the subject from treatment.

8.3.3. Replacement of Subjects

Subjects will not be replaced.

9. TREATMENT OF SUBJECTS

9.1. Study Drug

SAGE-217 capsules at doses of 30 mg (or 20 mg for dose reductions), or matched placebo capsules, will be self-administered by subjects orally once daily in the evening with food for 14 days during treatment periods. Practical options include taking SAGE-217 within 1 hour of dinner or taking SAGE-217 later in the evening with solid food.

9.2. Prior Medications, Concomitant Medications, and Restrictions

9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route, dose/units, frequency, and indication for all medications and/or supplements taken within 30 days prior to Screening and throughout the duration of the study will be recorded. In addition, psychotropic medications taken 6 months prior to Screening and GABAergic medications taken 12 months prior to Screening will be recorded.

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

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

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system

9.2.2. Prohibited Medications

Initiation of any antidepressant, anxiolytic, insomnia, psychostimulant, or prescription opioid regimen is prohibited from Screening and for the duration of the DB Phase (ie, prior to meeting relapse criteria). Restrictions on specific classes of medications include the following:

- Use of benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, zolpidem, brexanolone) is prohibited from Day -28 through the duration of the DB Phase
- Use of benzodiazepines or $GABA_A$ modulators with a half-life of $\geq$48 hours (eg, diazepam) is prohibited from Day -60 and through the duration of the DB Phase
- Use of non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids) is prohibited from Day -14 through the duration of the DB Phase. Note that non-sedating anti-histamines are permitted.
- Use of first generation or second generation (typical/atypical) antipsychotics is prohibited from Day -14 through the duration of the DB Phase.

- Use of psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as-needed, is prohibited from Day -28 through the duration of the DB Phase
- Exposure to another investigational medication or device within 30 days prior to Screening and through the duration of the DB Phase is prohibited.
- Use of known strong inhibitors of CYP3A4 within 28 days or 5 half-lives (whichever is longer) is prohibited prior to the first dose of study drug and during any treatment period
- Use of any of the following strong CYP3A inducers is prohibited within 28 days prior to the first dose of study drug for any treatment period and throughout any treatment period: rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, and St John's Wort

9.2.3. Other Restrictions

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

Consumption of alcohol or use of drugs of abuse (including tetrahydrocannabinol [THC]) is discouraged throughout the duration of the DB Phase.

Elective surgeries or procedures requiring general anesthesia are prohibited from Screening through the duration of the DB Phase. Procedures requiring conscious sedation and ambulatory procedures performed under local anesthesia may be scheduled under the following guidelines:

- Procedures requiring conscious sedation (eg, colonoscopy) no later than 7 days prior to the start of the first dose of each treatment period and no earlier than 7 days after the last dose of each treatment period from screening throughout the duration of the study.
- Elective ambulatory procedures performed under local anesthesia are allowed at any time during the study.

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

Subjects receiving psychotherapy (except CBT-I) on a regular schedule for at least 60 days prior to Day 1 are permitted if the subject intends to continue the therapy for the duration of the DB Phase.

Female subjects who 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 in each treatment period.

Male subjects are prohibited from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.

9.3. Treatment Adherence

Study drug (SAGE-217 or placebo) will be self-administered by subjects once daily in the evening with food. Sites will dispense study drug to the subjects to take at home with instructions for use (see Section 10.5).

Administration of study drug will be monitored by a medication adherence monitoring platform used on smartphones to visually confirm medication ingestion. Subjects will receive a reminder

within a predefined time window to take study drug while using the application. Subjects will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application will record the date and time of study drug administration, as well as missed doses.

In addition, the subject will be instructed to bring their dosing kit to the site as outlined in Table 3, at which time the Investigator or designee will be responsible for ensuring the kit contains sufficient doses for the duration of the treatment period, including ensuring the subject has taken the expected number of doses.

