Official Title:	**A Phase 3, Randomized, Double-Blind Study Comparing the Efficacy and Safety of SAGE-217 Plus an Antidepressant Versus Placebo Plus an Antidepressant in Adults With Major Depressive Disorder**
NCT Number:	NCT04476030
Document Dates:	Protocol Version 4.0: 10 January 2022 Protocol Version 3.0: 22 January 2021 Protocol Version 2.0: 14 September 2020 Protocol Version 1.0: 14 May 2020

1. PROTOCOL AND AMENDMENTS

The original/initial protocol, Version 1.0, dated 13 May 2020, was amended 3 times.

The title of the study was updated as of Version 2.0.

Version Number	Date	Title
4.0	10 January 2022	A Phase 3, Randomized, Double-blind Study Comparing the Efficacy and Safety of SAGE-217 plus an Antidepressant versus Placebo plus an Antidepressant in Adults with Major Depressive Disorder
3.0	22 January 2021	
2.0	11 September 2020	
1.0	13 May 2020	A Phase 3, Randomized, Double-blind Study Comparing the Efficacy and Safety of SAGE-217 plus Sertraline versus Placebo plus Sertraline in Adults with Major Depressive Disorder

Summary of Changes by Version

Summary of Changes to Version 4.0, 10 January 2022

Summary of Changes to Version 3.0, 22 January 2021

Summary of Changes to Version 2.0, 11 September 2020

STUDY TITLE: A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY COMPARING THE EFFICACY AND SAFETY OF SAGE-217 PLUS AN ANTIDEPRESSANT VERSUS PLACEBO PLUS AN ANTIDEPRESSANT IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

PROTOCOL NUMBER: 217-MDD-305

Investigational Product	SAGE-217
Clinical Phase	Phase 3
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted], MPH [redacted] Tel: [redacted] e-mail [redacted]
Sponsor Medical Monitor	[redacted] MD, MBA [redacted] Tel: [redacted] e-mail [redacted]
Date of Original Protocol	13 MAY 2020
Date of Amendment 1	11 SEP 2020
Date of Amendment 2	22 JAN 2021
Date of Amendment 3	10 JAN 2022

SPONSOR APPROVAL

Protocol Number: 217-MDD-305

Study Title: A Phase 3, Randomized, Double-Blind Study Comparing the Efficacy and Safety of SAGE-217 plus an Antidepressant Versus Placebo plus an Antidepressant in Adults with Major Depressive Disorder

Protocol Version and Date: Version 4, 10 January 2022

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Signer Name: [redacted]
Signing Reason: I approve this document
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[redacted], MD, MBA
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Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-MDD-305 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD/MMM/YYYY)

CONTACT INFORMATION

Table 1: Contact Information

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

2. SYNOPSIS

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

Name of Investigational Product: SAGE-217 Capsules

Name of Active Ingredient: SAGE-217

Title of Study: A Phase 3, Randomized, Double-Blind Study Comparing the Efficacy and Safety of SAGE-217 plus an Antidepressant Versus Placebo plus an Antidepressant in Adults with Major Depressive Disorder

Number of Sites and Study Location: This study will take place at approximately 55 sites in United States.

Phase of Development: 3

Planned Duration for each Study Participant: Up to 70 days (up to 28-day Screening Period, 14-day Double-blind Treatment Period, and a 28-day Antidepressant Therapy (ADT) Continuation Period)

Objectives:

Primary:

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

Secondary:

- To assess patient-reported outcome (PRO) measures as they relate to depressive symptoms
- To evaluate the safety and tolerability of SAGE-217 plus an antidepressant

[redacted]

Endpoints:

Primary:

- Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 3

Key Secondary:

- Change from baseline in HAM-D total score over the blinded treatment period (using equal weights for the scheduled visits – Day 3, Day 8, Day 12, Day 15)

Other Secondary:

- Change from baseline in HAM-D total score at Day 15 and Day 42
- Change from baseline in HAM-D total score around end of blinded treatment (using equal weights for the scheduled visits –Day 12, Day 15, Day 18)
- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- Change from baseline in Clinical Global Impression – Severity (CGI-S) at Day 15
- CGI-I response, defined as “much improved” or “very much improved”, at Day 3 and Day 15
- Change from baseline in MADRS total score at Day 15
- MADRS response at Day 15

- MADRS remission at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline in depressive symptoms at Day 15, as assessed by the PHQ-9
- Incidence and severity of treatment-emergent adverse events (TEAEs)

[redacted]

Study Description:

This is a randomized, double-blind, parallel-group, placebo-controlled study in adults with MDD. 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.

The study will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day ADT Continuation Period. The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit. Preliminary screening procedures to determine eligibility include completion of the MGH-ATRQ and HAM-D.

Participants will be randomized to receive blinded SAGE-217 50 mg or placebo for administration each evening from Days 1 through 14. In addition, all participants will receive 1 of 2 classes of ADTs: a selective serotonin reuptake inhibitor (SSRI; sertraline, escitalopram, citalopram) or a serotonin-norepinephrine reuptake inhibitor (SNRI; duloxetine or desvenlafaxine) in an open-label manner from Day 1 through the end of the study. The ADT will be administered per labeled prescribing information. The investigator will assign 1 of the 5 ADTs based on clinical standard of care; the participant must not have been previously treated with the assigned ADT within the current depressive episode and must not have taken any ADT within 30 days prior to Day 1 (or taken fluoxetine within 60 days prior to Day 1). Randomization will be stratified by ADT class (SSRI or SNRI).

After the double-blind Treatment Period, the ADT will be continued each evening for the remainder of the study (ADT Continuation Period). During this period (Weeks 3 to 6), ADT dosing may be modified based on individual response, at the discretion of the investigator and per the labeled prescribing information.

Initiation of other antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of assessments at Day 42/end-of-study visit.

Participants will self-administer blinded investigational product (IP) once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. The ADT and SAGE-217/placebo will be administered at the same time during the Treatment Period; participants assigned duloxetine will also

administer ADT in the morning (for twice-daily dosing) as part of a divided dose for the first 7 days. Participants will return to the study center as outlined in the Schedule of Assessments (Table 2).

During the Treatment Period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate SAGE-217/placebo 50 mg will receive 40 mg for the remainder of the Treatment Period. Participants who, in the opinion of the investigator, cannot tolerate the SAGE-217/placebo 40-mg dose may be discontinued from SAGE-217/placebo at the discretion of the investigator. If blinded IP is discontinued, the ADT may be continued at the discretion of the investigator.

Upon completion of the current study, eligible participants will have the opportunity to enter a long-term open-label study of SAGE-217.

Number of Participants (planned): It is estimated that approximately 424 participants will be randomized and treated to obtain 382 evaluable participants at Day 3 (assuming a 10% dropout rate). Additional participants may be randomized if the dropout rate is greater than 10%.

Eligibility Criteria:

Inclusion Criteria

1. Participant has signed an ICF prior to any study-specific procedures being performed.
2. Participant is a male or female between 18 and 64 years of age, inclusive.
3. Participant is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Participant agrees to adhere to the study requirements.
5. Participant 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. Participant has a HAM-D-17 total score of ≥24 at Screening and Day 1 (prior to dosing).
7. Participant is willing to delay start of any antidepressant (except as per protocol), anxiolytic, anti-insomnia, psychostimulant, prescription opioid regimens, or new psychotherapy (including Cognitive Behavioral Therapy for Insomnia [CBT-I]) until after study completion. Participants receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1 and intend to maintain that schedule for the duration of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence).
9. Female participant who is breastfeeding at Screening or on Day 1 (prior to administration of IP) must be willing to temporarily cease giving breast milk to her child(ren) from just prior to receiving IP on Day 1 until 7 days after the last dose of SAGE-217/placebo.
10. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 5 days after receiving IP, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
11. Male participant is willing to abstain from sperm donation for the treatment period and for 5 days after receiving the last dose of the IP.

12. Participant agrees to refrain from drugs of abuse and alcohol for the duration of the study.
13. Participant is willing, able, and eligible to take at least 1 of the 5 ADTs specified in the protocol (an eligible ADT is an ADT that has not been taken during the current depressive episode and for which the participant has no contraindications; further, a participant is not eligible for citalopram if escitalopram has been taken during the current depressive episode, and vice versa).

Exclusion Criteria

1. Participant is currently at significant risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of MDD.
2. Participant had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the participant has presented for screening during the 6-month postpartum period.
3. Participant has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eye, ear, nose, and throat disorders, or any other acute or chronic condition that, in the investigator's opinion, would limit the participant's ability to complete or participate in this clinical study; a BMI $\leq$18 or $\geq$45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
4. Participant 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 2 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. Participant has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Participant is receiving Cognitive Behavioral Therapy for Insomnia (CBT-I) within 28 days prior to Day 1.
7. Participant has a known allergy to SAGE-217, allopregnanolone, or related compounds.
8. Participant has taken antidepressants within 30 days prior to Day 1, and/or has taken fluoxetine within 60 days prior to Day 1.
9. Female participant has a positive pregnancy test or confirmed pregnancy.
10. Participant has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
11. Participant has active psychosis per investigator assessment.
12. Participant has a medical history of seizures.
13. Participant has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
14. Participant has a history of severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to Screening or participant has a history of mild or moderate substance use disorder not in sustained remission for at least 6 months prior to Screening.
15. Participant has had exposure to another investigational medication or device within 30 days prior to Screening.

16. Participant has previously received brexanolone or participated in a SAGE-217 or SAGE-547 (brexanolone) clinical trial.
17. Participant has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these, within 14 days prior to Day 1.
18. Participant has used any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort, within 28 days prior to Day 1.
19. Participant has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
20. Participant plans to undergo elective surgery before completion of the Day 42 visit.
21. Participant is taking benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Day 1, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Participant is taking any benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1.
22. Participant is taking non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids), or first or second generation (typical/atypical) antipsychotics within 14 days prior to Day 1. Note that nonsedating antihistamines are permitted.
23. Participant has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
24. Participant has a history of sleep apnea.
25. Participant has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
26. Participant is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as needed, within 28 days prior to Day 1.
27. Participant is a dependent of the sponsor, investigator, investigator's deputy, or study site staff.
28. Participant expects to perform night shift work during the 14-day Treatment Period.
29. Participant has detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at Screening.

Investigational Product Dosage and Mode of Administration: SAGE-217 will be available as hard gelatin capsules for oral administration; multiple capsules (in 30-mg or 20-mg dose strengths) will be provided to total a 50-mg dose, with option to reduce to 40 mg based on tolerability.

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217, for oral administration.

Sertraline, escitalopram, citalopram, duloxetine, or desvenlafaxine will be administered as per labeled prescribing information

Duration of Treatment: Blinded SAGE-217 or placebo will be administered once daily for 14 days; open-label ADT will be administered according to labeled prescribing information for 42 days.

Statistical Methods:

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock and treatment unblinding. Any deviations from or changes to the SAP following database lock will be detailed in the Clinical Study Report.

General Considerations

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

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized participants who administered blinded IP and have a valid baseline total score and at least 1 valid postbaseline total score in at least one of HAM-D, HAM-A, MADRS, PHQ-9 or have a valid baseline and at least 1 valid post-baseline value in at least one of CGI-S or CGI-I score.

The Safety Set is defined as all participants who administered blinded IP.

The Safety Set – ADT Only is defined as all participants who administered assigned ADT at baseline but did not administer any dose of blinded IP.

The Randomized Set, defined as all participants who are randomized.

[redacted]

The definition and details of the Per Protocol Set are outlined in the SAP.

Determination of Sample Size

Using a two-sided alpha level of 0.05, a sample size of 382 total evaluable participants would provide 90% power to detect a treatment difference (between SAGE-217 + an antidepressant and placebo + an antidepressant) of approximately 3 points in the primary endpoint, change from baseline in HAM-D total score at Day 3, assuming standard deviation of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each treatment group, approximately 424 total randomized participants will be required to obtain a total of 382 evaluable participants. Evaluable participants are defined as those randomized participants who receive IP and have valid baseline and at least 1 postbaseline HAM-D assessment.

Analysis of Primary Endpoint

The estimand for the primary analysis is the mean change from baseline in HAM-D total score at Day 3 (see Section 13.5 for more details). Using FAS, this will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline time points will be included in the model. The main comparison will be between SAGE-217 + an antidepressant and placebo + an antidepressant at the 3-day time point. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p values) will be reported along with 95% confidence intervals, and p-values. An unstructured covariance structure (with the default Newton-Raphson algorithm used by SAS PROC MIXED) will be used to model the within-participant errors. If there is a convergence issue with the unstructured covariance model, the Fisher Scoring algorithm (via the SCORING option of the PROC MIXED statement), the no-diagonal factor analytic structure (via the TYPE=FA0(*T*) option of the REPEATED statement, where *T* is the total number of time points),Toeplitz compound symmetry, Autoregressive

(1) [AR(1)] covariance structure will be used, following this sequence. If convergence is still not achieved, no results will be reported.

Analysis of Secondary Endpoints

Similar to those methods described above for the primary endpoint, an MMRM will be used for the analysis of the change from baseline in other time points in HAM-D total score, MADRS total score, HAM-A total score, CGI-S score, and PHQ-9 total score.

Generalized estimating equation methods will be used for the analysis of HAM-D response (defined as ≥50% reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of ≤7.0). GEE models will include terms for center, treatment, baseline score, 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 for all assessment time points.

A GEE method will also be used for the analysis of CGI-I response including terms for center, treatment, baseline CGI-S score, 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 for all assessment time points.

Safety Analysis

Safety and tolerability of IP will be evaluated by adverse events (AEs)/serious adverse event (SAEs), [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set and Safety Set – ADT only.

[redacted]

Table 2: Schedule of Assessments

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

Visits	Screening Period	Double-Blind, Placebo-Controlled Treatment Period					ADT Continuation Period				
Visit Days	**D-28 to D-1**	**D1**	**D3 (±1d)**	**D8 (+1d)**	**D12 (±1d)**	**D15 (+1d)**	**D18 (±1d)**	**D21 (±1d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d) /ET**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Study Procedure											
[redacted]											
Vital Signs [k]	X	X	X	X	X	X	X		X		X
12-Lead ECG [l]	X	X				X					X
[redacted]											
HAM-D [n, o]	X	X	X	X	X	X	X	X	X	X	X
MADRS		X		X		X			X		X
HAM-A [o]		X		X		X			X		X
CGI-S	X	X	X	X	X	X		X	X	X	X
CGI-I			X	X	X	X		X	X	X	X
[redacted]											
PHQ-9		X	X	X		X			X		X
[redacted]											
SAGE-217/Placebo Dispensation		X		X							
SAGE-217/Placebo Administration		X (once daily in the evening through Day 14 - inclusive)									
IP Adherence [q]		X									

Visits	Screening Period	Double-Blind, Placebo-Controlled Treatment Period					ADT Continuation Period				
Visit Days	D-28 to D-1	D1	D3 (±1d)	D8 (+1d)	D12 (±1d)	D15 (+1d)	D18 (±1d)	D21 (±1d)	D28 (±3d)	D35 (±3d)	D42 (±3d) /ET
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Study Procedure											
ADT Administration [r]		X									
IP Accountability/Return			X	X		X		X	X	X	X
AEs/SAEs [c, s]	X										
Prior/Concomitant Medications/Procedures [c, t]	X										

Abbreviations: ADT = Antidepressant therapy; AE = adverse event; CGI-I = Clinical Global Impression – Improvement; CGI-S – Clinical Global Impression – Severity; [redacted] D = day; ET = early termination; ECG = electrocardiogram; FSH = follicle stimulating hormone; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; IP = investigational product; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; PHQ-9 = 9-item Patient Health Questionnaire; [redacted] O = Optional; [redacted] SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Clinical Trials Version; [redacted] V = visit.

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

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

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

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

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

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

[g] Urine toxicology for selected drugs of abuse (Table 3) and breath test for alcohol.

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

[redacted]

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

[l] Triplicate ECGs will be collected. [redacted]

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

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

[redacted]

[q] IP administration will be monitored via a medication adherence monitoring platform used on smartphones to confirm IP ingestion. IP adherence will not be captured after participants discontinue IP.

[r] ADT will be administered as per labeled prescribing information

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

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

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

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation	Definition
ADT	Antidepressant therapy
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulation
CRO	contract research organization
CSR	clinical study report
IEC	independent ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
IP	investigational product
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PI	prescribing information
PK	pharmacokinetic
PV	pharmacovigilance
QA	quality assurance
QC	quality control
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SOP	Standard Operating Procedure

Abbreviation	Definition
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Major Depressive Disorder and Unmet Medical Need

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

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

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association 2013) provides diagnostic criteria for major depressive disorder (MDD). These include at least 5 of 9 depressive symptoms (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 (SNRI), serotonin norepinephrine reuptake inhibitors (SSRI), tricyclic antidepressants, monoamine oxidase inhibitors (MAOI), 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). Furthermore, these agents can take 4 to 8 weeks to demonstrate full clinical efficacy (Rush 2006; Trivedi 2006), and in the case of the most commonly prescribed classes—SSRIs and SNRIs—common side effects including weight gain, GI symptoms, and sexual dysfunction can prevent titration into an adequate therapeutic range (Sadock and Sadock 2007).

In the largest study to assess the effectiveness of depression treatments in patients with MDD, time to patient remission after treatment was 5.4 to 7.4 weeks; approximately one-half of the patients who ultimately remitted did so after 6 weeks, and 40% of those who achieved remission required 8 or more weeks to do so (Rush 2006; Trivedi 2006). Even following remission, many patients report the presence of residual symptoms, often related to decreased positive affect, such as loss of interest in activities once considered enjoyable, fatigue, loss of energy, as well as sleep and appetite/weight disturbances (Nierenberg 2009; Nierenberg 2015). Thus, patients may remain symptomatic for up to 2 months while waiting for current standard-of-care pharmacotherapy to take full effect. They may also have to contend with undesirable side effects and residual symptoms. These aspects underscore the need for newer, rapid-acting therapies.

SAGE-217 is a synthetic positive allosteric modulator of $GABA_A$ receptors, the major class of inhibitory neurotransmitter receptors in the brain. In pharmacokinetic (PK) studies in mice and

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

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) associated with SAGE-217 (overall) were sedation, somnolence, and dizziness; most adverse events (AEs) were reported as mild or moderate in intensity. Refer to the SAGE-217 Investigator's Brochure for a detailed description of the chemistry, pharmacology, efficacy, and safety of SAGE-217.

This study was designed to target the unmet need of symptom improvement during the latency to SSRI and SNRI efficacy in the acute phase of a major depressive episode. This study will assess the safety and efficacy of SAGE-217 50 mg plus an antidepressant, examining if SAGE-217 plus an antidepressant produces more rapid or more profound reduction in depressive symptoms than an antidepressant alone.

5.2. Potential Risks and Benefits

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

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

Based on nonclinical findings, embryo-fetal toxicity and withdrawal effects are considered important potential risk for SAGE-217. Risk mitigation measures in this study include monitoring for adverse effects, monitoring for potential withdrawal effects, requiring highly effective contraceptive measures for study participants, and inclusion of dose adjustment criteria and guidance for blinded IP discontinuation (Section 8.4). Finally, due to the sedation/somnolence observed, SAGE-217 is administered in the evening in this study.

Given the outcome of the completed studies of SAGE-217 in participants with MDD and PDD, the current significant unmet need for well-tolerated and rapid-acting depression treatments, and a favorable benefit-risk profile, further investigation of SAGE-217 as a novel rapid response treatment in adults with MDD is justified.

5.3. Dose Justification

Results from a large, multicenter study of SAGE-217 20 and 30 mg in MDD (217-MDD-301) support the need for higher steady-state concentrations of SAGE-217 to allow participants to experience maximum antidepressant and anti-anxiety benefits. SAGE-217 will be administered as a 14-day regimen of an evening dose of 50 mg with reduction to 40 mg as needed based on tolerability. The 50-mg dose of SAGE-217 is expected to exhibit a favorable benefit-risk profile in the context of results from previous SAGE-217 studies utilizing a 30-mg dose, now identified as a minimally effective dose. SAGE-217 is expected to maintain an acceptable tolerability

profile, based on a current safety database of over 2000 participants exposed across different doses/concentrations.

Sertraline is a commercially available SSRI indicated for the treatment of MDD and other psychiatric disorders. Dosage and administration of sertraline as described in the approved US Prescribing Information (PI) recommends a starting dose of 50 mg per day in patients with MDD, with an incremental weekly increase in dose of 25-50 mg per day, if there is an inadequate response to the starting dose, to a maximum dose of 200 mg per day. . In this study, a starting dose of 50 mg per day is recommended for 7 days, with a subsequent increase to 100 mg per day.

Citalopram and escitalopram are commercially available SSRIs that are both indicated for acute and maintenance treatment of MDD. Escitalopram is also indicated for treatment of generalized anxiety disorder. The starting dosage for MDD in the US PI for citalopram is 20 mg/day and for escitalopram is 10 mg/day, with maxima of 40 mg/day and 20 mg/day, respectively. In this study, a starting dose of 20 mg/day is recommended for citalopram and of 10 mg/day is recommended for escitalopram for the first 14 days; subsequent dose increases may be considered, except for participants >60 years old taking citalopram.

Duloxetine is a commercially available SNRI indicated for the treatment of MDD, generalized anxiety disorder, and pain disorders. The starting dosage for MDD in the US PI is 40 to 60 mg/day. The maximum dosage is 120 mg/day, although there is no evidence that dosages greater than 60 mg/day confer any additional benefits. In this study, a starting dose of 40 or 60 mg/day is recommended (divided as 20 or 30 mg, respectively, twice daily for the first 7 days).

Desvenlafaxine is a commercially available SNRI indicated for the treatment of MDD. The recommended dosage in the US PI is 50 mg/day. In this study, a dose of 50 mg/day is recommended. There has been no evidence that doses greater than 50 mg/day confer any additional benefit.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

To evaluate the efficacy of SAGE-217 plus an antidepressant in the treatment of MDD compared to placebo plus an antidepressant

6.1.2. Secondary Objectives

- To assess patient-reported outcome (PRO) measures as they relate to depressive symptoms
- To evaluate the safety and tolerability of SAGE-217 plus an antidepressant

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoint

- Change from baseline in 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 3

6.2.2. Secondary Endpoints

6.2.2.1. Key Secondary Endpoint

- Change from baseline in HAM-D total score over the blinded treatment period (using equal weights for the scheduled visits – Day 3, Day 8, Day 12, Day 15)

6.2.2.2. Other Secondary Endpoints

- Change from baseline in HAM-D total score at Day 15 and Day 42
- Change from baseline in HAM-D total score around end of blinded treatment at (using equal weights for the scheduled visits –Day 12, Day 15, Day 18)
- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- Change from baseline in CGI-S at Day 15
- CGI-I response, defined as “much improved” or “very much improved”, at Day 3 and Day 15
- Change from baseline in MADRS total score at Day 15
- MADRS response at Day 15

- MADRS remission at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline in depressive symptoms at Day 15, as assessed by the PHQ-9
- Incidence and severity of treatment-emergent AEs

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, parallel-group, placebo-controlled study in adults with MDD. 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.

The study will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day ADT Continuation Period. The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit. Preliminary screening procedures to determine eligibility include completion of the MGH-ATRQ and HAM-D.

Participants will be randomized to receive blinded SAGE-217 or placebo for administration each evening from Day 1 through 14. In addition, all participants will receive 1 of 2 classes of ADTs: a selective serotonin reuptake inhibitor (SSRI; sertraline, escitalopram, citalopram) or a serotonin-norepinephrine reuptake inhibitor (SNRI; duloxetine, desvenlafaxine) in an open-label manner from Day 1 through the end of the study. The investigator will assign 1 of the 5 ADTs based on clinical standard of care; the participant must not have been previously treated with the assigned ADT within the current depressive episode (and must not have been treated with citalopram if escitalopram is assigned, and vice versa) and must not haven taken any ADT within 30 days prior to Day 1 (or taken fluoxetine within 60 days prior to Day 1). Randomization will be stratified by antidepressant class (SSRI or SNRI).

The open-label ADT will be administered as per labeled prescribing information.

After the Double-blind Treatment Period, the ADT will be continued each evening for the remainder of the study (ADT Continuation Period). During this period (Week 3 to 6), ADT dosing may be modified as appropriate per the labeled prescribing information and based on individual response.

Initiation of other antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of assessments at Day 42/end-of-study visit.

Participants will self-administer blinded investigational product (IP) once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. The ADT and SAGE-217 or placebo will be administered at the same time during the Treatment Period; participants assigned duloxetine will also administer ADT in the morning (for twice-daily dosing) as part of a divided dose for the first 7 days. Participants will return to the study center as outlined in the Schedule of Assessments.

During the Treatment Period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate SAGE-217 or placebo 50 mg will receive 40 mg for the remainder of the Treatment Period. Participants who cannot tolerate the SAGE-217/placebo 40-mg dose may be discontinued from SAGE-217 or placebo at the discretion of the investigator. If blinded IP is discontinued, the ADT may be continued at the discretion of the investigator.

Upon completion of the current study, eligible participants will have the opportunity to enter a long-term open-label study of SAGE-217. Participants that do not enter the open-label study or that terminate the current study early may, per the investigator, receive a supply of the ADT with instructions on how to taper the drug, if needed, or, if they wish to continue the ADT, a bridge supply to permit them to obtain a prescription from another provider.

7.2. Number of Participants

It is estimated that approximately 424 participants will be randomized and treated to obtain 382 evaluable participants at Day 3 (assuming 10% dropout rate). Additional participants may be randomized if the dropout rate is greater than 10%.

7.3. Treatment Assignment

Participants will be assigned to blinded IP (SAGE-217 or placebo) in accordance with the randomization schedule on Day 1. The investigator will assign 1 of the 5 ADTs based on clinical standard of care. The assigned ADT for a participant cannot have been taken previously by the participant during the current depressive episode. Further, citalopram cannot be assigned if escitalopram has been taken during the current depressive episode, and vice versa.

Randomization will be stratified by antidepressant class (SSRI or SNRI).Additional details on randomization and blinding are provided in Section 9.5.

Sage will monitor the ratio of SSRIs:SNRIs on an ongoing basis and may restrict assignment of any ADT(s) to reflect the ratio expected with standard of care (approximately 3:1; Luo 2020).

7.4. Dose Adjustment Criteria

During the treatment period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate 50 mg (as determined by the investigator) will receive 40 mg for the remainder of the treatment period.

At the discretion of the investigator, participants who cannot tolerate the 40-mg dose at any time may be discontinued from dosing. These participants should be followed and complete assessments as per the Schedule of Assessments (Table 2).

During Weeks 3 to 6, the ADT dosing may be modified, based on individual response, per investigator discretion and per the labeled prescribing information.

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 participants, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the investigator. Investigational sites must promptly notify their IRB, where required, and initiate withdrawal procedures for participating participants.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

1. Participant has signed an ICF prior to any study-specific procedures being performed.
2. Participant is a male or female between 18 and 64 years of age, inclusive.
3. Participant is in good physical health and has no clinically significant findings, as determined by the investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Participant agrees to adhere to the study requirements.
5. Participant 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. Participant has a HAM-D-17 total score of ≥24 at Screening and Day 1 (prior to dosing).
7. Participant is willing to delay start of any antidepressant (except as per protocol), anxiolytic, anti-insomnia, psychostimulant, prescription opioid regimens, or new psychotherapy (including Cognitive Behavioral Therapy for Insomnia [CBT-I]) until after study completion. Participants receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1 and intend to maintain that schedule for the duration of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence).
9. Female participant who is breastfeeding at Screening or on Day 1 (prior to administration of IP) must be willing to temporarily cease giving breast milk to her child(ren) from just prior to receiving IP on Day 1 until 7 days after the last dose of SAGE-217/placebo.
10. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 5 days after receiving IP, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
11. Male participant is willing to abstain from sperm donation for the treatment period and for 5 days after receiving the last dose of the IP.
12. Participant agrees to refrain from drugs of abuse and alcohol for the duration of the study.
13. Participant is willing, able, and eligible to take at least 1 of the 5 ADTs specified in the protocol (an eligible ADT is an ADT that has not been taken during the current depressive episode and for which the participant has no contraindications; further, a participant is not eligible for citalopram if escitalopram has been taken during the current depressive episode, and vice versa).

8.2. Participant Exclusion Criteria

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

1. Participant is currently at significant risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of MDD.
2. Participant had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the participant has presented for screening during the 6-month postpartum period.
3. Participant 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 participant's ability to complete or participate in this clinical study; a BMI $\leq$18 or $\geq$45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
4. Participant 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 2 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. Participant has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Participant is receiving Cognitive Behavioral Therapy for Insomnia (CBT-I) within 28 days prior to Day 1.
7. Participant has a known allergy to SAGE-217, allopregnanolone, or related compounds.
8. Participant has taken antidepressants within 30 days prior to Day 1, and/or has taken fluoxetine within 60 days prior to Day 1.
9. Female participant has a positive pregnancy test or confirmed pregnancy.
10. Participant has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
11. Participant has active psychosis per investigator assessment.
12. Participant has a medical history of seizures.
13. Participant has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.

14. Participant has a history of severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to Screening or participant has a history of mild or moderate substance use disorder not in sustained remission for at least 6 months prior to Screening.
15. Participant has had exposure to another investigational medication or device within 30 days prior to Screening.
16. Participant has previously received brexanolone or participated in a SAGE-217 or SAGE-547 (brexanolone) clinical trial.
17. Participant has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to Day 1.
18. Participant has used any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort, within 28 days prior to Day 1.
19. Participant has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
20. Participant plans to undergo elective surgery before completion of the Day 42 visit.
21. Participant is taking benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Day 1, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Participant is taking any benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1.
22. Participant 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 within 14 days prior to Day 1. Note that nonsedating antihistamines are permitted.
23. Participant has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
24. Participant has a history of sleep apnea.
25. Participant has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
26. Participant is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as needed, within 28 days prior to Day 1.
27. Participant is a dependent of the sponsor, investigator, investigator's deputy, or study site staff.
28. Participant expects to perform night shift work during the 14-day treatment period.
29. Participant has detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at Screening.

8.3. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

8.4. Investigational Product Discontinuation and Early Termination from the Study

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

Based on known withdrawal symptoms with other GABAergic drugs and nonclinical 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 blinded IP discontinuation or dose reduction are presented to support participant safety:

1. Any participant reporting a confirmed or suspected seizure at any time will be discontinued from blinded IP but will continue to be followed in the study.
2. The investigator should monitor the course of CNS-based signs and symptoms suggestive of a seizure which are not accounted for by comorbid psychiatric or medical conditions. Examples of reported serious or severe events which may reflect an oncoming and/or increased risk for seizure may include temporary confusion, tremors, involuntary muscle fasciculations or jerking movements of arms or legs, or paresthesia. Should such symptoms occur, the investigator should consider decreasing the dose of SAGE-217 or placebo to 40 mg, stopping treatment to assess the effect on the symptom(s) (eg, resolution, improvement), or discontinuing the participant from treatment. A participant who discontinues treatment should remain in the study and continue protocol-required assessments until the end of the study.

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

8.4.1. Investigational Product Discontinuation

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

Participants who discontinue treatment early should complete remaining study visits as scheduled through Day 42 (ie, relative to Day 1), unless the participant withdraws consent.

8.4.2. Early Termination from the Study

If a participant decides to terminate the study, the participant should return for an early termination (ET) visit, if possible. The primary reason for early termination from the study must

be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF).

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

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

Participants who terminate from the study early may, per the investigator, receive a supply of the ADT with instructions on how to taper the drug, if needed, or, if they wish to continue the ADT, a bridge supply to permit them to obtain a prescription from another provider.

8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after 3 attempts at contacting the participant have been unsuccessful.

8.4.4. Replacement of Participants

Participants will not be replaced.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Products

SAGE-217 will be available as hard gelatin capsules for oral administration; 2 capsules (one 30 mg and one 20 mg) will be provided to total a 50-mg dose, with option to reduce to 40 mg based on tolerability, as per criteria described in Section 7.4. If the dose is reduced to 40 mg, it will be administered as 2 20-mg capsules.

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217, for oral administration.

All participants will self-administer blinded and open-label IP orally at approximately 8 PM with fat-containing food for 14 days. Participants assigned duloxetine will also administer duloxetine in the morning (for twice daily dosing) as part of a divided dose for the first 7 days (see below).

It is recommended that sertraline be administered as per labeled prescribing information, starting with 50 mg each evening during Week 1. and It is recommended that the dose be increased to 100 mg each evening during Week 2.

It is recommended that citalopram be administered per labeled prescribing information, starting with 20 mg/day.

It is recommended that escitalopram be administered per labeled prescribing information, starting with 10 mg/day.

It is recommended that duloxetine be administered per labeled prescribing information, starting with 40 or 60 mg/day (divided as 20 or 30 mg, respectively, twice daily for the first 7 days).

It is recommended that desvenlafaxine be administered per labeled prescribing information, starting with 50 mg/day.

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

9.2.1. Prior and Concomitant Medications and/or Supplements

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

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

9.2.2. Prohibited Medications

The following specific classes of medications are prohibited:

- Initiation of new psychotropic medications through the Day 42 visit
- Initiation of new antidepressant therapy from 30 days (60 days for fluoxetine) prior to Day 1 through the Day 42 visit

- Use of any benzodiazepines, barbiturates, $GABA_A$ modulators, GABA-containing agents from Day -28 through the Day 42 visit (from Day -60 for benzodiazepines or GABA modulators with a half-life ≥48 hours)
- Chronic or as-needed psychostimulants (eg, methylphenidate, amphetamine) or opioids from Day -28 through the Day 42 visit
- First generation (typical) antipsychotics (eg, haloperidol, perphenazine) and second generation (atypical) antipsychotics (eg, aripiprazole, quetiapine) from Day -14 through the Day 42 visit
- Use of any non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids) from Day -14 to Day 1. Note that nonsedating antihistamines are permitted.
- Exposure to another investigational medication or device from 30 days prior to Screening through the Day 42 visit
- Any known strong inhibitors of CYP3A4 from Day -28 or 5 half-lives prior to Day 1 (whichever is longer) through the Treatment Period
- Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort from Day -28 through the Treatment Period
- Any contraindications to the assigned SSRI/SNRI per labeled prescribing information

9.2.3. Other Restrictions

Any specific restrictions for the assigned SSRI/SNRI with concomitant medications per the labeled prescribing information should be considered.

The consumption of grapefruit juice, grapefruit, or Seville oranges, or products containing these is prohibited within 14 days prior to Day 1 and throughout the treatment period.

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

Female participants who are lactating or actively breastfeeding must stop giving breast milk to the baby(ies) starting on Day 1 until 7 days after the last dose of SAGE-217/placebo.

Elective surgeries or procedures are prohibited through the Day 42 visit.

Participants must not participate in night shift work during the Treatment Period.

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

Participants receiving psychotherapy on a regular schedule for at least 60 days prior to Day 1 are permitted if the participant intends to continue that schedule through the Follow-up Period (Day 42). Initiation of new psychotherapy is prohibited until after study completion.

9.2.4. Acceptable Forms of Contraception

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

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

Acceptable forms of contraception for male participants include:

- History of vasectomy (performed at least 3 months prior to screening)
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

9.3. Intervention after the End of the Study

Upon completion of the current study, eligible participants will have the opportunity to enter an open-label, long-term study of SAGE-217 in which additional treatment with SAGE-217 will be offered. Participants that do not enter the open-label study or that terminate the current study early may continue to receive ADT as prescribed by the investigator either to taper the drug appropriately or—if the participant wishes to continue ADT—to bridge the participant until he or she receives a new prescription.

9.4. Treatment Adherence

Investigational products will be self-administered by participants (see Section 10.5).

Administration of blinded and open-label IP will be monitored by a medication adherence monitoring platform used on smartphones to confirm IP ingestion. Participants will receive a reminder within a predefined time window to take IP while using the application and will follow a series of prescribed steps to confirm their ingestion of the medication. For visually confirmed IP ingestion, the application will record the date and time of IP administration by dose level, as well as missed doses.

In addition, participants will be instructed to bring their SAGE-217 or placebo dosing kit and ADT to the site as outlined in Table 2, at which time the investigator or designee will be responsible for ensuring the kit contains sufficient doses for the duration of the treatment period.

All participants should be reinstructed about the dosing requirements during study contacts. The authorized study personnel conducting the reeducation must document the process in the participant source records.

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

9.5. Randomization and Blinding

Participants will be randomized in a 1:1 ratio to receive SAGE-217 or matched placebo. Participants, site staff, and the sponsor will be blinded to treatment allocation. All participants will also receive an open-label ADT. Randomization will be performed centrally via an interactive response technology (IRT) system. Randomization schedules will be generated by an independent statistician. The allocation to blinded treatment (SAGE-217or placebo) will be based on the randomization schedule. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

9.5.1. Emergency Unblinding

During the study, the blind is to be broken by the investigator via the IRT system only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate risk, the investigator should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a participant. The responsibility to break the treatment code resides solely with the investigator. If the unblinding occurs without Sage's knowledge, the investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the IP allocation for a participant is unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's records and on the eCRF.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Products

10.1.1. Blinded Investigational Products

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

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217.