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

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

9.4. Randomization and Blinding

This study contains an open-label phase followed by a randomized double-blind, placebo-controlled phase. Subjects who complete the OL Phase with no significant tolerability issues as judged by the Investigator and who meet HAM-D response criteria (Section 7.1) will be randomized in a 1:1 ratio to receive SAGE-217 30 mg or matched placebo. Subjects, clinicians, and the study team will be blinded to treatment allocation. Randomization will be performed centrally via an interactive response technology (IRT) system.

Randomization schedules will be generated by an independent statistician. The allocation to treatment group will be based on the randomization schedule. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding.

The randomization schedule will be provided to an independent chemist in order to select appropriate [redacted] (active treatment only).

An independent third party will be unblinded to conduct an interim analysis to re-estimate the sample size with specific directions on how to conclude depending on the range of hazard ratio observed (Section 13.8). The decision will be communicated to Sage personnel only in terms of "no change in sample size necessary" or "increase the sample size to XXX"; hence Sage personnel will remain blinded. Further details will be provided in the Statistical Analysis Plan (SAP).

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IRT.

9.4.1. Emergency Unblinding

During the DB Phase, the blind is to be broken by the Investigator only when the safety of a subject is at risk and the treatment plan is dependent on the study drug received. Unless a subject is at immediate risk, the Investigator must make diligent attempts to contact Sage prior to unblinding the study drug administered to a subject. Any request from the Investigator about the treatment administered to study subjects must be discussed with Sage. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be

clearly documented in the source records. Unless a subject is at immediate risk, any request for the unblinding of individual subjects must be made in writing to Sage and approved by the appropriate Sage personnel, according to standard operating procedures.

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

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Description of Study Drugs

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

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

10.2. Study Drug Packaging and Labeling

SAGE-217 capsules and matched placebo capsules will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the study drug in appropriately labeled, subject-specific kits containing sealed unit doses. Each unit dose consists of 1 capsule. Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Study drug labels with all required information and conforming to all applicable FDA Code of Federal Regulations and Good Manufacturing Practice/Good Clinical Practice guidelines will be prepared by Sage Therapeutics.

10.3. Study Drug Storage

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

10.4. Study Drug Preparation

Not applicable.

10.5. Study Drug Administration

SAGE-217 and matched placebo is to be administered orally once daily in the evening with food. Practical options include taking study drug within 1 hour of dinner or taking study drug later in the evening with solid food. If a subject misses a dose, the subject should skip that dose (ie, they should not take the dose in the morning) and take the next scheduled dose in the evening the next day.

10.6. Study Drug Accountability

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

The designated site staff will dispense the supplied subject-specific kits to subjects at the planned dispensation visit intervals outlined in Table 3.

Site staff will access the IRT at the Screening Visit to obtain a subject identification (ID) number for each subject. On Day 1, site staff will access the IRT and provide the necessary subject-identifying information, including the subject ID number assigned at Screening, to enroll the eligible subject into the initial OL treatment period 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.

If eligible, subjects will be randomized at the appropriate visit via the IRT. For this and subsequent study drug-dispensing visits for any other treatment periods, 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 any visit must be recorded.

If dispensing errors or discrepancies are discovered by site staff or sponsor's designee, the Sponsor must be notified immediately. Additional instructions regarding accountability can be found in the Pharmacy Manual.

The study drug provided is for use only as directed in this protocol. After the study is completed, all unused study drug must be returned as directed or destroyed on site per the Sponsor's instructions. The Investigator or designee must keep a record of all study drug received, dispensed and discarded.

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

10.7. Study Drug Handling and Disposal

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

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

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

10.8. Product Complaints

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

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

Where possible, personnel should segregate any product, materials, or packaging associated with the product complaint.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

All assessments will be conducted according to the schedule of assessments (Table 2, Table 3, and Table 4). Study assessments that involve subject interviews, including the HAM-D and SCID-5-CT, may be audiotaped for independent quality control purposes. All assessments must be conducted by raters that have been trained and certified to conduct assessments in this study.

11.1. Efficacy Assessments

11.1.1. Hamilton Rating Scale for Depression

Every effort should be made for the same rater to perform all HAM-D assessments for an individual subject. An assessment timeframe of 7 days will be used at Screening, at Days 28 and 42 of the OL Phase, at each Day 56/Day 1 during the DB period, and at any visit for assessment of relapse; 'Since Last Visit' will be used for all other visits.

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

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

Hamilton Rating Scale for Depression subscale scores will be calculated as the sum of the items comprising each subscale. Hamilton Rating Scale for Depression response will be defined as having a 50% or greater reduction from baseline in HAM-D total score. Hamilton Rating Scale for Depression remission will be defined as having a HAM-D total score of $\leq$7.

11.1.2. 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= among the most extremely ill patients (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]

11.1.5. Patient Health Questionnaire

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 will complete questionnaires at baseline and at regular intervals thereafter. Scoring is based on responses to specific questions, as follows: 0=not at all; 1=several days; 2=more than half the days; and 3=nearly every day.

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

Subjects will complete the PHQ-9 via web browser.

[redacted]

11.2.1. Blood Sample Collection

[redacted] (eg, for unusual or severe AEs).

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

11.2.2. Sample Analysis

[redacted]

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

All assessments will be conducted according to the schedule of assessments (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. 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.

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

The severity of the depressive episode upon entry into the study will be evaluated using the HAM-D (Section 11.1.1) and the MADRS. 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

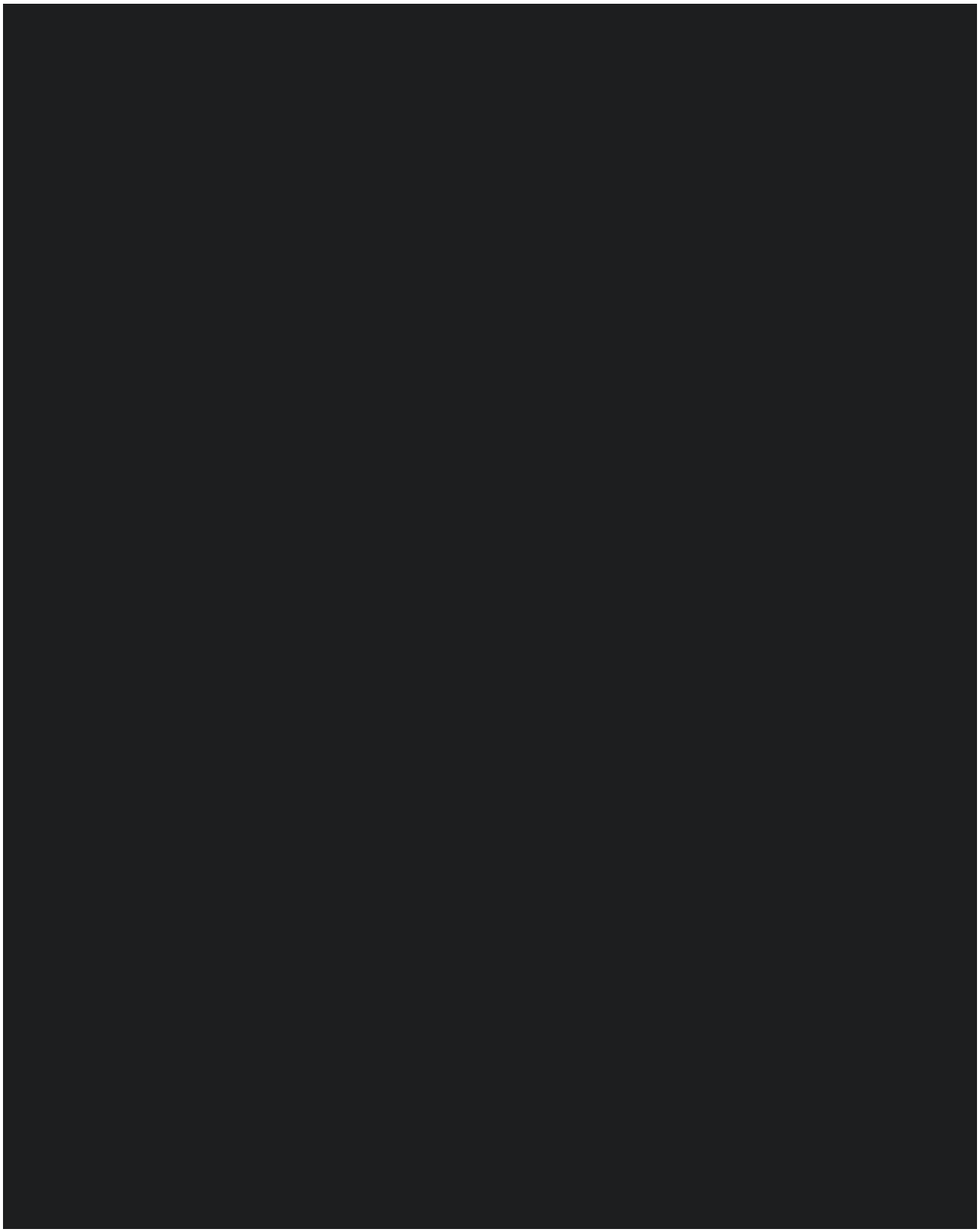
Height (Screening only) and weight will be measured and documented. BMI will be calculated at Screening.