10.1.2. Open-label Investigational Product

Sertraline, escitalopram, citalopram, duloxetine, and desvenlafaxine, packaged and labeled by the commercial manufacturer, will be supplied by a third-party vendor. Open-label IP is to be stored and administered according to the package insert. Open-label IP during this study is for use only as directed in this protocol.

10.2. Blinded Investigational Product Packaging and Labeling

SAGE-217 and placebo will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the blinded IP in appropriately labeled, participant-specific kits containing sealed unit doses. Each unit dose for 40-mg and 50-mg dose levels consists of 2 capsules. Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Labels with all required information and conforming to all applicable FDA Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices guidelines will be prepared by the sponsor for SAGE-217 and placebo.

10.3. Blinded Investigational Product Storage

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

10.4. Blinded Investigational Product Preparation

Not applicable.

10.5. Blinded and Open-label Investigational Product Administration

Blinded IP and open-label ADT are to be administered orally at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack). Examples of fat-containing snacks include nuts, peanut butter, avocado, eggs, and cheese. Participants assigned duloxetine will also administer duloxetine in the morning (for twice-daily divided dosing) for the first 7 days (see Section 9.1).

If a participant misses a dose of blinded IP or open-label IP, the participant should skip that dose (ie, they should not take the dose in the morning) and take the next scheduled dose.

10.6. Blinded Investigational Product Accountability, Handling, and Disposal

Upon receipt of blinded IP dosing kits, the investigator(s), or the responsible pharmacist or designee, will inspect the kits and complete and follow the instructions regarding receipt and storage in the SAGE-217 Investigator's Brochure and (where applicable) in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the participant-specific kits to participants at the planned dispensation visit intervals outlined in Table 2. Site staff will access the IRT at the Screening Visit to obtain a participant identification (ID) number for each participant that has signed an informed consent form. On Day 1, site staff will access the IRT and provide the necessary participant-identifying information, including the participant ID number assigned at Screening, to randomize the eligible participant into the study and obtain the medication ID number for the blinded IP to be dispensed to that participant. The medication ID number and the number of blinded capsules dispensed must be recorded.

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

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

The blinded IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all blinded IP received, used and returned/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.

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

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

10.7. Blinded Investigational 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 provided in Table 1.

Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

11. EFFICACY AND CLINICAL PHARMACOLOGY ASSESSMENTS

11.1. Efficacy Assessments

11.1.1. Hamilton Rating Scale for Depression

The primary outcome measure is the change from baseline in 17-item HAM-D total score at Day 3. Every effort should be made for the same rater to perform all HAM-D assessments for an individual participant. An assessment timeframe of past 7 days (1 week) will be used at Screening, and 'Since Last Visit' will be used for all other visits.

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

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

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

11.1.2. Montgomery-Åsberg Depression Rating Scale

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

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

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

11.1.3. Hamilton Anxiety Rating Scale

The 14-item HAM-A will be used to rate the severity of symptoms of anxiety (Williams 2013c; Williams 2013d). Each of the 14 items is defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Scoring for HAM-A is calculated by assigning scores of 0 (not present) to 4 (very severe), with a total score range of 0 to 56, where <17 indicates mild severity, 18 to 24, mild to moderate severity, and 25 to 30, moderate to severe severity. The HAM-A total score will be calculated as the sum of the 14 individual item scores.

11.1.4. Clinical Global Impressions

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

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

The CGI-I employs a 7-point Likert scale to measure the overall improvement in the participant's condition posttreatment. The investigator will rate the participant's total improvement whether or not it is due entirely to drug treatment. Response choices include: 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]

11.1.6. Patient Health Questionnaire

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

The PHQ-9 total score will be calculated as the sum of the 9 individual item scores. The PHQ-9 total score will be categorized as follows: 0 to 4 = minimal depression, 5 to 9 = mild depression, 10 to 14 = moderate depression, 15 to 19 = moderately severe depression; and 20 to 27 = severe depression.

[redacted]

[redacted]

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

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

12.1.1. Demographic/Medical History

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including: family psychiatric history, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, persistent depressive disorder, postpartum depression, substance use disorder, alcohol use disorder, MDD with seasonal pattern, MDD with psychotic features, premenstrual dysphoric disorder, MDD with atypical features, schizophrenia; or schizoaffective disorder will be documented. The diagnosis of MDD will be determined using the SCID-5-CT. If available, the disease code associated with the diagnosis of MDD based on the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used to determine whether the participant has treatment-resistant depression, defined as persistent depressive symptoms despite treatment during the current major depressive episode with adequate doses of antidepressants from 2 different classes for at least 4 weeks of treatment.

12.1.2. Weight and Height

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

12.1.3. Physical Examination

Physical examinations assessing body systems (eg, head, eyes, ears, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Thereafter, abbreviated physical examinations will include brief assessments of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical examination as needed. Unscheduled, symptom-directed physical examinations may also be conducted at the investigator's discretion. Whenever possible, the same individual is to perform all physical examinations for a given participant. Unscheduled brief, symptom-driven physical examinations may also be conducted per the investigator's discretion.

Any abnormality in physical examinations will be interpreted by the investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.

12.1.4. COVID-19 Questions

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

Questions to be asked are as follows:

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

12.1.5. Vital Signs

Vital signs comprise both supine and standing for systolic and diastolic blood pressure and heart rate measurements. Heart rate and blood pressure are to be collected in supine position after the participant has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Respiratory rate and temperature are collected once, in either position. Vital signs will be documented. When vital signs are scheduled at the same time as blood draws, vital signs will be obtained first.

Any abnormality in vital signs will be interpreted by the investigator as abnormal, NCS or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.

12.1.6. Electrocardiogram (ECG)

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

12.1.7. Laboratory Assessments

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

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

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

All clinical laboratory test results outside the central laboratory's reference range will be interpreted by the investigator as abnormal, NCS; or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs,

assessed according to Section 12.2.1. A clinically significant laboratory abnormality following participant randomization will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

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

Table 3: Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis**	**Coagulation**
Red blood cell count Hemoglobin Hematocrit White blood cell count with differential Platelet count Red Blood Cell Indices (MCV, MCH, MCHC) Reflex to Red blood cell morphology if indices are abnormal	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase Gamma-glutamyl transferase Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphorus Triglycerides Thyroid stimulating hormone (TSH) Reflex to free T3/T4 if TSH is abnormal	pH Specific gravity Protein Glucose Red blood cell Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio
Diagnostic			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C Reflex HCV RNA HIV-1 and -2 Female participants that are not surgically sterile and do not meet the protocol-	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine Female participants that are not surgically sterile and do	Alcohol	

defined criteria for being postmenopausal: serum hCG Female participants, if menopause is suspected and not surgically sterile: FSH	not meet the protocol-defined criteria for being postmenopausal: urine hCG		

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

A serum follicle stimulating hormone test will be conducted at Screening to confirm whether a female participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal (Section 8.1).

12.1.7.1. Drugs of Abuse and Alcohol

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

12.1.7.2. Pregnancy Screen

For female participants that are not surgically sterile, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at all other scheduled time points thereafter, including the ET visit for participants who prematurely discontinue.

[redacted]

12.2. Adverse and Serious Adverse Events

12.2.1. Adverse Event Definition

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

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

[redacted] are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for an SAE should be reported in an expedited manner. [redacted] that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

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

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

12.2.2. Serious Adverse Event Definition

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

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

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

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

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

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

12.2.3. Relationship to Investigational Product

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

Not Related	An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the IP. Factors pointing towards this assessment include but are not limited to: the lack of temporal relationship between administration of the IP and the event, the presence of biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE

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

12.2.4. Recording Adverse Events

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

Intensity will be assessed according to the following scale:

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

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

12.2.5. Reporting Serious Adverse Events

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

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

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

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

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

12.3. Pregnancy

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

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

clinical manifestation(s) of overdose must also be recorded as an AE on the eCRF. In addition, all overdoses must be recorded on an Overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose.

13. STATISTICS

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

13.1. Data Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized participants who administered blinded IP and have a valid baseline total score and at least 1 valid post-baseline total score in at least one of HAM-D, HAM-A, MADRS, PHQ-9 or have a valid baseline and at least 1 valid post-baseline value in at least one of CGI-S or CGI-I score.

The Randomized Set is defined as all participants who are randomized.

The Safety Set is defined as all participants who administered blinded IP.

The Safety Set – ADT Only is defined as all participants who administered assigned ADT at baseline but did not administer any dose of blinded IP.

[redacted]

The definition and details of the Per Protocol Set are outlined in the SAP.

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all non-missing data available. Missing data for particular visits may be imputed using the visit window and available data, as described in the SAP. Sensitivity analyses will be used to investigate the impact of missing data.

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in a participant data listing, some may be presented with a corresponding table or figure; these will be indicated in relevant sections below. All summaries will be provided by treatment – either by randomized treatment or actual treatment received. Actual treatment is defined as SAGE-217 if the participant received any SAGE-217 (50 mg or 40 mg) at any time; otherwise, it is placebo.

If a participant takes any dose of SAGE-217, the participant's actual treatment is considered as SAGE-217 regardless of the treatment to which the participant has been randomized.

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

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

13.4. Demographics and Baseline Characteristics

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

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 history will be listed by participant.

13.5. Efficacy Analysis

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

The estimand for the primary and key secondary efficacy analysis is defined as follows:

1) The treatment regimens for participants are: SAGE-217 + ADT and placebo + ADT for 14 days.
2) The target population is adult participants with a diagnosis of major depressive disorder and within a current depressive episode of severity HAM-D total score ≥24.
3) The variable of interest is the change from baseline in HAM-D total score.
4) The intercurrent events could be:
    a) The premature discontinuation of treatment for any reason.
    b) Certain medications including, but not limited to, new antidepressants (except for assigned ADT) or benzodiazepines are prohibited, or ADT discontinuation may occur during the study; however, the treatment policy strategy dictates that the results following these prohibited medication use will not be manipulated but will rather be used ‘as is’ in analysis. Please note that the protocol does not specify any rescue process, hence there is no rescue medication.
5) The population summary level is the model-based estimate of the difference between SAGE-217 + ADT and placebo + ADT in change from baseline in HAM-D total score.
    a) The population summary level for the primary endpoint is the model-based estimate of the difference between SAGE-217 + ADT and placebo + ADT in change from baseline in HAM-D total score at Day 3.
    b) The population summary level for the key secondary endpoint is the model-based estimate of the difference between SAGE-217 + ADT and placebo + ADT in change from baseline in HAM-D total score over the blinded treatment period using equal weight to Days 3, 8, 12 and 15.

Using the FAS, this will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline time points will be included in the model. The main comparison

will be between SAGE-217 + assigned ADT and placebo + assigned ADT at the Day 3 time point. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p values) will be reported along with 95% confidence intervals, and p-values. An unstructured covariance structure (with the default Newton-Raphson algorithm used by SAS PROC MIXED) will be used to model the within-participant errors. If there is a convergence issue with the unstructured covariance model, the Fisher Scoring algorithm (via the SCORING option of the PROC MIXED statement), the no-diagonal factor analytic structure (via the TYPE=FA0(*T*) option of the REPEATED statement, where *T* is the total number of time points), Toeplitz compound symmetry, Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If convergence is still not achieved, no results will be reported.

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

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response (defined as ≥50% reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score ≤7.0). GEE models will include terms for treatment, baseline score, 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 for all assessment time points.

A GEE method will also be used for the analysis of CGI-I response, including terms for treatment, baseline CGI-S score, 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 for all assessment time points.

13.5.1. Multiplicity Adjustment for Key Secondary Endpoint

Multiplicity adjustment to statistical testing of the hypothesis of the key secondary endpoint will be conducted by using a fixed-sequence strategy. Only if the primary endpoint is statistically significant at 0.05 level, the key secondary endpoint will be tested at 5% level of significance.

None of the 'other secondary' or 'other' endpoints will be adjusted for multiplicity, and hence all p-values are considered nominal.

13.6. Safety Analyses

Safety and tolerability of SAGE-217 will be evaluated by TEAEs, changes from baseline in [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be presented for the safety sets using actual treatment received. Where applicable, ranges of potentially clinically significant values will be provided in the SAP.

13.6.1. Adverse Events

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

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

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

[redacted]

13.6.3. Physical Examinations

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

[redacted]

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each of the triplicate ECGs for each participant: heart rate, PR, QRS, QT, and QTcF. The derived mean of each parameter will also be listed. Mean ECG data will be summarized by visit. Potentially clinically significant values of QTcF will be summarized by treatment. Electrocardiogram findings will be listed by participant and visit.

13.6.6. Prior and Concomitant Medications

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

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

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

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

[redacted]

[redacted]

13.6.9. Other Safety Analysis

[redacted]

13.8. Sample Size and Power

Using a 2-sided alpha level of 0.05, a sample size of 382 total evaluable participants would provide 90% power to detect a treatment difference (between SAGE-217 + assigned ADT and placebo + assigned ADT) of approximately 3 points in the primary endpoint, change from baseline in HAM-D total score at Day 3, assuming standard deviation of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each treatment group, approximately 424 total randomized participants will be required to obtain a total of 382 evaluable participants. Evaluable participants are defined as those randomized participants who receive IP and have valid baseline and at least 1 postbaseline HAM-D assessment.

13.8.1. Interim and Data Monitoring Committee Analyses

No interim analyses or data monitoring committee analyses will be conducted.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage 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 IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or independent ethics committee.

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

14.2. Audits and Inspections

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

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

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

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

16.3. Written Informed Consent

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

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

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

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

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

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

17.2. Retention of Records

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

18. PUBLICATION POLICY

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

19. LIST OF REFERENCES

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STUDY TITLE: A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY COMPARING THE EFFICACY AND SAFETY OF SAGE-217 PLUS AN ANTIDEPRESSANT VERSUS PLACEBO PLUS AN ANTIDEPRESSANT IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

PROTOCOL NUMBER: 217-MDD-305

Investigational Product	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, MBA Tel: [redacted] e-mail: [redacted]
Date of Original Protocol	13 MAY 2020
Date of Amendment 1	11 SEP 2020
Date of Amendment 2	22 JAN 2021

SPONSOR APPROVAL

Protocol Number: 217-MDD-305

Study Title: A Phase 3, Randomized, Double-Blind Study Comparing the Efficacy and Safety of SAGE-217 plus an Antidepressant Versus Placebo plus an Antidepressant in Adults with Major Depressive Disorder

Protocol Version and Date: Version 3, 22 January 2021

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 22-Jan-2021 | 12:32 EST
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[redacted], MD, MBA
[redacted]

Date

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Signer Name: [redacted]
Signing Reason: I approve this document
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[redacted], RAC
[redacted]

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[redacted], PhD
[redacted]

Date

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Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 26-Jan-2021 | 16:13 EST
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26-Jan-2021 | 16:13 EST

[redacted], MBBS (MD)
[redacted]

Date

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Signer Name: [redacted]
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22-Jan-2021 | 15:02 EST

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Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-MDD-305 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD/MMM/YYYY)

CONTACT INFORMATION

Table 1: Contact Information

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

2. SYNOPSIS

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

Name of Investigational Product: SAGE-217 Capsules

Name of Active Ingredient: SAGE-217

Title of Study: A Phase 3, Randomized, Double-Blind Study Comparing the Efficacy and Safety of SAGE-217 plus an Antidepressant Versus Placebo plus an Antidepressant in Adults with Major Depressive Disorder

Number of Sites and Study Location: This study will take place at approximately 55 sites in United States.

Phase of Development: 3

Planned Duration for each Study Participant: Up to 70 days (up to 28-day Screening Period, 14-day Double-blind Treatment Period, and a 28-day Antidepressant Therapy (ADT) Continuation Period)

Objectives:

Primary:

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

Secondary:

- To assess patient-reported outcome (PRO) measures as they relate to depressive symptoms
- To evaluate the safety and tolerability of SAGE-217 plus an antidepressant

[redacted]

Endpoints:

Primary:

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

Key Secondary:

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

Other Secondary:

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as “much improved” or “very much improved”, at Day 15
- Change from baseline in MADRS total score at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline to Day 15 in depressive symptoms, as assessed by the PHQ-9
- Incidence and severity of treatment-emergent adverse events (TEAEs)

[redacted]

Study Description:

This is a randomized, double-blind, parallel-group, placebo-controlled study in adults with MDD. 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.

The study will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day ADT Continuation Period. The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit. Preliminary screening procedures to determine eligibility include completion of the MGH-ATRQ and HAM-D.

Participants will be randomized to receive blinded SAGE-217 50 mg or placebo for administration each evening from Days 1 through 14. In addition, all participants will receive 1 of 2 classes of ADTs: a selective serotonin reuptake inhibitor (SSRI; sertraline, escitalopram, citalopram) or a serotonin-norepinephrine reuptake inhibitor (SNRI; duloxetine or desvenlafaxine) in an open-label manner from Day 1 through the end of the study. The ADT will be administered per labeled prescribing information. The investigator will assign 1 of the 5 ADTs based on clinical standard of care; the participant must not have been previously treated with the assigned ADT within the current depressive episode and must not have taken any ADT within 30 days prior to Day 1 (or taken fluoxetine within 60 days prior to Day 1). Randomization will be stratified by ADT class (SSRI or SNRI).

After the double-blind Treatment Period, the ADT will be continued each evening for the remainder of the study (ADT Continuation Period). During this period (Weeks 3 to 6), ADT dosing may be modified based on individual response, at the discretion of the investigator and per the labeled prescribing information.

Initiation of other antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of assessments at Day 42/end-of-study visit.

Participants will self-administer blinded investigational product (IP) once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. The ADT and SAGE-217/placebo will be administered at the same time during the Treatment Period; participants assigned duloxetine will also administer ADT in the morning (for twice-daily dosing) as part of a divided dose for the first 7 days. Participants will return to the study center as outlined in the Schedule of Assessments (Table 2).

During the Treatment Period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate SAGE-217/placebo 50 mg will receive 40 mg for the remainder of the Treatment Period. Participants who, in the opinion of the investigator, cannot tolerate the SAGE-217/placebo 40-mg dose may be discontinued from SAGE-217/placebo at the discretion of the investigator. If blinded IP is discontinued, the ADT may be

continued at the discretion of the investigator.

Upon completion of the current study, eligible participants will have the opportunity to enter a long-term open-label study of SAGE-217.

Number of Participants (planned): It is estimated that approximately 424 participants will be randomized and treated to obtain 382 evaluable participants at Day 15 (assuming a 10% dropout rate). Additional participants may be randomized if the dropout rate is greater than 10%.