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 [redacted] and neurological examinations and mental status examinations will be conducted and documented. An abbreviated physical examination will include assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems. 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.

[redacted]



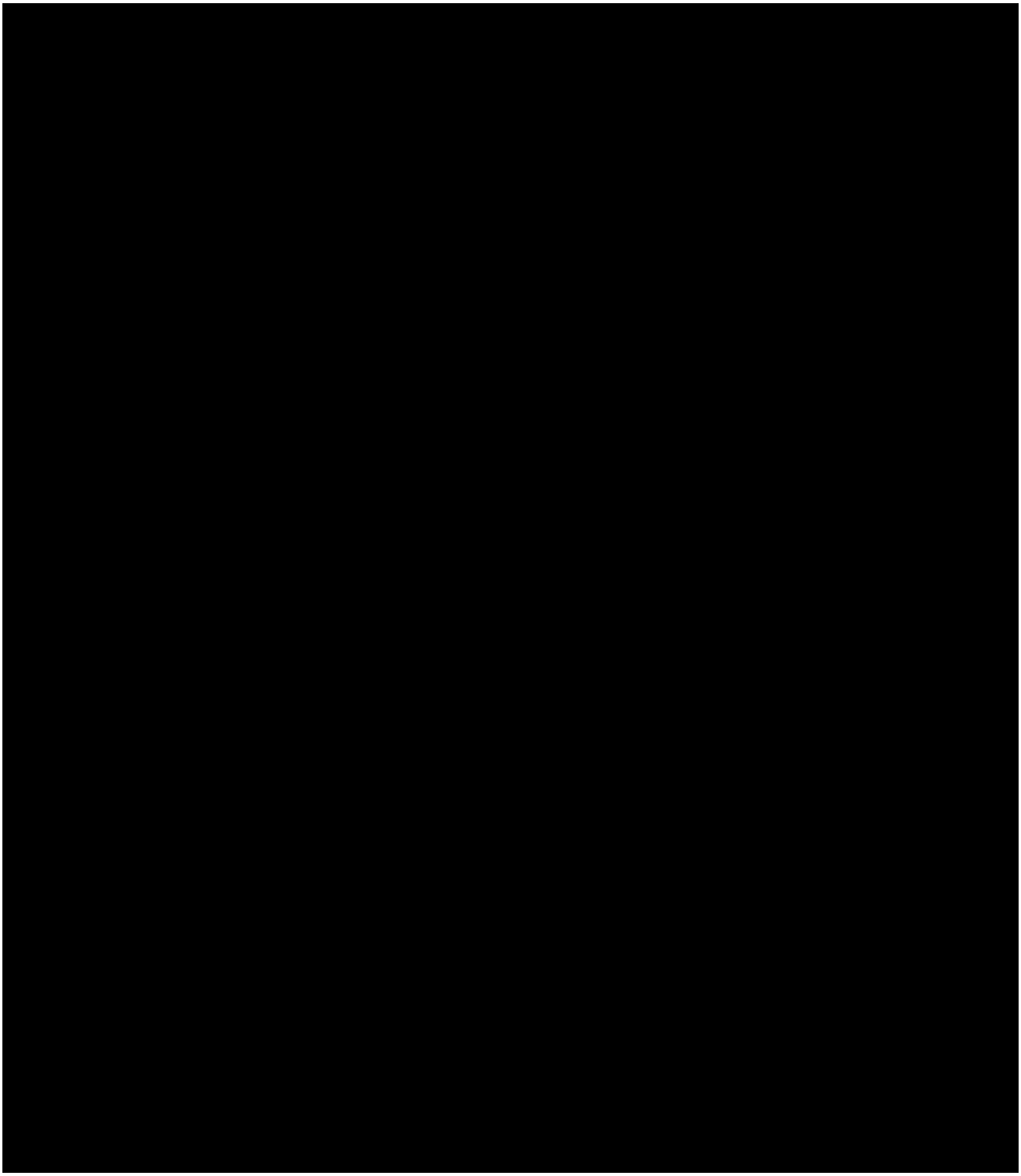
[redacted]