Eligibility Criteria:

Inclusion Criteria

1. Participant has signed an ICF prior to any study-specific procedures being performed.
2. Participant is a male or female between 18 and 64 years of age, inclusive.
3. Participant is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Participant agrees to adhere to the study requirements.
5. Participant 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. Participant has a HAM-D-17 total score of ≥24 at Screening and Day 1 (prior to dosing).
7. Participant is willing to delay start of any antidepressant (except as per protocol), anxiolytic, anti-insomnia, psychostimulant, prescription opioid regimens, or new psychotherapy (including Cognitive Behavioral Therapy for Insomnia [CBT-I]) until after study completion. Participants receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1 and intend to maintain that schedule for the duration of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence).
9. Female participant who is breastfeeding at Screening or on Day 1 (prior to administration of IP) must be willing to temporarily cease giving breast milk to her child(ren) from just prior to receiving IP on Day 1 until 7 days after the last dose of SAGE-217/placebo.
10. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 5 days after receiving IP, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
11. Male participant is willing to abstain from sperm donation for the treatment period and for 5 days after receiving the last dose of the IP.
12. Participant agrees to refrain from drugs of abuse and alcohol for the duration of the study.
13. Participant is willing, able, and eligible to take at least 1 of the 5 ADTs specified in the protocol (an eligible ADT is an ADT that has not been taken during the current depressive episode and for which the participant has no contraindications; further, a participant is not eligible for citalopram if escitalopram has been taken during the current depressive episode, and vice versa).

Exclusion Criteria

1. Participant is currently at significant risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of MDD.
2. Participant had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the participant has presented for screening during the 6-month postpartum period.
3. Participant has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eye, ear, nose, and throat disorders, or any other acute or chronic condition that, in the investigator's opinion, would limit the participant's ability to complete or participate in this clinical study; a BMI $\leq$18 or $\geq$45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
4. Participant 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 2 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. Participant has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Participant is receiving Cognitive Behavioral Therapy for Insomnia (CBT-I) within 28 days prior to Day 1.
7. Participant has a known allergy to SAGE-217, allopregnanolone, or related compounds.
8. Participant has taken antidepressants within 30 days prior to Day 1, and/or has taken fluoxetine within 60 days prior to Day 1.
9. Female participant has a positive pregnancy test or confirmed pregnancy.
10. Participant has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
11. Participant has active psychosis per investigator assessment.
12. Participant has a medical history of seizures.
13. Participant has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
14. Participant has a history of severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to Screening or participant has a history of mild or moderate substance use disorder not in sustained remission for at least 6 months prior to Screening.
15. Participant has had exposure to another investigational medication or device within 30 days prior to Screening.
16. Participant has previously received brexanolone or participated in a SAGE-217 or SAGE-547 (brexanolone) clinical trial.
17. Participant has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these, within 14 days prior to Day 1.
18. Participant has used any strong CYP3A inducer, such as rifampin, carbamazepine,

enzalutamide, mitotane, phenytoin, or St John's Wort, within 28 days prior to Day 1.

19. Participant has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
20. Participant plans to undergo elective surgery before completion of the Day 42 visit.
21. Participant is taking benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Day 1, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Participant is taking any benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1.
22. Participant is taking non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids), or first or second generation (typical/atypical) antipsychotics within 14 days prior to Day 1. Note that nonsedating antihistamines are permitted.
23. Participant has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
24. Participant has a history of sleep apnea.
25. Participant has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
26. Participant is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as needed, within 28 days prior to Day 1.
27. Participant is a dependent of the sponsor, investigator, investigator's deputy, or study site staff.
28. Participant expects to perform night shift work during the 14-day Treatment Period.
29. Participant has detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at Screening.

Investigational Product Dosage and Mode of Administration: SAGE-217 will be available as hard gelatin capsules for oral administration; multiple capsules (in 30-mg or 20-mg dose strengths) will be provided to total a 50-mg dose, with option to reduce to 40 mg based on tolerability.

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217, for oral administration.

Sertraline, escitalopram, citalopram, duloxetine, or desvenlafaxine will be administered as per labeled prescribing information

Duration of Treatment: Blinded SAGE-217 or placebo will be administered once daily for 14 days; open-label ADT will be administered according to labeled prescribing information for 42 days.

Statistical Methods:

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock and treatment unblinding. Any deviations from or changes to the SAP following database lock will be detailed in the Clinical Study Report.

General Considerations

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

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized participants who administered blinded IP and have a valid baseline HAM-D total score and at least 1 valid postbaseline HAM-D total score.

The Safety Set is defined as all participants who administered blinded IP.

The Safety Set – ADT Only is defined as all participants who administered assigned ADT at baseline but did not administer any dose of blinded IP.

The Randomized Set, defined as all participants who are randomized.

[redacted]

The definition and details of the Per Protocol Set are outlined in the SAP.

Determination of Sample Size

Using a two-sided alpha level of 0.05, a sample size of 382 total evaluable participants would provide 90% power to detect a treatment difference (between SAGE-217 + an antidepressant and placebo + an antidepressant) of approximately 3 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each treatment group, approximately 424 total randomized participants will be required to obtain a total of 382 evaluable participants. Evaluable participants are defined as those randomized participants who receive IP and have valid baseline and at least 1 postbaseline HAM-D assessment.

Analysis of Primary Endpoint

The estimand for the primary analysis is the mean change from baseline in HAM-D total score at Day 15 (see Section 13.5 for more details). Using FAS, this will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline time points will be included in the model. The main comparison will be between SAGE-217 + an antidepressant and placebo + an antidepressant at the 15-day time point. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p values) will be reported where applicable. An unstructured covariance structure will be used to model the within-participant errors. The Toeplitz compound symmetry, Autoregressive (1) [AR(1)] covariance structure will be used in that sequence if there is a convergence issue with the unstructured covariance model. If convergence is still not achieved, no results will be reported.

Analysis of Secondary Endpoints

Similar to those methods described above for the primary endpoint, an MMRM will be used for the analysis of the change from baseline in other time points in HAM-D total score, MADRS total score,

HAM-A total score, CGI-S score, and PHQ-9 total score.

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

A GEE method will also be used for the analysis of CGI-I response including terms for center, treatment, baseline CGI-S score, assessment time point, and time point-by-treatment as explanatory variables.

Safety Analysis

Safety and tolerability of IP will be evaluated by adverse events (AEs)/serious adverse event (SAEs), [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set and Safety Set – ADT only.

[redacted]

Table 2: Schedule of Assessments

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

Visits	Screening Period	Double-Blind, Placebo-Controlled Treatment Period					ADT Continuation Period				
Visit Days	**D-28 to D-1**	**D1**	**D3 (±1d)**	**D8 (+1d)**	**D12 (±1d)**	**D15 (+1d)**	**D18 (±1d)**	**D21 (±1d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d) /ET**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Study Procedure											
[redacted]											
Vital Signs [k]	X	X	X	X	X	X	X		X		X
12-Lead ECG [l]	X	X				X					X
[redacted]											
HAM-D [n, o]	X	X	X	X	X	X	X	X	X	X	X
MADRS		X		X		X			X		X
HAM-A [o]		X		X		X			X		X
CGI-S	X	X	X	X	X	X		X	X	X	X
CGI-I			X	X	X	X		X	X	X	X
[redacted]											
PHQ-9		X	X	X		X			X		X
[redacted]											
SAGE-217/Placebo Dispensation		X		X							
SAGE-217/Placebo Administration		X (once daily in the evening through Day 14 - inclusive)									
IP Adherence [q]		X									

Visits	Screening Period	Double-Blind, Placebo-Controlled Treatment Period					ADT Continuation Period				
Visit Days	D-28 to D-1	D1	D3 (±1d)	D8 (+1d)	D12 (±1d)	D15 (+1d)	D18 (±1d)	D21 (±1d)	D28 (±3d)	D35 (±3d)	D42 (±3d) /ET
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Study Procedure											
ADT Administration [r]		X									
IP Accountability/Return			X	X		X		X	X	X	X
AEs/SAEs [c, s]	X										
Prior/Concomitant Medications/Procedures [c, t]	X										

Abbreviations: ADT = Antidepressant therapy; AE = adverse event; CGI-I = Clinical Global Impression – Improvement; CGI-S – Clinical Global Impression – Severity; [redacted] D = day; ET = early termination; ECG = electrocardiogram; FSH = follicle stimulating hormone; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; IP = investigational product; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; PHQ-9 = 9-item Patient Health Questionnaire; [redacted] O = Optional; [redacted] SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Clinical Trials Version; [redacted] V = visit.

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

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

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

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

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

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

[g] Urine toxicology for selected drugs of abuse (Table 3) and breath test for alcohol.

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

[redacted]

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

[l] Triplicate ECGs will be collected. [redacted]

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

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

[redacted]

[q] IP administration will be monitored via a medication adherence monitoring platform used on smartphones to confirm IP ingestion. IP adherence will not be captured after participants discontinue IP.

[r] ADT will be administered as per labeled prescribing information

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

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

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

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation	Definition
ADT	Antidepressant therapy
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulation
CRO	contract research organization
CSR	clinical study report
IEC	independent ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
IP	investigational product
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PI	prescribing information
PK	pharmacokinetic
PV	pharmacovigilance
QA	quality assurance
QC	quality control
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SOP	Standard Operating Procedure

Abbreviation	Definition
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Major Depressive Disorder and Unmet Medical Need

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

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

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association 2013) provides diagnostic criteria for major depressive disorder (MDD). These include at least 5 of 9 depressive symptoms (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 (SNRI), serotonin norepinephrine reuptake inhibitors (SSRI), tricyclic antidepressants, monoamine oxidase inhibitors (MAOI), 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). Furthermore, these agents can take 4 to 8 weeks to demonstrate full clinical efficacy (Rush 2006; Trivedi 2006), and in the case of the most commonly prescribed classes—SSRIs and SNRIs—common side effects including weight gain, GI symptoms, and sexual dysfunction can prevent titration into an adequate therapeutic range (Sadock and Sadock 2007).

In the largest study to assess the effectiveness of depression treatments in patients with MDD, time to patient remission after treatment was 5.4 to 7.4 weeks; approximately one-half of the patients who ultimately remitted did so after 6 weeks, and 40% of those who achieved remission required 8 or more weeks to do so (Rush 2006; Trivedi 2006). Even following remission, many patients report the presence of residual symptoms, often related to decreased positive affect, such as loss of interest in activities once considered enjoyable, fatigue, loss of energy, as well as sleep and appetite/weight disturbances (Nierenberg 2009; Nierenberg 2015). Thus, patients may remain symptomatic for up to 2 months while waiting for current standard-of-care pharmacotherapy to take full effect. They may also have to contend with undesirable side effects and residual symptoms. These aspects underscore the need for newer, rapid-acting therapies.

SAGE-217 is a synthetic positive allosteric modulator of $GABA_A$ receptors, the major class of inhibitory neurotransmitter receptors in the brain. In pharmacokinetic (PK) studies in mice and

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

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) associated with SAGE-217 (overall) were sedation, somnolence, and dizziness; most adverse events (AEs) were reported as mild or moderate in intensity. Refer to the SAGE-217 Investigator's Brochure for a detailed description of the chemistry, pharmacology, efficacy, and safety of SAGE-217.

This study was designed to target the unmet need of symptom improvement during the latency to SSRI and SNRI efficacy in the acute phase of a major depressive episode. This study will assess the safety and efficacy of SAGE-217 50 mg plus an antidepressant, examining if SAGE-217 plus an antidepressant produces more rapid or more profound reduction in depressive symptoms than an antidepressant alone.

5.2. Potential Risks and Benefits

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

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

Based on nonclinical findings, embryo-fetal toxicity and withdrawal effects are considered important potential risk for SAGE-217. Risk mitigation measures in this study include monitoring for adverse effects, monitoring for potential withdrawal effects, requiring highly effective contraceptive measures for study participants, and inclusion of dose adjustment criteria and guidance for blinded IP discontinuation (Section 8.4). Finally, due to the sedation/somnolence observed, SAGE-217 is administered in the evening in this study.

Given the outcome of the completed studies of SAGE-217 in participants with MDD and PDD, the current significant unmet need for well-tolerated and rapid-acting depression treatments, and a favorable benefit-risk profile, further investigation of SAGE-217 as a novel rapid response treatment in adults with MDD is justified.

5.3. Dose Justification

Results from a large, multicenter study of SAGE-217 20 and 30 mg in MDD (217-MDD-301) support the need for higher steady-state concentrations of SAGE-217 to allow participants to experience maximum antidepressant and anti-anxiety benefits. SAGE-217 will be administered as a 14-day regimen of an evening dose of 50 mg with reduction to 40 mg as needed based on tolerability. The 50-mg dose of SAGE-217 is expected to exhibit a favorable benefit-risk profile in the context of results from previous SAGE-217 studies utilizing a 30-mg dose, now identified as a minimally effective dose. SAGE-217 is expected to maintain an acceptable tolerability

profile, based on a current safety database of over 2000 participants exposed across different doses/concentrations.

Sertraline is a commercially available SSRI indicated for the treatment of MDD and other psychiatric disorders. Dosage and administration of sertraline as described in the approved US Prescribing Information (PI) recommends a starting dose of 50 mg per day in patients with MDD, with an incremental weekly increase in dose of 25-50 mg per day, if there is an inadequate response to the starting dose, to a maximum dose of 200 mg per day. . In this study, a starting dose of 50 mg per day is recommended for 7 days, with a subsequent increase to 100 mg per day.

Citalopram and escitalopram are commercially available SSRIs that are both indicated for acute and maintenance treatment of MDD. Escitalopram is also indicated for treatment of generalized anxiety disorder. The starting dosage for MDD in the US PI for citalopram is 20 mg/day and for escitalopram is 10 mg/day, with maxima of 40 mg/day and 20 mg/day, respectively. In this study, a starting dose of 20 mg/day is recommended for citalopram and of 10 mg/day is recommended for escitalopram for the first 14 days; subsequent dose increases may be considered, except for participants >60 years old taking citalopram.

Duloxetine is a commercially available SNRI indicated for the treatment of MDD, generalized anxiety disorder, and pain disorders. The starting dosage for MDD in the US PI is 40 to 60 mg/day. The maximum dosage is 120 mg/day, although there is no evidence that dosages greater than 60 mg/day confer any additional benefits. In this study, a starting dose of 40 or 60 mg/day is recommended (divided as 20 or 30 mg, respectively, twice daily for the first 7 days).

Desvenlafaxine is a commercially available SNRI indicated for the treatment of MDD. The recommended dosage in the US PI is 50 mg/day. In this study, a dose of 50 mg/day is recommended. There has been no evidence that doses greater than 50 mg/day confer any additional benefit.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

To evaluate the efficacy of SAGE-217 plus an antidepressant in the treatment of MDD compared to placebo plus an antidepressant

6.1.2. Secondary Objectives

- To assess patient-reported outcome (PRO) measures as they relate to depressive symptoms
- To evaluate the safety and tolerability of SAGE-217 plus an antidepressant

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoint

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

6.2.2. Secondary Endpoints

6.2.2.1. Key Secondary Endpoints

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

6.2.2.2. Other Secondary Endpoints

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as “much improved” or “very much improved”, at Day 15
- Change from baseline in MADRS total score at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline to Day 15 in depressive symptoms, as assessed by the PHQ-9
- Incidence and severity of treatment-emergent AEs

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, parallel-group, placebo-controlled study in adults with MDD. 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.

The study will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day ADT Continuation Period. The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit. Preliminary screening procedures to determine eligibility include completion of the MGH-ATRQ and HAM-D.

Participants will be randomized to receive blinded SAGE-217 or placebo for administration each evening from Day 1 through 14. In addition, all participants will receive 1 of 2 classes of ADTs: a selective serotonin reuptake inhibitor (SSRI; sertraline, escitalopram, citalopram) or a serotonin-norepinephrine reuptake inhibitor (SNRI; duloxetine, desvenlafaxine) in an open-label manner from Day 1 through the end of the study. The investigator will assign 1 of the 5 ADTs based on clinical standard of care; the participant must not have been previously treated with the assigned ADT within the current depressive episode (and must not have been treated with citalopram if escitalopram is assigned, and vice versa) and must not haven taken any ADT within 30 days prior to Day 1 (or taken fluoxetine within 60 days prior to Day 1). Randomization will be stratified by antidepressant class (SSRI or SNRI).

The open-label ADT will be administered as per labeled prescribing information.

After the Double-blind Treatment Period, the ADT will be continued each evening for the remainder of the study (ADT Continuation Period). During this period (Week 3 to 6), ADT dosing may be modified as appropriate per the labeled prescribing information and based on individual response.

Initiation of other antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of assessments at Day 42/end-of-study visit.

Participants will self-administer blinded investigational product (IP) once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. The ADT and SAGE-217 or placebo will be administered at the same time during the Treatment Period; participants assigned duloxetine will also administer ADT in the morning (for twice-daily dosing) as part of a divided dose for the first 7 days. Participants will return to the study center as outlined in the Schedule of Assessments.

During the Treatment Period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate SAGE-217 or placebo 50 mg will receive 40 mg for the remainder of the Treatment Period. Participants who cannot tolerate the SAGE-217/placebo 40-mg dose may be discontinued from SAGE-217 or placebo at the discretion of the investigator. If blinded IP is discontinued, the ADT may be continued at the discretion of the investigator.

Upon completion of the current study, eligible participants will have the opportunity to enter a long-term open-label study of SAGE-217. Participants that do not enter the open-label study or that terminate the current study early may, per the investigator, receive a supply of the ADT with instructions on how to taper the drug, if needed, or, if they wish to continue the ADT, a bridge supply to permit them to obtain a prescription from another provider.

7.2. Number of Participants

It is estimated that approximately 424 participants will be randomized and treated to obtain 382 evaluable participants at Day 15 (assuming 10% dropout rate). Additional participants may be randomized if the dropout rate is greater than 10%.

7.3. Treatment Assignment

Participants will be assigned to blinded IP (SAGE-217 or placebo) in accordance with the randomization schedule on Day 1. The investigator will assign 1 of the 5 ADTs based on clinical standard of care. The assigned ADT for a participant cannot have been taken previously by the participant during the current depressive episode. Further, citalopram cannot be assigned if escitalopram has been taken during the current depressive episode, and vice versa.

Randomization will be stratified by antidepressant class (SSRI or SNRI).Additional details on randomization and blinding are provided in Section 9.5.

Sage will monitor the ratio of SSRIs:SNRIs on an ongoing basis and may restrict assignment of any ADT(s) to reflect the ratio expected with standard of care (approximately 3:1; Luo 2020).

7.4. Dose Adjustment Criteria

During the treatment period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate 50 mg (as determined by the investigator) will receive 40 mg for the remainder of the treatment period.

At the discretion of the investigator, participants who cannot tolerate the 40-mg dose at any time may be discontinued from dosing. These participants should be followed and complete assessments as per the Schedule of Assessments (Table 2).

During Weeks 3 to 6, the ADT dosing may be modified, based on individual response, per investigator discretion and per the labeled prescribing information.

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 participants, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the investigator. Investigational sites must promptly notify their IRB, where required, and initiate withdrawal procedures for participating participants.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

1. Participant has signed an ICF prior to any study-specific procedures being performed.
2. Participant is a male or female between 18 and 64 years of age, inclusive.
3. Participant is in good physical health and has no clinically significant findings, as determined by the investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Participant agrees to adhere to the study requirements.
5. Participant 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. Participant has a HAM-D-17 total score of ≥24 at Screening and Day 1 (prior to dosing).
7. Participant is willing to delay start of any antidepressant (except as per protocol), anxiolytic, anti-insomnia, psychostimulant, prescription opioid regimens, or new psychotherapy (including Cognitive Behavioral Therapy for Insomnia [CBT-I]) until after study completion. Participants receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1 and intend to maintain that schedule for the duration of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence).
9. Female participant who is breastfeeding at Screening or on Day 1 (prior to administration of IP) must be willing to temporarily cease giving breast milk to her child(ren) from just prior to receiving IP on Day 1 until 7 days after the last dose of SAGE-217/placebo.
10. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 5 days after receiving IP, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
11. Male participant is willing to abstain from sperm donation for the treatment period and for 5 days after receiving the last dose of the IP.
12. Participant agrees to refrain from drugs of abuse and alcohol for the duration of the study.
13. Participant is willing, able, and eligible to take at least 1 of the 5 ADTs specified in the protocol (an eligible ADT is an ADT that has not been taken during the current depressive episode and for which the participant has no contraindications; further, a participant is not eligible for citalopram if escitalopram has been taken during the current depressive episode, and vice versa).

8.2. Participant Exclusion Criteria

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

1. Participant is currently at significant risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of MDD.
2. Participant had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the participant has presented for screening during the 6-month postpartum period.
3. Participant 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 participant's ability to complete or participate in this clinical study; a BMI $\leq$18 or $\geq$45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
4. Participant 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 2 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. Participant has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Participant is receiving Cognitive Behavioral Therapy for Insomnia (CBT-I) within 28 days prior to Day 1.
7. Participant has a known allergy to SAGE-217, allopregnanolone, or related compounds.
8. Participant has taken antidepressants within 30 days prior to Day 1, and/or has taken fluoxetine within 60 days prior to Day 1.
9. Female participant has a positive pregnancy test or confirmed pregnancy.
10. Participant has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
11. Participant has active psychosis per investigator assessment.
12. Participant has a medical history of seizures.
13. Participant has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.

14. Participant has a history of severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to Screening or participant has a history of mild or moderate substance use disorder not in sustained remission for at least 6 months prior to Screening.
15. Participant has had exposure to another investigational medication or device within 30 days prior to Screening.
16. Participant has previously received brexanolone or participated in a SAGE-217 or SAGE-547 (brexanolone) clinical trial.
17. Participant has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to Day 1.
18. Participant has used any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort, within 28 days prior to Day 1.
19. Participant has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
20. Participant plans to undergo elective surgery before completion of the Day 42 visit.
21. Participant is taking benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Day 1, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Participant is taking any benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1.
22. Participant 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 within 14 days prior to Day 1. Note that nonsedating antihistamines are permitted.
23. Participant has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
24. Participant has a history of sleep apnea.
25. Participant has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
26. Participant is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as needed, within 28 days prior to Day 1.
27. Participant is a dependent of the sponsor, investigator, investigator's deputy, or study site staff.
28. Participant expects to perform night shift work during the 14-day treatment period.
29. Participant has detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at Screening.

8.3. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

8.4. Investigational Product Discontinuation and Early Termination from the Study

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

Based on known withdrawal symptoms with other GABAergic drugs and nonclinical 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 blinded IP discontinuation or dose reduction are presented to support participant safety:

1. Any participant reporting a confirmed or suspected seizure at any time will be discontinued from blinded IP but will continue to be followed in the study.
2. The investigator should monitor the course of CNS-based signs and symptoms suggestive of a seizure which are not accounted for by comorbid psychiatric or medical conditions. Examples of reported serious or severe events which may reflect an oncoming and/or increased risk for seizure may include temporary confusion, tremors, involuntary muscle fasciculations or jerking movements of arms or legs, or paresthesia. Should such symptoms occur, the investigator should consider decreasing the dose of SAGE-217 or placebo to 40 mg, stopping treatment to assess the effect on the symptom(s) (eg, resolution, improvement), or discontinuing the participant from treatment. A participant who discontinues treatment should remain in the study and continue protocol-required assessments until the end of the study.

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

8.4.1. Investigational Product Discontinuation

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

Participants who discontinue treatment early should complete remaining study visits as scheduled through Day 42 (ie, relative to Day 1), unless the participant withdraws consent.

8.4.2. Early Termination from the Study

If a participant decides to terminate the study, the participant should return for an early termination (ET) visit, if possible. The primary reason for early termination from the study must

be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF).

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

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

Participants who terminate from the study early may, per the investigator, receive a supply of the ADT with instructions on how to taper the drug, if needed, or, if they wish to continue the ADT, a bridge supply to permit them to obtain a prescription from another provider.

8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after 3 attempts at contacting the participant have been unsuccessful.

8.4.4. Replacement of Participants

Participants will not be replaced.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Products

SAGE-217 will be available as hard gelatin capsules for oral administration; 2 capsules (one 30 mg and one 20 mg) will be provided to total a 50-mg dose, with option to reduce to 40 mg based on tolerability, as per criteria described in Section 7.4. If the dose is reduced to 40 mg, it will be administered as 2 20-mg capsules.

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217, for oral administration.

All participants will self-administer blinded and open-label IP orally at approximately 8 PM with fat-containing food for 14 days. Participants assigned duloxetine will also administer duloxetine in the morning (for twice daily dosing) as part of a divided dose for the first 7 days (see below).

It is recommended that sertraline be administered as per labeled prescribing information, starting with 50 mg each evening during Week 1. and It is recommended that the dose be increased to 100 mg each evening during Week 2.

It is recommended that citalopram be administered per labeled prescribing information, starting with 20 mg/day.

It is recommended that escitalopram be administered per labeled prescribing information, starting with 10 mg/day.

It is recommended that duloxetine be administered per labeled prescribing information, starting with 40 or 60 mg/day (divided as 20 or 30 mg, respectively, twice daily for the first 7 days).

It is recommended that desvenlafaxine be administered per labeled prescribing information, starting with 50 mg/day.

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

9.2.1. Prior and Concomitant Medications and/or Supplements

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

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

9.2.2. Prohibited Medications

The following specific classes of medications are prohibited:

- Initiation of new psychotropic medications through the Day 42 visit
- Initiation of new antidepressant therapy from 30 days (60 days for fluoxetine) prior to Day 1 through the Day 42 visit

- Use of any benzodiazepines, barbiturates, $GABA_A$ modulators, GABA-containing agents from Day -28 through the Day 42 visit (from Day -60 for benzodiazepines or GABA modulators with a half-life ≥48 hours)
- Chronic or as-needed psychostimulants (eg, methylphenidate, amphetamine) or opioids from Day -28 through the Day 42 visit
- First generation (typical) antipsychotics (eg, haloperidol, perphenazine) and second generation (atypical) antipsychotics (eg, aripiprazole, quetiapine) from Day -14 through the Day 42 visit
- Use of any non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids) from Day -14 to Day 1. Note that nonsedating antihistamines are permitted.
- Exposure to another investigational medication or device from 30 days prior to Screening through the Day 42 visit
- Any known strong inhibitors of CYP3A4 from Day -28 or 5 half-lives prior to Day 1 (whichever is longer) through the Treatment Period
- Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort from Day -28 through the Treatment Period
- Any contraindications to the assigned SSRI/SNRI per labeled prescribing information

9.2.3. Other Restrictions

Any specific restrictions for the assigned SSRI/SNRI with concomitant medications per the labeled prescribing information should be considered.

The consumption of grapefruit juice, grapefruit, or Seville oranges, or products containing these is prohibited within 14 days prior to Day 1 and throughout the treatment period.

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

Female participants who are lactating or actively breastfeeding must stop giving breast milk to the baby(ies) starting on Day 1 until 7 days after the last dose of SAGE-217/placebo.

Elective surgeries or procedures are prohibited through the Day 42 visit.

Participants must not participate in night shift work during the Treatment Period.

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

Participants receiving psychotherapy on a regular schedule for at least 60 days prior to Day 1 are permitted if the participant intends to continue that schedule through the Follow-up Period (Day 42). Initiation of new psychotherapy is prohibited until after study completion.

9.2.4. Acceptable Forms of Contraception

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

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

Acceptable forms of contraception for male participants include:

- History of vasectomy (performed at least 3 months prior to screening)
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

9.3. Intervention after the End of the Study

Upon completion of the current study, eligible participants will have the opportunity to enter an open-label, long-term study of SAGE-217 in which additional treatment with SAGE-217 will be offered. Participants that do not enter the open-label study or that terminate the current study early may continue to receive ADT as prescribed by the investigator either to taper the drug appropriately or—if the participant wishes to continue ADT—to bridge the participant until he or she receives a new prescription.

9.4. Treatment Adherence

Investigational products will be self-administered by participants (see Section 10.5).

Administration of blinded and open-label IP will be monitored by a medication adherence monitoring platform used on smartphones to confirm IP ingestion. Participants will receive a reminder within a predefined time window to take IP while using the application and will follow a series of prescribed steps to confirm their ingestion of the medication. For visually confirmed IP ingestion, the application will record the date and time of IP administration by dose level, as well as missed doses.

In addition, participants will be instructed to bring their SAGE-217 or placebo dosing kit and ADT to the site as outlined in Table 2, at which time the investigator or designee will be responsible for ensuring the kit contains sufficient doses for the duration of the treatment period.

All participants should be reinstructed about the dosing requirements during study contacts. The authorized study personnel conducting the reeducation must document the process in the participant source records.

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

9.5. Randomization and Blinding

Participants will be randomized in a 1:1 ratio to receive SAGE-217 or matched placebo. Participants, site staff, and the sponsor will be blinded to treatment allocation. All participants will also receive an open-label ADT. Randomization will be performed centrally via an interactive response technology (IRT) system. Randomization schedules will be generated by an independent statistician. The allocation to blinded treatment (SAGE-217or placebo) will be based on the randomization schedule. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

9.5.1. Emergency Unblinding

During the study, the blind is to be broken by the investigator via the IRT system only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate risk, the investigator should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a participant. The responsibility to break the treatment code resides solely with the investigator. If the unblinding occurs without Sage's knowledge, the investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the IP allocation for a participant is unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's records and on the eCRF.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Products

10.1.1. Blinded Investigational Products

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

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217.

10.1.2. Open-label Investigational Product

Sertraline, escitalopram, citalopram, duloxetine, and desvenlafaxine, packaged and labeled by the commercial manufacturer, will be supplied by a third-party vendor. Open-label IP is to be stored and administered according to the package insert. Open-label IP during this study is for use only as directed in this protocol.

10.2. Blinded Investigational Product Packaging and Labeling

SAGE-217 and placebo will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the blinded IP in appropriately labeled, participant-specific kits containing sealed unit doses. Each unit dose for 40-mg and 50-mg dose levels consists of 2 capsules. Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Labels with all required information and conforming to all applicable FDA Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices guidelines will be prepared by the sponsor for SAGE-217 and placebo.

10.3. Blinded Investigational Product Storage

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

10.4. Blinded Investigational Product Preparation

Not applicable.

10.5. Blinded and Open-label Investigational Product Administration

Blinded IP and open-label ADT are to be administered orally at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack). Examples of fat-containing snacks include nuts, peanut butter, avocado, eggs, and cheese. Participants assigned duloxetine will also administer duloxetine in the morning (for twice-daily divided dosing) for the first 7 days (see Section 9.1).

If a participant misses a dose of blinded IP or open-label IP, the participant should skip that dose (ie, they should not take the dose in the morning) and take the next scheduled dose.

10.6. Blinded Investigational Product Accountability, Handling, and Disposal

Upon receipt of blinded IP dosing kits, the investigator(s), or the responsible pharmacist or designee, will inspect the kits and complete and follow the instructions regarding receipt and storage in the SAGE-217 Investigator's Brochure and (where applicable) in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the participant-specific kits to participants at the planned dispensation visit intervals outlined in Table 2. Site staff will access the IRT at the Screening Visit to obtain a participant identification (ID) number for each participant that has signed an informed consent form. On Day 1, site staff will access the IRT and provide the necessary participant-identifying information, including the participant ID number assigned at Screening, to randomize the eligible participant into the study and obtain the medication ID number for the blinded IP to be dispensed to that participant. The medication ID number and the number of blinded capsules dispensed must be recorded.

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

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

The blinded IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all blinded IP received, used and returned/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.

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

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

10.7. Blinded Investigational 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 provided in Table 1.

Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

11. EFFICACY AND CLINICAL PHARMACOLOGY ASSESSMENTS

11.1. Efficacy Assessments

11.1.1. Hamilton Rating Scale for Depression

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

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

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

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

11.1.2. Montgomery-Åsberg Depression Rating Scale

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

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

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

11.1.3. Hamilton Anxiety Rating Scale

The 14-item HAM-A will be used to rate the severity of symptoms of anxiety (Williams 2013c; Williams 2013d). Each of the 14 items is defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Scoring for HAM-A is calculated by assigning scores of 0 (not present) to 4 (very severe), with a total score range of 0 to 56, where <17 indicates mild severity, 18 to 24, mild to moderate severity, and 25 to 30, moderate to severe severity. The HAM-A total score will be calculated as the sum of the 14 individual item scores.

11.1.4. Clinical Global Impressions

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

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

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

[redacted]

11.1.6. Patient Health Questionnaire

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

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

[redacted]

[redacted]

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

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

12.1.1. Demographic/Medical History

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including: family psychiatric history, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, persistent depressive disorder, postpartum depression, substance use disorder, alcohol use disorder, MDD with seasonal pattern, MDD with psychotic features, premenstrual dysphoric disorder, MDD with atypical features, schizophrenia; or schizoaffective disorder will be documented. The diagnosis of MDD will be determined using the SCID-5-CT. If available, the disease code associated with the diagnosis of MDD based on the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used to determine whether the participant has treatment-resistant depression, defined as persistent depressive symptoms despite treatment during the current major depressive episode with adequate doses of antidepressants from 2 different classes for at least 4 weeks of treatment.

12.1.2. Weight and Height

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

12.1.3. Physical Examination

Physical examinations assessing body systems (eg, head, eyes, ears, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Thereafter, abbreviated physical examinations will include brief assessments of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical examination as needed. Unscheduled, symptom-directed physical examinations may also be conducted at the investigator's discretion. Whenever possible, the same individual is to perform all physical examinations for a given participant. Unscheduled brief, symptom-driven physical examinations may also be conducted per the investigator's discretion.

Any abnormality in physical examinations will be interpreted by the investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.

12.1.4. COVID-19 Questions

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

Questions to be asked are as follows:

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

12.1.5. Vital Signs

Vital signs comprise both supine and standing for systolic and diastolic blood pressure and heart rate measurements. Heart rate and blood pressure are to be collected in supine position after the participant has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Respiratory rate and temperature are collected once, in either position. Vital signs will be documented. When vital signs are scheduled at the same time as blood draws, vital signs will be obtained first.

Any abnormality in vital signs will be interpreted by the investigator as abnormal, NCS or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.

12.1.6. Electrocardiogram (ECG)

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

12.1.7. Laboratory Assessments

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

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

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

All clinical laboratory test results outside the central laboratory's reference range will be interpreted by the investigator as abnormal, NCS; or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs,

assessed according to Section 12.2.1. A clinically significant laboratory abnormality following participant randomization will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

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

Table 3: Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis**	**Coagulation**
Red blood cell count Hemoglobin Hematocrit White blood cell count with differential Platelet count Red Blood Cell Indices (MCV, MCH, MCHC) Reflex to Red blood cell morphology if indices are abnormal	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase Gamma-glutamyl transferase Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphorus Triglycerides Thyroid stimulating hormone (TSH) Reflex to free T3/T4 if TSH is abnormal	pH Specific gravity Protein Glucose Red blood cell Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio
Diagnostic			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C Reflex HCV RNA HIV-1 and -2 Female participants that are not surgically sterile and do not meet the protocol-	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine Female participants that are not surgically sterile and do	Alcohol	

defined criteria for being postmenopausal: serum hCG Female participants, if menopause is suspected and not surgically sterile: FSH	not meet the protocol-defined criteria for being postmenopausal: urine hCG		

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

A serum follicle stimulating hormone test will be conducted at Screening to confirm whether a female participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal (Section 8.1).

12.1.7.1. Drugs of Abuse and Alcohol

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

12.1.7.2. Pregnancy Screen

For female participants that are not surgically sterile, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at all other scheduled time points thereafter, including the ET visit for participants who prematurely discontinue.

[redacted]

[redacted]

12.2. Adverse and Serious Adverse Events

12.2.1. Adverse Event Definition

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

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

[redacted] are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for an SAE should be reported in an expedited manner. [redacted] that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

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

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

12.2.2. Serious Adverse Event Definition

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

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

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

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

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

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

12.2.3. Relationship to Investigational Product

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

Not Related	An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the IP. Factors pointing towards this assessment include but are not limited to: the lack of temporal relationship between administration of the IP and the event, the presence of biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE

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

12.2.4. Recording Adverse Events

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

Intensity will be assessed according to the following scale:

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

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

12.2.5. Reporting Serious Adverse Events

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

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

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

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

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

12.3. Pregnancy

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

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

clinical manifestation(s) of overdose must also be recorded as an AE on the eCRF. In addition, all overdoses must be recorded on an Overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose.

13. STATISTICS

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

13.1. Data Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized participants who administered blinded IP and have a valid baseline HAM-D total score and at least 1 valid post-baseline HAM-D total score.

The Randomized Set is defined as all participants who are randomized.

The Safety Set is defined as all participants who administered blinded IP.

The Safety Set – ADT Only is defined as all participants who administered assigned ADT at baseline but did not administer any dose of blinded IP.

[redacted]

The definition and details of the Per Protocol Set are outlined in the SAP.

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all non-missing data available. Missing data for particular visits may be imputed using the visit window and available data, as described in the SAP. A sensitivity analysis will be used to investigate the impact of missing data if ≥5% of participants in any treatment group have missing data.

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in a participant data listing, some may be presented with a corresponding table or figure; these will be indicated in relevant sections below. All summaries will be provided by treatment – either by randomized treatment or actual treatment received. Actual treatment is defined as SAGE-217 if the participant received any SAGE-217 (50 mg or 40 mg) at any time; otherwise, it is placebo.