12.1.6.1. Drugs of Abuse and Alcohol

Urine toxicology tests will be performed for selected drugs of abuse (see Table 8). A breath test for alcohol will be performed.

12.1.6.2. Pregnancy Screen

A serum pregnancy test will be conducted for all female subjects at Screening. For female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal, urine pregnancy tests will be performed at scheduled timepoints.



12.2. Adverse and Serious Adverse Events

12.2.1. Definition of 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 drug has been administered.

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

[redacted] and changes from baseline in [redacted], and physical examinations are considered AEs if they result in discontinuation or interruption of study drug, require therapeutic medical intervention, meet protocol specific criteria (if applicable) and/or if the Investigator considers them to be CS. Any abnormality or change from baseline that meets the criteria for an SAE should be reported in an expedited manner. [redacted] and changes from baseline in [redacted] 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.

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. Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor or its representative retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event Definition

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. Any SAE that is ongoing when the subject completes their final study visit, will be followed by the Investigator until the event has resolved, stabilized, returned to baseline status, or until death or lost to follow up.

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.

12.2.3. Relationship to Study Drug

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

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

12.2.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time),

resolution (date and time), intensity, causality, action taken, outcome, and seriousness (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 12.2.2 . An AE of severe intensity may not be considered serious.

12.2.5. Reporting Serious Adverse Events

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

Additional follow-up information, if required or available, should all be sent to Sage 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.

Serious events occurring after the designated follow up time for the study, should be reported to Sage or designee according to the timelines noted above only if the investigator considers the SAE related to study drug. 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. In addition, appropriate personnel in Sage Drug Safety and Pharmacovigilance, or designee, will unblind SUSARs for the purpose of regulatory reporting. Sage, or designee, will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Sage, or designee, will submit SUSARS to Investigators in a blinded fashion.

12.3. Pregnancy

If a participant becomes pregnant after the first administration of study drug, pregnancy information must be collected and recorded on the 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 participant's partner who becomes pregnant while the participant is participating in study. After obtaining the necessary signed informed consent from the

pregnant partner directly, the Investigator will follow the same pregnancy reporting procedures specified for pregnant participants.

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

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

12.4. Overdose

An overdose is defined as more than 2 capsules of study drug given to a subject or taken by a subject in a 24-hour period. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an Overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded.

13. STATISTICS

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

13.1. Data Analysis Sets

The Enrolled Set is defined as all subjects who receive a dose of study drug in the OL phase.

The Randomized Set is defined as all subjects who are randomized in the DB phase.

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

The Full Analysis Set is defined as all randomized subjects in the Safety Set with a valid baseline and at least 1 post-baseline HAM-D total score.

[redacted]

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available.