If a participant takes any dose of SAGE-217, the participant's actual treatment is considered as SAGE-217 regardless of the treatment to which the participant has been randomized.

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

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

13.4. Demographics and Baseline Characteristics

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

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 history will be listed by participant.

13.5. Efficacy Analysis

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

The estimand for the primary efficacy analysis is defined as follows:

1) The treatment regimens for participants are: SAGE-217 + assigned ADT and placebo + assigned ADT for 14 days.
2) The target population is adult participants with a diagnosis of major depressive disorder and within a current depressive episode of severity (HAM-D total score >=24).
3) The variable of interest is the change from baseline in HAM-D total score at Day 15.
4) The intercurrent events could be:

a. The premature discontinuation of treatment for any reason, thus not having a Day 15 HAM-D total score available. This will be dealt with by a sensitivity analysis using multiple imputation techniques as described below.

b. Certain medications including, but not limited to, new antidepressants (except for assigned ADT) or benzodiazepines are prohibited during the study; however, the treatment policy strategy dictates that the results following these prohibited medication use will not be manipulated but will rather be used ‘as is’ in analysis. Please note that the protocol does not specify any rescue process, hence there is no rescue medication.

5) The population summary level deals with the difference between SAGE-217 + assigned ADT and placebo + assigned ADT treatments in mean change from baseline in HAM-D total score at Day 15.

Using the FAS, this will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline time points will be included in the model. The main comparison will be between SAGE-217 + assigned ADT and placebo + assigned ADT at the Day 15 time point. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p values) will be reported where applicable. An unstructured covariance structure will be used to model the within-participant errors. The Toeplitz compound symmetry, Autoregressive (1) [AR(1)] covariance structure will be used in that sequence if there is a convergence issue with

the unstructured covariance model. If convergence is still not achieved, no results will be reported.

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

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

A GEE method will also be used for the analysis of CGI-I response, including terms for treatment, baseline CGI-S score, assessment time point, and time point-by-treatment as explanatory variables.

13.5.1. Multiplicity Adjustment for Key Secondary Endpoints

Multiplicity adjustment to statistical testing of hypotheses of the key secondary endpoints will be conducted by using a fixed-sequence strategy. Only if the primary endpoint is statistically significant at 0.05 level, the key secondary endpoints will be tested sequentially, testing each endpoint at 5% level of significance only if the previous endpoint in the sequence has been significant at 5% level. If an endpoint is not significant at 5% level, the next endpoint in the sequence will be interpreted with nominal p value.

The sequence of testing key secondary endpoints is as follows:

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

Any secondary or other endpoint not included above will not be adjusted for multiplicity, and will be interpreted with nominal p-value.

13.6. Safety Analyses

Safety and tolerability of SAGE-217 will be evaluated by TEAEs, changes from baseline in [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be presented for the safety sets using actual treatment received. Where applicable, ranges of potentially clinically significant values will be provided in the SAP.

13.6.1. Adverse Events

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

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

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

[redacted]

13.6.3. Physical Examinations

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

[redacted]

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each of the triplicate ECGs for each participant: heart rate, PR, QRS, QT, and QTcF. The derived mean of each parameter will also be listed. Mean ECG data will be summarized by visit. Potentially clinically significant values of QTcF will be summarized by treatment. Electrocardiogram findings will be listed by participant and visit.

13.6.6. Prior and Concomitant Medications

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

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

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

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

[redacted]

[redacted]

13.6.9. Other Safety Analysis

[redacted]

13.8. Sample Size and Power

Using a 2-sided alpha level of 0.05, a sample size of 382 total evaluable participants would provide 90% power to detect a treatment difference (between SAGE-217 + assigned ADT and placebo + assigned ADT) of approximately 3 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each treatment group, approximately 424 total randomized participants will be required to obtain a total of 382 evaluable participants. Evaluable participants are defined as those randomized participants who receive IP and have valid baseline and at least 1 postbaseline HAM-D assessment.

13.8.1. Interim and Data Monitoring Committee Analyses

No interim analyses or data monitoring committee analyses will be conducted.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage 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 IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or independent ethics committee.

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

14.2. Audits and Inspections

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

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

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

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

16.3. Written Informed Consent

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

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

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

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

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

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

17.2. Retention of Records

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

18. PUBLICATION POLICY

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

19. LIST OF REFERENCES

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STUDY TITLE: A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY COMPARING THE EFFICACY AND SAFETY OF SAGE-217 PLUS AN ANTIDEPRESSANT VERSUS PLACEBO PLUS AN ANTIDEPRESSANT IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

PROTOCOL NUMBER: 217-MDD-305

Investigational Product	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	13 MAY 2020
Date of Amendment 1	11 SEP 2020

SPONSOR APPROVAL

Protocol Number:	217-MDD-305
Study Title:	A Phase 3, Randomized, Double-Blind Study Comparing the Efficacy and Safety of SAGE-217 plus an Antidepressant Versus Placebo plus an Antidepressant in Adults with Major Depressive Disorder
Protocol Version and Date:	Version 2, 11 September 2020

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[redacted], RAC
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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-305 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD/MMM/YYYY)

CONTACT INFORMATION

Table 1: Contact Information

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

2. SYNOPSIS

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

Name of Investigational Product: SAGE-217 Capsules

Name of Active Ingredient: SAGE-217

Title of Study: A Phase 3, Randomized, Double-Blind Study Comparing the Efficacy and Safety of SAGE-217 plus an Antidepressant Versus Placebo plus an Antidepressant in Adults with Major Depressive Disorder

Number of Sites and Study Location: This study will take place at approximately 55 sites in United States.

Phase of Development: 3

Planned Duration for each Study Participant: Up to 70 days (up to 28-day Screening Period, 14-day Double-blind Treatment Period, and a 28-day Antidepressant Therapy (ADT) Continuation Period)

Objectives:

Primary:

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

Secondary:

- To assess patient-reported outcome (PRO) measures as they relate to depressive symptoms
- To evaluate the safety and tolerability of SAGE-217 plus an antidepressant

[redacted]

Endpoints:

Primary:

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

Key Secondary:

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

Other Secondary:

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as “much improved” or “very much improved”, at Day 15
- Change from baseline in MADRS total score at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline to Day 15 in depressive symptoms, as assessed by the PHQ-9
- Incidence and severity of treatment-emergent adverse events (TEAEs)

[redacted]

Study Description:

This is a randomized, double-blind, parallel-group, placebo-controlled study in adults with MDD. 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.

The study will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day ADT Continuation Period. The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit. Preliminary screening procedures to determine eligibility include completion of the MGH-ATRQ and HAM-D.

Participants will be randomized to receive blinded SAGE-217 50 mg or placebo for administration each evening from Days 1 through 14. In addition, all participants will receive 1 of 2 classes of ADTs: a selective serotonin reuptake inhibitor (SSRI; sertraline, escitalopram, citalopram) or a serotonin-norepinephrine reuptake inhibitor (SNRI; duloxetine or desvenlafaxine) in an open-label manner from Day 1 through the end of the study. The ADT will be administered per labeled prescribing information. The investigator will assign 1 of the 5 ADTs based on clinical standard of care; the participant must not have been previously treated with the assigned ADT within the current depressive episode and must not have taken any ADT within 30 days prior to Day 1 (or taken fluoxetine within 60 days prior to Day 1). Randomization will be stratified by ADT class (SSRI or SNRI).

After the double-blind Treatment Period, the ADT will be continued each evening for the remainder of the study (ADT Continuation Period). During this period (Weeks 3 to 6), ADT dosing may be modified based on individual response, at the discretion of the investigator and per the labeled prescribing information.

Initiation of other antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of assessments at Day 42/end-of-study visit.

Participants will self-administer blinded investigational product (IP) once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. The ADT and SAGE-217/placebo will be administered at the same time during the Treatment Period; participants assigned duloxetine will also administer ADT in the morning (for twice-daily dosing) as part of a divided dose for the first 7 days. Participants will return to the study center as outlined in the Schedule of Assessments (Table 2).

During the Treatment Period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate SAGE-217/placebo 50 mg will receive 40 mg for the remainder of the Treatment Period. Participants who, in the opinion of the investigator, cannot tolerate the SAGE-217/placebo 40-mg dose may be discontinued from SAGE-217/placebo at the discretion of the investigator. If blinded IP is discontinued, the ADT may be

continued at the discretion of the investigator.

Upon completion of the current study, eligible participants will have the opportunity to enter a long-term open-label study of SAGE-217.

Number of Participants (planned): It is estimated that approximately 424 participants will be randomized and treated to obtain 382 evaluable participants at Day 15 (assuming a 10% dropout rate). Additional participants may be randomized if the dropout rate is greater than 10%.

Eligibility Criteria:

Inclusion Criteria

1. Participant has signed an ICF prior to any study-specific procedures being performed.
2. Participant is a male or female between 18 and 64 years of age, inclusive.
3. Participant is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Participant agrees to adhere to the study requirements.
5. Participant 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. Participant has a HAM-D-17 total score of ≥24 at Screening and Day 1 (prior to dosing).
7. Participant is willing to delay start of any antidepressant (except as per protocol), anxiolytic, anti-insomnia, psychostimulant, prescription opioid regimens, or new psychotherapy (including Cognitive Behavioral Therapy for Insomnia [CBT-I]) until after study completion. Participants receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1 and intend to maintain that schedule for the duration of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence).
9. Female participant who is breastfeeding at Screening or on Day 1 (prior to administration of IP) must be willing to temporarily cease giving breast milk to her child(ren) from just prior to receiving IP on Day 1 until 7 days after the last dose of SAGE-217/placebo.
10. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 5 days after receiving IP, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
11. Male participant is willing to abstain from sperm donation for the treatment period and for 5 days after receiving the last dose of the IP.
12. Participant agrees to refrain from drugs of abuse and alcohol for the duration of the study.
13. Participant is willing, able, and eligible to take at least 1 of the 5 ADTs specified in the protocol (an eligible ADT is an ADT that has not been taken during the current depressive episode and for which the participant has no contraindications; further, a participant is not eligible for citalopram if escitalopram has been taken during the current depressive episode, and vice versa).

Exclusion Criteria

1. Participant is currently at significant risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of MDD.
2. Participant had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the participant has presented for screening during the 6-month postpartum period.
3. Participant has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eye, ear, nose, and throat disorders, or any other acute or chronic condition that, in the investigator's opinion, would limit the participant's ability to complete or participate in this clinical study; a BMI $\leq$18 or $\geq$45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
4. Participant 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 2 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. Participant has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Participant is receiving Cognitive Behavioral Therapy for Insomnia (CBT-I) within 28 days prior to Day 1.
7. Participant has a known allergy to SAGE-217, allopregnanolone, sertraline, or related compounds.
8. Participant has taken antidepressants within 30 days prior to Day 1, and/or has taken fluoxetine within 60 days prior to Day 1.
9. Female participant has a positive pregnancy test or confirmed pregnancy.
10. Participant has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
11. Participant has active psychosis per investigator assessment.
12. Participant has a medical history of seizures.
13. Participant has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
14. Participant has a history of severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to Screening or participant has a history of mild or moderate substance use disorder not in sustained remission for at least 6 months prior to Screening.
15. Participant has had exposure to another investigational medication or device within 30 days prior to Screening.
16. Participant has previously received brexanolone or participated in a SAGE-217 or SAGE-547 (brexanolone) clinical trial.
17. Participant has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these, within 14 days prior to Day 1.

18. Participant has used any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort, within 28 days prior to Day 1.
19. Participant has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
20. Participant plans to undergo elective surgery before completion of the Day 42 visit.
21. Participant is taking benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Day 1, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Participant is taking any benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1.
22. Participant is taking non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids), or first or second generation (typical/atypical) antipsychotics within 14 days prior to Day 1. Note that nonsedating antihistamines are permitted.
23. Participant has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
24. Participant has a history of sleep apnea.
25. Participant has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
26. Participant is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as needed, within 28 days prior to Day 1.
27. Participant is a dependent of the sponsor, investigator, investigator's deputy, or study site staff.
28. Participant expects to perform night shift work during the 14-day Treatment Period.
29. Participant has detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at Screening.

Investigational Product Dosage and Mode of Administration: SAGE-217 will be available as hard gelatin capsules for oral administration; multiple capsules (in 30-mg or 20-mg dose strengths) will be provided to total a 50-mg dose, with option to reduce to 40 mg based on tolerability.

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217, for oral administration.

Sertraline, escitalopram, citalopram, duloxetine, or desvenlafaxine will be administered as per labeled prescribing information

Duration of Treatment: Blinded SAGE-217 or placebo will be administered once daily for 14 days; open-label ADT will be administered according to labeled prescribing information for 42 days.

Statistical Methods:

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock and treatment unblinding. Any deviations from or changes to the SAP following database lock will be detailed in the Clinical Study Report.

General Considerations

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

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized participants who receive at least 1 dose of IP and who have a valid baseline as well as at least 1 postbaseline HAM-D evaluation.

The Safety Set is defined as all participants who receive at least 1 dose of IP.

The Randomized Set, defined as all participants who are randomized.

[redacted]

Determination of Sample Size

Using a two-sided alpha level of 0.05, a sample size of 382 total evaluable participants would provide 90% power to detect a treatment difference (between SAGE-217 + an antidepressant and placebo + an antidepressant) of approximately 3 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each treatment group, approximately 424 total randomized participants will be required to obtain a total of 382 evaluable participants. Evaluable participants are defined as those randomized participants who receive IP and have valid baseline and at least 1 postbaseline HAM-D assessment.

Analysis of Primary Endpoint

The estimand for the primary analysis is the mean change from baseline in HAM-D total score at Day 15. Using FAS, this will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline time points will be included in the model. The main comparison will be between SAGE-217 + an antidepressant and placebo + an antidepressant at the 15-day time point. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p values) will be reported where applicable. An unstructured covariance structure will be used to model the within-participant errors. The Toeplitz compound symmetry, Autoregressive (1) [AR(1)] covariance structure will be used in that sequence if there is a convergence issue with the unstructured covariance model. If convergence is still not achieved, no results will be reported.

Analysis of Secondary Endpoints

Similar to those methods described above for the primary endpoint, an MMRM will be used for the analysis of the change from baseline in other time points in HAM-D total score, MADRS total score, HAM-A total score, CGI-S score, and PHQ-9 total score.

Generalized estimating equation methods will be used for the analysis of HAM-D response (defined as ≥50% reduction from baseline in HAM-D total score) and HAM-D remission (defined as HAM-D total score of ≤7.0). GEE models will include terms for center, treatment, baseline score, assessment time

point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 + an antidepressant and placebo + an antidepressant at the 15-day time point. Model-based point estimates (ie, odds ratios), 95% confidence intervals, and p values will be reported.

A GEE method will also be used for the analysis of CGI-I response including terms for center, treatment, baseline CGI-S score, assessment time point, and time point-by-treatment as explanatory variables.

Safety Analysis

Safety and tolerability of IP will be evaluated by adverse events (AEs)/serious adverse event (SAEs), [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set.

[redacted]

Table 2: Schedule of Assessments

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

Visits	Screening Period	Double-Blind, Placebo-Controlled Treatment Period					ADT Continuation Period				
Visit Days	D-28 to D-1	D1	D3 (±1d)	D8 (+1d)	D12 (±1d)	D15 (+1d) and/or EOT [a]	D18 (±1d)	D21 (±1d)	D28 (±3d)	D35 (±3d)	D42 (±3d) /ET
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Study Procedure											
Pregnancy Test [i]	X	X				X			X		X
Hepatitis & HIV Screen	X										
[redacted]											
Vital Signs [l]	X	X	X	X	X	X	X		X		X
12-Lead ECG [m]	X	X				X					X
[redacted]											
HAM-D [o, p]	X	X	X	X	X	X	X	X	X	X	X
MADRS		X		X		X			X		X
HAM-A [p]		X		X		X			X		X
CGI-S	X	X	X	X	X	X		X	X	X	X
CGI-I			X	X	X	X		X	X	X	X
[redacted]											
PHQ-9		X	X	X		X			X		X
[redacted]											
SAGE-217/Placebo Dispensation		X		X							

Visits	Screening Period	Double-Blind, Placebo-Controlled Treatment Period					ADT Continuation Period				
Visit Days	D-28 to D-1	D1	D3 (±1d)	D8 (+1d)	D12 (±1d)	D15 (+1d) and/or EOT [a]	D18 (±1d)	D21 (±1d)	D28 (±3d)	D35 (±3d)	D42 (±3d) /ET
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Study Procedure											
SAGE-217/Placebo Administration		X (once daily in the evening through Day 14 - inclusive)									
IP Adherence [s]		X									
ADT Administration [t]		X									
IP Accountability/Return			X	X		X		X	X	X	X [r]
AEs/SAEs [d, u]		X									
Prior/Concomitant Medications/Procedures [d, v]		X									

Abbreviations: ADT = Antidepressant therapy; AE = adverse event; CGI-I = Clinical Global Impression – Improvement; CGI-S – Clinical Global Impression – Severity; [redacted] D = day; EOT = end of treatment; ET = early termination; ECG = electrocardiogram; FSH = follicle stimulating hormone; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; IP = investigational product; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; PHQ-9 = 9-item Patient Health Questionnaire; [redacted] O = Optional; [redacted] SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Clinical Trials Version; [redacted] V = visit.

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

[b] Participants will be asked to authorize that their unique participant identifiers be entered into a registry (www.subjectregistry.com) with the intent of identifying participants who may meet exclusion criteria for participation in another clinical study.

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

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

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

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

[g] Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis.
[h] Urine toxicology for selected drugs of abuse (Table 3) and breath test for alcohol.
[i] Serum pregnancy test at screening and urine pregnancy test thereafter for female participants who are not surgically sterile and do not meet the protocol-defined criteria for being postmenopausal.
[redacted]
[l] When vital signs are scheduled at the same time as blood draws, vital signs will be obtained first. Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Heart rate and blood pressure to be collected in supine position at all scheduled time points after the participant has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Vital signs may be repeated at the discretion of the investigator as clinically indicated.
[m] Triplicate ECGs will be collected. [redacted]
[o] The HAM-D is to be completed as early during the visit as possible.
[p] The assessment timeframe for HAM-D scales will refer to the past 7 days (1 week) at Screening and "Since Last Visit" for all other visits. The assessment timeframe for HAM-A scales will refer to the past 7 days (1 week) at all visits.
[redacted]
[r] To be performed at the ET visit only.
[s] IP administration will be monitored via a medication adherence monitoring platform used on smartphones to visually confirm IP ingestion.
[t] ADT will be administered as per labeled prescribing information
[u] AEs will be collected starting at the time of informed consent and throughout the duration of the participant's participation in the study.
[v] Prior medications will be collected at Screening and concomitant medications and/or procedures will be collected at each subsequent visit.

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

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation	Definition
ADT	Antidepressant therapy
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulation
CRO	contract research organization
CSR	clinical study report
IEC	independent ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
IP	investigational product
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PI	prescribing information
PK	pharmacokinetic
PV	pharmacovigilance
QA	quality assurance
QC	quality control
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SOP	Standard Operating Procedure

Abbreviation	Definition
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Major Depressive Disorder and Unmet Medical Need

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

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

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association 2013) provides diagnostic criteria for major depressive disorder (MDD). These include at least 5 of 9 depressive symptoms (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 (SNRI), serotonin norepinephrine reuptake inhibitors (SSRI), tricyclic antidepressants, monoamine oxidase inhibitors (MAOI), 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). Furthermore, these agents can take 4 to 8 weeks to demonstrate full clinical efficacy (Rush 2006; Trivedi 2006), and in the case of the most commonly prescribed classes—SSRIs and SNRIs—common side effects including weight gain, GI symptoms, and sexual dysfunction can prevent titration into an adequate therapeutic range (Sadock and Sadock 2007).

In the largest study to assess the effectiveness of depression treatments in patients with MDD, time to patient remission after treatment was 5.4 to 7.4 weeks; approximately one-half of the patients who ultimately remitted did so after 6 weeks, and 40% of those who achieved remission required 8 or more weeks to do so (Rush 2006; Trivedi 2006). Even following remission, many patients report the presence of residual symptoms, often related to decreased positive affect, such as loss of interest in activities once considered enjoyable, fatigue, loss of energy, as well as sleep and appetite/weight disturbances (Nierenberg 2009; Nierenberg 2015). Thus, patients may remain symptomatic for up to 2 months while waiting for current standard-of-care pharmacotherapy to take full effect. They may also have to contend with undesirable side effects and residual symptoms. These aspects underscore the need for newer, rapid-acting therapies.

SAGE-217 is a synthetic positive allosteric modulator of $GABA_A$ receptors, the major class of inhibitory neurotransmitter receptors in the brain. In pharmacokinetic (PK) studies in mice and

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

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) associated with SAGE-217 (overall) were sedation, somnolence, and dizziness; most adverse events (AEs) were reported as mild or moderate in intensity. Refer to the SAGE-217 Investigator's Brochure for a detailed description of the chemistry, pharmacology, efficacy, and safety of SAGE-217.

This study was designed to target the unmet need of symptom improvement during the latency to SSRI and SNRI efficacy in the acute phase of a major depressive episode. This study will assess the safety and efficacy of SAGE-217 50 mg plus an antidepressant, examining if SAGE-217 plus an antidepressant produces more rapid or more profound reduction in depressive symptoms than an antidepressant alone.

5.2. Potential Risks and Benefits

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

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

Based on nonclinical findings, embryo-fetal toxicity and withdrawal effects are considered important potential risk for SAGE-217. Risk mitigation measures in this study include monitoring for adverse effects, monitoring for potential withdrawal effects, requiring highly effective contraceptive measures for study participants, and inclusion of dose adjustment criteria and guidance for blinded IP discontinuation (Section 8.4). Finally, due to the sedation/somnolence observed, SAGE-217 is administered in the evening in this study.

Given the outcome of the completed studies of SAGE-217 in participants with MDD and PDD, the current significant unmet need for well-tolerated and rapid-acting depression treatments, and a favorable benefit-risk profile, further investigation of SAGE-217 as a novel rapid response treatment in adults with MDD is justified.

5.3. Dose Justification

Results from a large, multicenter study of SAGE-217 20 and 30 mg in MDD (217-MDD-301) support the need for higher steady-state concentrations of SAGE-217 to allow participants to experience maximum antidepressant and anti-anxiety benefits. SAGE-217 will be administered as a 14-day regimen of an evening dose of 50 mg with reduction to 40 mg as needed based on tolerability. The 50-mg dose of SAGE-217 is expected to exhibit a favorable benefit-risk profile in the context of results from previous SAGE-217 studies utilizing a 30-mg dose, now identified as a minimally effective dose. SAGE-217 is expected to maintain an acceptable tolerability

profile, based on a current safety database of over 2000 participants exposed across different doses/concentrations.

Sertraline is a commercially available SSRI indicated for the treatment of MDD and other psychiatric disorders. Dosage and administration of sertraline as described in the approved US Prescribing Information (PI) recommends a starting dose of 50 mg per day in patients with MDD, with an incremental weekly increase in dose of 25-50 mg per day, if there is an inadequate response to the starting dose, to a maximum dose of 200 mg per day. . In this study, a starting dose of 50 mg per day is recommended for 7 days, with a subsequent increase to 100 mg per day.

Citalopram and escitalopram are commercially available SSRIs that are both indicated for acute and maintenance treatment of MDD. Escitalopram is also indicated for treatment of generalized anxiety disorder. The starting dosage for MDD in the US PI for citalopram is 20 mg/day and for escitalopram is 10 mg/day, with maxima of 40 mg/day and 20 mg/day, respectively. In this study, a starting dose of 20 mg/day is recommended for citalopram and of 10 mg/day is recommended for escitalopram for the first 14 days; subsequent dose increases may be considered, except for participants >60 years old taking citalopram.

Duloxetine is a commercially available SNRI indicated for the treatment of MDD, generalized anxiety disorder, and pain disorders. The starting dosage for MDD in the US PI is 40 to 60 mg/day. The maximum dosage is 120 mg/day, although there is no evidence that dosages greater than 60 mg/day confer any additional benefits. In this study, a starting dose of 60 mg/day is recommended (divided as 30 mg twice daily for the first 7 days).

Desvenlafaxine is a commercially available SNRI indicated for the treatment of MDD. The recommended dosage in the US PI is 50 mg/day. In this study, a dose of 50 mg/day is recommended. There has been no evidence that doses greater than 50 mg/day confer any additional benefit.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

To evaluate the efficacy of SAGE-217 plus an antidepressant in the treatment of MDD compared to placebo plus an antidepressant

6.1.2. Secondary Objectives

- To assess patient-reported outcome (PRO) measures as they relate to depressive symptoms
- To evaluate the safety and tolerability of SAGE-217 plus an antidepressant

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoint

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

6.2.2. Secondary Endpoints

6.2.2.1. Key Secondary Endpoints

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

6.2.2.2. Other Secondary Endpoints

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as “much improved” or “very much improved”, at Day 15
- Change from baseline in MADRS total score at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline to Day 15 in depressive symptoms, as assessed by the PHQ-9
- Incidence and severity of treatment-emergent AEs

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, parallel-group, placebo-controlled study in adults with MDD. 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.

The study will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day ADT Continuation Period. The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit. Preliminary screening procedures to determine eligibility include completion of the MGH-ATRQ and HAM-D.

Participants will be randomized to receive blinded SAGE-217 or placebo for administration each evening from Day 1 through 14. In addition, all participants will receive 1 of 2 classes of ADTs: a selective serotonin reuptake inhibitor (SSRI; sertraline, escitalopram, citalopram) or a serotonin-norepinephrine reuptake inhibitor (SNRI; duloxetine, desvenlafaxine) in an open-label manner from Day 1 through the end of the study. The investigator will assign 1 of the 5 ADTs based on clinical standard of care; the participant must not have been previously treated with the assigned ADT within the current depressive episode (and must not have been treated with citalopram if escitalopram is assigned, and vice versa) and must not haven taken any ADT within 30 days prior to Day 1 (or taken fluoxetine within 60 days prior to Day 1). Randomization will be stratified by antidepressant class (SSRI or SNRI).

The open-label ADT will be administered as per labeled prescribing information.

After the Double-blind Treatment Period, the ADT will be continued each evening for the remainder of the study (ADT Continuation Period). During this period (Week 3 to 6), ADT dosing may be modified as appropriate per the labeled prescribing information and based on individual response,.

Initiation of other antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of assessments at Day 42/end-of-study visit.

Participants will self-administer blinded investigational product (IP) once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. The ADT and SAGE-217 or placebo will be administered at the same time during the Treatment Period; participants assigned duloxetine will also administer ADT in the morning (for twice-daily dosing) as part of a divided dose for the first 7 days. Participants will return to the study center as outlined in the Schedule of Assessments.

During the Treatment Period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate SAGE-217 or placebo 50 mg will receive 40 mg for the remainder of the Treatment Period. Participants who cannot tolerate the SAGE-217/placebo 40-mg dose may be discontinued from SAGE-217 or placebo at the discretion of the investigator. If blinded IP is discontinued, the ADT may be continued at the discretion of the investigator.

Upon completion of the current study, eligible participants will have the opportunity to enter a long-term open-label study of SAGE-217. Participants that do not enter the open-label study or that terminate the current study early may, per the investigator, receive a supply of the ADT with instructions on how to taper the drug, if needed, or, if they wish to continue the ADT, a bridge supply to permit them to obtain a prescription from another provider.

7.2. Number of Participants

It is estimated that approximately 424 participants will be randomized and treated to obtain 382 evaluable participants at Day 15 (assuming 10% dropout rate). Additional participants may be randomized if the dropout rate is greater than 10%.

7.3. Treatment Assignment

Participants will be assigned to blinded IP (SAGE-217 or placebo) in accordance with the randomization schedule on Day 1. The investigator will assign 1 of the 5 ADTs based on clinical standard of care. The assigned ADT for a participant cannot have been taken previously by the participant during the current depressive episode. Further, citalopram cannot be assigned if escitalopram has been taken during the current depressive episode, and vice versa.

Randomization will be stratified by antidepressant class (SSRI or SNRI).Additional details on randomization and blinding are provided in Section 9.5.

Sage will monitor the ratio of SSRIs:SNRIs on an ongoing basis and may restrict assignment of any ADT(s) to reflect the ratio expected with standard of care (approximately 3:1; Luo 2020).

7.4. Dose Adjustment Criteria

During the treatment period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate 50 mg (as determined by the investigator) will receive 40 mg for the remainder of the treatment period.

At the discretion of the investigator, participants who cannot tolerate the 40-mg dose at any time may be discontinued from dosing upon completion of an end of treatment (EOT) visit as soon as possible. These participants should be followed and complete assessments as per the Schedule of Assessments (Table 2).

During Weeks 3 to 6, the ADT dosing may be modified, based on individual response, per investigator discretion and per the labeled prescribing information.

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 participants, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the investigator. Investigational sites must promptly notify their IRB, where required, and initiate withdrawal procedures for participating participants.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

1. Participant has signed an ICF prior to any study-specific procedures being performed.
2. Participant is a male or female between 18 and 64 years of age, inclusive.
3. Participant is in good physical health and has no clinically significant findings, as determined by the investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Participant agrees to adhere to the study requirements.
5. Participant 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. Participant has a HAM-D-17 total score of ≥24 at Screening and Day 1 (prior to dosing).
7. Participant is willing to delay start of any antidepressant (except sertraline as per protocol), anxiolytic, anti-insomnia, psychostimulant, prescription opioid regimens, or new psychotherapy (including Cognitive Behavioral Therapy for Insomnia [CBT-I]) until after study completion. Participants receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1 and intend to maintain that schedule for the duration of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence).
9. Female participant who is breastfeeding at Screening or on Day 1 (prior to administration of IP) must be willing to temporarily cease giving breast milk to her child(ren) from just prior to receiving IP on Day 1 until 7 days after the last dose of SAGE-217/placebo.
10. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 5 days after receiving IP, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
11. Male participant is willing to abstain from sperm donation for the treatment period and for 5 days after receiving the last dose of the IP.
12. Participant agrees to refrain from drugs of abuse and alcohol for the duration of the study.
13. Participant is willing, able, and eligible to take at least 1 of the 5 ADTs specified in the protocol (an eligible ADT is an ADT that has not been taken during the current depressive episode and for which the participant has no contraindications; further, a participant is not eligible for citalopram if escitalopram has been taken during the current depressive episode, and vice versa).

8.2. Participant Exclusion Criteria

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

1. Participant is currently at significant risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of MDD.
2. Participant had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the participant has presented for screening during the 6-month postpartum period.
3. Participant 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 participant's ability to complete or participate in this clinical study; a BMI $\leq$18 or $\geq$45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
4. Participant 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 2 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. Participant has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Participant is receiving Cognitive Behavioral Therapy for Insomnia (CBT-I) within 28 days prior to Day 1.
7. Participant has a known allergy to SAGE-217, allopregnanolone, sertraline, or related compounds.
8. Participant has taken antidepressants within 30 days prior to Day 1, and/or has taken fluoxetine within 60 days prior to Day 1.
9. Female participant has a positive pregnancy test or confirmed pregnancy.
10. Participant has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
11. Participant has active psychosis per investigator assessment.
12. Participant has a medical history of seizures.
13. Participant has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.

14. Participant has a history of severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to Screening or participant has a history of mild or moderate substance use disorder not in sustained remission for at least 6 months prior to Screening.
15. Participant has had exposure to another investigational medication or device within 30 days prior to Screening.
16. Participant has previously received brexanolone or participated in a SAGE-217 or SAGE-547 (brexanolone) clinical trial.
17. Participant has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to Day 1.
18. Participant has used any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort, within 28 days prior to Day 1.
19. Participant has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
20. Participant plans to undergo elective surgery before completion of the Day 42 visit.
21. Participant is taking benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Day 1, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Participant is taking any benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1.
22. Participant 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 within 14 days prior to Day 1. Note that nonsedating antihistamines are permitted.
23. Participant has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
24. Participant has a history of sleep apnea.
25. Participant has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
26. Participant is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as needed, within 28 days prior to Day 1.
27. Participant is a dependent of the sponsor, investigator, investigator's deputy, or study site staff.
28. Participant expects to perform night shift work during the 14-day treatment period.
29. Participant has detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at Screening.

8.3. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

8.4. Investigational Product Discontinuation and Early Termination from the Study

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

Based on known withdrawal symptoms with other GABAergic drugs and nonclinical 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 blinded IP discontinuation or dose reduction are presented to support participant safety:

1. Any participant reporting a confirmed or suspected seizure at any time will be discontinued from blinded IP but will continue to be followed in the study.
2. The investigator should monitor the course of CNS-based signs and symptoms suggestive of a seizure which are not accounted for by comorbid psychiatric or medical conditions. Examples of reported serious or severe events which may reflect an oncoming and/or increased risk for seizure may include temporary confusion, tremors, involuntary muscle fasciculations or jerking movements of arms or legs, or paresthesia. Should such symptoms occur, the investigator should consider decreasing the dose of SAGE-217 or placebo to 40 mg, stopping treatment to assess the effect on the symptom(s) (eg, resolution, improvement), or discontinuing the participant from treatment. A participant who discontinues treatment should remain in the study and continue protocol-required assessments until the end of the study.

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

8.4.1. Investigational Product Discontinuation

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

Participants who discontinue treatment early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place as scheduled relative to the last dose of treatment (eg, if a participant's last dose is on Day 13, their first follow-up visit, Visit 7, should occur 4 days later), and will continue safety and efficacy assessments as scheduled for 6 weeks following the final dose.

Participants that discontinue blinded IP early may, per the investigator, receive a supply of the ADT with instructions on how to taper the drug, if needed, or, if they wish to continue the ADT, a bridge supply to permit them to obtain a prescription from another provider.

8.4.2. Early Termination from the Study

If a participant decides to terminate the study, the participant should return for an early termination (ET) visit, if possible. The primary reason for early termination from the study must be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF). If a participant discontinues IP and terminates the study on the same day during a clinic visit, the EOT and ET visits can be on the same day; in this case, all EOT visit assessments should be conducted in addition to an abbreviated physical examination

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

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

Participants who terminate from the study early may, per the investigator, receive a supply of the ADT with instructions on how to taper the drug, if needed, or, if they wish to continue the ADT, a bridge supply to permit them to obtain a prescription from another provider.

8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after 3 attempts at contacting the participant have been unsuccessful.

8.4.4. Replacement of Participants

Participants will not be replaced.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Products

SAGE-217 will be available as hard gelatin capsules for oral administration; 2 capsules (one 30 mg and one 20 mg) will be provided to total a 50-mg dose, with option to reduce to 40 mg based on tolerability, as per criteria described in Section 7.4. If the dose is reduced to 40 mg, it will be administered as 2 20-mg capsules.

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217, for oral administration.

All participants will self-administer blinded and open-label IP orally at approximately 8 PM with fat-containing food for 14 days. Participants assigned duloxetine will also administer duloxetine in the morning (for twice daily dosing) as part of a divided dose for the first 7 days (see below).

It is recommended that sertraline be administered as per labeled prescribing information, starting with 50 mg each evening during Week 1. and It is recommended that the dose be increased to 100 mg each evening during Week 2.

It is recommended that citalopram be administered per labeled prescribing information, starting with 20 mg/day.

It is recommended that escitalopram be administered per labeled prescribing information, starting with 10 mg/day.

It is recommended that duloxetine be administered per labeled prescribing information, starting with 60 mg/day (divided as 30 mg twice daily for the first 7 days).

It is recommended that desvenlafaxine be administered per labeled prescribing information, starting with 50 mg/day.

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

9.2.1. Prior and Concomitant Medications and/or Supplements

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

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

9.2.2. Prohibited Medications

The following specific classes of medications are prohibited:

- Initiation of new psychotropic medications through the Day 42 visit
- Initiation of new antidepressant therapy from 30 days (60 days for fluoxetine) prior to Day 1 through the Day 42 visit

- Use of any benzodiazepines, barbiturates, $GABA_A$ modulators, GABA-containing agents from Day -28 through the Day 42 visit (from Day -60 for benzodiazepines or GABA modulators with a half-life ≥48 hours)
- Chronic or as-needed psychostimulants (eg, methylphenidate, amphetamine) or opioids from Day -28 through the Day 42 visit
- First generation (typical) antipsychotics (eg, haloperidol, perphenazine) and second generation (atypical) antipsychotics (eg, aripiprazole, quetiapine) from Day -14 through the Day 42 visit
- Use of any non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids) from Day -14 to Day 1. Note that nonsedating antihistamines are permitted.
- Exposure to another investigational medication or device from 30 days prior to Screening through the Day 42 visit
- Any known strong inhibitors of CYP3A4 from Day -28 or 5 half-lives prior to Day 1 (whichever is longer) through the Treatment Period
- Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort from Day -28 through the Treatment Period
- Any contraindications to the assigned SSRI/SNRI per labeled prescribing information

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 Day 1 and throughout the treatment period.

The concomitant use of sertraline with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate; therefore, decrease the dosage of a CYP2D6 substrate if needed.