13.3. General Considerations

Continuous endpoints will be summarized descriptively with n, mean, standard deviation, median, minimum, and maximum. 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 BMI, will be summarized using the Safety Set.

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

Medical/family history will be listed by subject.

13.5. Efficacy Analyses

13.5.1. Primary Efficacy Analysis

The estimand is the time to relapse – number of days between the first dose in the first treatment period of the DB phase to the day of relapse. The analysis will use the Full Analysis Set. Kaplan-Meier survival curves will be provided, along with the median time to relapse. Log-rank test will be used to compare the survival curves at the significance level of 0.05.

13.5.2. Secondary and [redacted]

Using FAS, the change from baseline will be summarized by randomized treatment group and each scheduled time point where the evaluation has been made. Baseline is defined as the last measurement prior to dosing in the DB Phase. A mixed effects model for repeated measures

(MMRM) will be used for analysis; the model will include treatment, baseline value, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All post-baseline time points for the specific study period will be included in the model. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

For analysis of binary endpoints, the estimand is the odds ratio. The Generalized estimating equation (GEE) methods will be used for the analysis. GEE models will include terms for treatment, baseline value, assessment time point, and time point-by-treatment as explanatory variables. Model-based point estimates (ie, odds ratios), 95% confidence intervals, and p-values will be reported.

Time to relapse for remitters at the end of OL phase will be analyzed the same way as done for primary efficacy analysis.

Endpoints for the OL phase will be summarized by each scheduled timepoint, based on Enrolled Set.

Analysis of exploratory endpoints will be detailed in the SAP.

13.6. Safety Analyses

Safety and tolerability of SAGE-217 will be evaluated by incidence of adverse events/serious adverse events, and [redacted] Safety Set will be used for safety analyses.

Safety and tolerability will be summarized for the OL phase using the Enrolled Set.

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.

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).

[redacted]

13.6.3. Physical Examinations

The occurrence of a physical examination (Y/N) and the date performed will be listed by subject.

[redacted]

13.6.6. Prior and Concomitant Medications

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

All medications taken within 30 days prior to signing the ICF through the duration of the study will be recorded. In addition, all psychotropic medications taken 6 months prior to Screening and all GABAergic medications taken 12 months prior to Screening will be recorded. Those medications taken prior to the initiation of the start of study drug will be denoted “Prior”. Those medications taken prior to the initiation of the study drug and continuing beyond the initiation of the study drug or those medications started at the same time or after the initiation of the study drug will be denoted “Concomitant” (ie, those with a start date on or after the first dose of study drug, or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug).

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

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

[redacted]

13.8. Determination of Sample Size

The randomization in the DB phase is 1:1, with 150 subjects randomized in each treatment arm – placebo and SAGE-217. Assuming a relapse rate of 34% in the placebo arm (Borges 2014) and 17% in the SAGE-217 arm for a fixed 40-week repeated treatment regimen (Hazard ratio = 0.448), this sample size will provide a 90% power with 0.05 level of significance in comparing time to relapse (through comparison of survival curves) by Log-Rank test. Further, assuming that only 55% of the subjects dosed in the OL phase will qualify as responders to be randomized in the DB phase, 546 subjects will need to be dosed in the OL phase.

An interim analysis is planned when about 50% of expected relapse events occur (ie, 34 of 67 expected relapse events) to estimate the hazard ratio with a view to re-estimate the sample size. This unblinded interim analysis will be performed by an independent third party, external to the Sponsor, with specific directions on how to conclude depending on the range of hazard ratio observed. The final analysis will be performed after the last randomized subject completes (or ET) the study. The methods to control the type I error rate will be provided in the SAP.

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 will visit the investigational study site per Sage SOPs 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 or EC.

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

14.2. Audits and Inspections

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board or Ethics Committee

The Principal Investigator must obtain IRB (or EC) approval for the investigation. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practice 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 ICF, must be approved or given a favorable opinion in writing by an IRB or EC as appropriate. The investigator must submit written approval to Sage Therapeutics before he or she can enroll any subject into the study.

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

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

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice, 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 and its representative 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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