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

Female participants who are lactating or actively breastfeeding must stop giving breast milk to the baby(ies) starting on Day 1 until 7 days after the last dose of SAGE-217/placebo.

Elective surgeries or procedures are prohibited through the Day 42 visit.

Participants must not participate in night shift work during the Treatment Period.

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

Participants receiving psychotherapy on a regular schedule for at least 60 days prior to Day 1 are permitted if the participant intends to continue that schedule through the Follow-up Period (Day 42). Initiation of new psychotherapy is prohibited until after study completion.

9.2.4. Acceptable Forms of Contraception

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

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation or bilateral tubal occlusion (performed at least 3 months prior to screening)
- Vasectomized partner (performed at least 3 months prior to screening)

Acceptable forms of contraception for male participants include:

- History of vasectomy (performed at least 3 months prior to screening)
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

9.3. Intervention after the End of the Study

Upon completion of the current study, eligible participants will have the opportunity to enter an open-label, long-term study of SAGE-217 in which additional treatment with SAGE-217 will be offered. Participants that do not enter the open-label study or that terminate the current study early may continue to receive ADT as prescribed by the investigator either to taper the drug appropriately or—if the participant wishes to continue ADT—to bridge the participant until he or she receives a new prescription.

9.4. Treatment Adherence

Investigational products will be self-administered by participants (see Section 10.5).

Administration of blinded and open-label IP will be monitored by a medication adherence monitoring platform used on smartphones to confirm medication ingestion. Participants will receive a reminder within a predefined time window to take IP while using the application and will follow a series of prescribed steps to confirm their ingestion of the medication. The application will record the date and time of IP administration by dose level, as well as missed doses.

In addition, participants will be instructed to bring their SAGE-217 or placebo dosing kit and ADT to the site as outlined in Table 2, at which time the investigator or designee will be responsible for ensuring the kit contains sufficient doses for the duration of the treatment period.

All participants should be reinstructed about the dosing requirements during study contacts. The authorized study personnel conducting the reeducation must document the process in the participant source records.

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

9.5. Randomization and Blinding

Participants will be randomized in a 1:1 ratio to receive SAGE-217 or matched placebo. Participants, site staff, and the sponsor will be blinded to treatment allocation. All participants will also receive an open-label ADT. Randomization will be performed centrally via an interactive response technology (IRT) system. Randomization schedules will be generated by an independent statistician. The allocation to blinded treatment (SAGE-217or placebo) will be based on the randomization schedule. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

9.5.1. Emergency Unblinding

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

In all cases where the IP allocation for a participant is unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's records and on the eCRF.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Products

10.1.1. Blinded Investigational Products

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

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217.

10.1.2. Open-label Investigational Product

Sertraline, escitalopram, citalopram, duloxetine, and desvenlafaxine, packaged and labeled by the commercial manufacturer, will be supplied by a third-party vendor. Open-label IP is to be stored and administered according to the package insert. Open-label IP during this study is for use only as directed in this protocol.

10.2. Blinded Investigational Product Packaging and Labeling

SAGE-217 and placebo will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the blinded IP in appropriately labeled, participant-specific kits containing sealed unit doses. Each unit dose for 40-mg and 50-mg dose levels consists of 2 capsules. Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Labels with all required information and conforming to all applicable FDA Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices guidelines will be prepared by the sponsor for SAGE-217 and placebo.

10.3. Blinded Investigational Product Storage

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

10.4. Blinded Investigational Product Preparation

Not applicable.

10.5. Blinded and Open-label Investigational Product Administration

Blinded IP and open-label sertraline are to be administered orally at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack). Examples of fat-containing snacks include nuts, peanut butter, avocado, eggs, and cheese. Participants assigned duloxetine will also administer duloxetine in the morning (for twice-daily divided dosing) for the first 7 days (see Section 9.1).

If a participant misses a dose of blinded IP or open-label IP, the participant should skip that dose (ie, they should not take the dose in the morning) and take the next scheduled dose.

10.6. Blinded Investigational Product Accountability, Handling, and Disposal

Upon receipt of blinded IP dosing kits, the investigator(s), or the responsible pharmacist or designee, will inspect the kits and complete and follow the instructions regarding receipt and storage in the SAGE-217 Investigator's Brochure and (where applicable) in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the participant-specific kits to participants at the planned dispensation visit intervals outlined in Table 2. Site staff will access the IRT at the Screening Visit to obtain a participant identification (ID) number for each participant that has signed an informed consent form. On Day 1, site staff will access the IRT and provide the necessary participant-identifying information, including the participant ID number assigned at Screening, to randomize the eligible participant into the study and obtain the medication ID number for the blinded IP to be dispensed to that participant. The medication ID number and the number of blinded capsules dispensed must be recorded.

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

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

The blinded IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all blinded IP received, used and returned/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.

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

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

10.7. Blinded Investigational 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 provided in Table 1.

Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

11. EFFICACY AND CLINICAL PHARMACOLOGY ASSESSMENTS

11.1. Efficacy Assessments

11.1.1. Hamilton Rating Scale for Depression

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

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

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

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

11.1.2. Montgomery-Åsberg Depression Rating Scale

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

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

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

11.1.3. Hamilton Anxiety Rating Scale

The 14-item HAM-A will be used to rate the severity of symptoms of anxiety (Williams 2013c; Williams 2013d). Each of the 14 items is defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Scoring for HAM-A is calculated by assigning scores of 0 (not present) to 4 (very severe), with a total score range of 0 to 56, where <17 indicates mild severity, 18 to 24, mild to moderate severity, and 25 to 30, moderate to severe severity. The HAM-A total score will be calculated as the sum of the 14 individual item scores.

11.1.4. Clinical Global Impressions

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

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

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

[redacted]

11.1.6. Patient Health Questionnaire

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

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

[redacted]

[redacted]

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

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

12.1.1. Demographic/Medical History

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including: family psychiatric history, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, persistent depressive disorder, postpartum depression, substance use disorder, alcohol use disorder, MDD with seasonal pattern, MDD with psychotic features, premenstrual dysphoric disorder, MDD with atypical features, schizophrenia; or schizoaffective disorder will be documented. The diagnosis of MDD will be determined using the SCID-5-CT. If available, the disease code associated with the diagnosis of MDD based on the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used to determine whether the participant has treatment-resistant depression, defined as persistent depressive symptoms despite treatment during the current major depressive episode with adequate doses of antidepressants from 2 different classes for at least 4 weeks of treatment.

12.1.2. Weight and Height

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

12.1.3. Physical Examination

Physical examinations assessing body systems (eg, head, eyes, ears, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Thereafter, abbreviated physical examinations will include brief assessments of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical examination as needed. Unscheduled, symptom-directed physical examinations may also be conducted at the investigator's discretion. Whenever possible, the same individual is to perform all physical examinations for a given participant. Unscheduled brief, symptom-driven physical examinations may also be conducted per the investigator's discretion.

Any abnormality in physical examinations will be interpreted by the investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.

12.1.4. COVID-19 Questions

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

Questions to be asked are as follows:

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

12.1.5. Vital Signs

Vital signs comprise both supine and standing for systolic and diastolic blood pressure and heart rate measurements. Heart rate and blood pressure are to be collected in supine position after the participant has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Respiratory rate and temperature are collected once, in either position. Vital signs will be documented. When vital signs are scheduled at the same time as blood draws, vital signs will be obtained first.

Any abnormality in vital signs will be interpreted by the investigator as abnormal, NCS or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.

12.1.6. Electrocardiogram (ECG)

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

12.1.7. Laboratory Assessments

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

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

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

All clinical laboratory test results outside the central laboratory's reference range will be interpreted by the investigator as abnormal, NCS; or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs,

assessed according to Section 12.2.1. A clinically significant laboratory abnormality following participant randomization will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

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

Table 3: Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis**	**Coagulation**
Red blood cell count Hemoglobin Hematocrit White blood cell count with differential Platelet count Red Blood Cell Indices (MCV, MCH, MCHC) Reflex to Red blood cell morphology if indices are abnormal	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase Gamma-glutamyl transferase Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphorus Triglycerides Thyroid stimulating hormone (TSH) Reflex to free T3/T4 if TSH is abnormal	pH Specific gravity Protein Glucose Red blood cell Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio
Diagnostic			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C Reflex HCV RNA HIV-1 and -2 Female participants that are not surgically sterile and do not meet the protocol-	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine Female participants that are not surgically sterile and do	Alcohol	

defined criteria for being postmenopausal: serum hCG Female participants, if menopause is suspected and not surgically sterile: FSH	not meet the protocol-defined criteria for being postmenopausal: urine hCG		

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

A serum follicle stimulating hormone test will be conducted at Screening to confirm whether a female participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal (Section 8.1).

12.1.7.1. Drugs of Abuse and Alcohol

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

12.1.7.2. Pregnancy Screen

For female participants that are not surgically sterile, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at all other scheduled time points thereafter, including the ET visit for participants who prematurely discontinue.

[redacted]

12.2. Adverse and Serious Adverse Events

12.2.1. Adverse Event Definition

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

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

[redacted] are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for an SAE should be reported in an expedited manner. [redacted] that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

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

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

12.2.2. Serious Adverse Event Definition

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

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

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

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

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

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

12.2.3. Relationship to Investigational Product

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

Not Related	An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the IP. Factors pointing towards this assessment include but are not limited to: the lack of temporal relationship between administration of the IP and the event, the presence of biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE

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

12.2.4. Recording Adverse Events

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

Intensity will be assessed according to the following scale:

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

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

12.2.5. Reporting Serious Adverse Events

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

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

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

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

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

12.3. Pregnancy

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

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

clinical manifestation(s) of overdose must also be recorded as an AE on the eCRF. In addition, all overdoses must be recorded on an Overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose.

13. STATISTICS

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

13.1. Data Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized participants in the Safety Set who have a valid baseline as well as at least 1 postbaseline HAM-D evaluation.

The Randomized Set is defined as all participants who are randomized.

The Safety Set is defined as all participants who receive at least 1 dose of IP.

[redacted]

13.2. Handling of Missing Data

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

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in a participant data listing, some may be presented with a corresponding table or figure; these will be indicated in relevant sections below. All summaries will be provided by treatment – either by randomized treatment or actual treatment received. Actual treatment is defined as SAGE-217 if the participant received any SAGE-217 (50 mg or 40 mg) at any time; otherwise, it is placebo.

If a participant takes any dose of SAGE-217, the participant's actual treatment is considered as SAGE-217 regardless of the treatment to which the participant has been randomized.

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

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

13.4. Demographics and Baseline Characteristics

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

13.5. Efficacy Analysis

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

The estimand for the primary efficacy analysis is the mean change from baseline in HAM-D total score at Day 15. The estimand for the primary efficacy analysis is defined as follows:

- The target population is adults with a diagnosis of MDD and within a current depressive episode of severity (HAM-D total score ≥24).
- The variable of interest is the change from baseline in HAM-D total score at Day 15.
- The population summary level deals with the difference between the treatments (SAGE-217 + an antidepressant and placebo + an antidepressant) in mean change from baseline in HAM-D total score at Day 15.

The intercurrent events could be:

- The premature discontinuation of treatment for any reason, thus not having a Day 15 HAM-D total score available. This will be dealt with by a sensitivity analysis using multiple imputation techniques as described below.
- Certain medications including, but not limited to new antidepressants (except as described in the protocol) or benzodiazepines are prohibited during the study; however, the treatment policy strategy dictates that if any of these prohibited medications are used, the results will not be manipulated but will rather be used ‘as is’ in analysis. Please note that the protocol does not specify any rescue process, hence there is no rescue medication.

Using the FAS, this will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline time points will be included in the model. The main comparison will be between SAGE-217 + an antidepressant and placebo + an antidepressant at the Day 15 time point. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p values) will be reported where applicable. An unstructured covariance structure will be used to model the within-participant errors. The Toeplitz compound symmetry, Autoregressive (1) [AR(1)] covariance structure will be used in that sequence if there is a convergence issue with the unstructured covariance model. If convergence is still not achieved, no results will be reported.

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

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

A GEE method will also be used for the analysis of CGI-I response, including terms for treatment, baseline CGI-S score, assessment time point, and time point-by-treatment as explanatory variables.

13.5.1. Multiplicity Adjustment for Key Secondary Endpoints

Multiplicity adjustment to statistical testing of hypotheses of the key secondary endpoints will be conducted by using a fixed-sequence strategy. Only if the primary endpoint is statistically significant at 0.05 level, the key secondary endpoints will be tested sequentially, testing each endpoint at 5% level of significance only if the previous endpoint in the sequence has been significant at 5% level. If an endpoint is not significant at 5% level, the next endpoint in the sequence will be interpreted with nominal p value.

The sequence of testing key secondary endpoints is as follows:

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

Any secondary or other endpoint not included above will not be adjusted for multiplicity, and will be interpreted with nominal p-value.

13.6. Safety Analyses

Safety and tolerability of SAGE-217 will be evaluated by TEAEs, changes from baseline in [redacted]. Safety data will be listed by participant and summarized by treatment group. All safety summaries will be presented for the Safety Set using actual treatment received. Where applicable, ranges of potentially clinically significant values will be provided in the SAP.

13.6.1. Adverse Events

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

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

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

[redacted]

13.6.3. Physical Examinations

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

[redacted]

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each of the triplicate ECGs for each participant: heart rate, PR, QRS, QT, and QTcF. The derived mean of each parameter will also be listed. Mean ECG data will be summarized by visit. Potentially clinically significant values of QTcF will be summarized by treatment. Electrocardiogram findings will be listed by participant and visit.

13.6.6. Prior and Concomitant Medications

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

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

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

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

[redacted]

[redacted]

13.6.9. Other Safety Analysis

[redacted]

13.8. Sample Size and Power

Using a 2-sided alpha level of 0.05, a sample size of 382 total evaluable participants would provide 90% power to detect a treatment difference (between SAGE-217 + an antidepressant and placebo + an antidepressant) of approximately 3 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each treatment group, approximately 424 total randomized participants will be required to obtain a total of 382 evaluable participants. Evaluable participants are defined as those randomized participants who receive IP and have valid baseline and at least 1 postbaseline HAM-D assessment.

13.8.1. Interim and Data Monitoring Committee Analyses

No interim analyses or data monitoring committee analyses will be conducted.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage 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 IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or independent ethics committee.

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

14.2. Audits and Inspections

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

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

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

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

16.3. Written Informed Consent

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

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

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

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

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

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

17.2. Retention of Records

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

18. PUBLICATION POLICY

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

19. LIST OF REFERENCES

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STUDY TITLE: A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY COMPARING THE EFFICACY AND SAFETY OF SAGE-217 PLUS SERTRALINE VERSUS PLACEBO PLUS SERTRALINE IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

PROTOCOL NUMBER: 217-MDD-305

Investigational Product	SAGE-217
Clinical Phase	Phase 3
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] [redacted] Tel: [redacted] e-mail: [redacted]
Sponsor Medical Monitor	[redacted], MD, PhD, MSc [redacted] [redacted] e-mail: [redacted]
Date of Original Protocol	13 May 2020

SPONSOR APPROVAL

Protocol Number: 217-MDD-305

Study Title: A Phase 3, Randomized, Double-Blind Study Comparing the Efficacy and Safety of SAGE-217 plus Sertraline Versus Placebo plus Sertraline in Adults with Major Depressive Disorder

Protocol Version and Date: Version 1, 13 May 2020

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[redacted], MBBS (MD) — Date (DD/MMM/YYYY)

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INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-MDD-305 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD/MMM/YYYY)

CONTACT INFORMATION

Table 1: Contact Information

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

2. SYNOPSIS

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

Name of Investigational Product: SAGE-217 Capsules

Name of Active Ingredient: SAGE-217

Title of Study: A Phase 3, Randomized, Double-Blind Study Comparing the Efficacy and Safety of SAGE-217 plus Sertraline Versus Placebo plus Sertraline in Adults with Major Depressive Disorder

Number of Sites and Study Location: This study will take place at approximately 55 sites in United States.

Phase of Development: 3

Planned Duration for each Study Participant: Up to 70 days (up to 28-day Screening Period, 14-day Double-blind Treatment Period, and a 28-day Sertraline Continuation Period)

Objectives:

Primary:

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

Secondary:

- To assess patient-reported outcome (PRO) measures as they relate to depressive symptoms
- To evaluate the safety and tolerability of SAGE-217 plus sertraline

[redacted]

Endpoints:

Primary:

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

Key Secondary:

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

Other Secondary:

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as “much improved” or “very much improved”, at Day 15
- Change from baseline in MADRS total score at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline to Day 15 in depressive symptoms, as assessed by the PHQ-9
- Incidence and severity of treatment-emergent adverse events (TEAEs)

[redacted]

Study Description:

This is a randomized, double-blind, parallel-group, placebo-controlled study in adults with MDD. 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. Participants cannot have been treated with sertraline in the current depressive episode.

The study will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day sertraline Continuation Period. The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit. Preliminary screening procedures to determine eligibility include completion of the MGH-ATRQ and HAM-D.

Participants will be randomized to receive blinded SAGE-217 50 mg or placebo for administration each evening from Days 1 through 14. In addition, all participants will receive open-label sertraline from Day 1 through the end of the study. Sertraline will be administered per labeled prescribing information, starting with 50 mg each evening during Week 1 and 100 mg each evening during Week 2.

After the double-blind Treatment Period, sertraline will be continued each evening for the remainder of the study (sertraline Continuation Period). During this period (Weeks 3 to 6), sertraline dosing may be increased based on individual response, at the discretion of the investigator and per the labeled prescribing information in 50-mg increments (up to 200 mg per day).

Initiation of other antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of assessments at Day 42/end-of-study visit.

Participants will self-administer investigational product (IP) once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. Sertraline and SAGE-217/placebo will be administered at the same time during the Treatment Period. Participants will return to the study center as outlined in the Schedule of Assessments (Table 2).

During the Treatment Period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate SAGE-217/placebo 50 mg will receive 40 mg for the remainder of the Treatment Period. Participants who, in the opinion of the investigator, cannot tolerate the SAGE-217/placebo 40-mg dose may be discontinued from SAGE-217/placebo at the discretion of the investigator. If blinded IP is discontinued, sertraline may be continued at the discretion of the investigator.

Upon completion of the current study, eligible participants will have the opportunity to enter a long-term open-label study of SAGE-217.

Number of Participants (planned): It is estimated that approximately 424 participants will be randomized and treated to obtain 382 evaluable participants at Day 15 (assuming a 10% dropout rate). Additional participants may be randomized if the dropout rate is greater than 10%.

Eligibility Criteria:

Inclusion Criteria

1. Participant has signed an ICF prior to any study-specific procedures being performed.
2. Participant is a male or female between 18 and 64 years of age, inclusive.
3. Participant is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Participant agrees to adhere to the study requirements.
5. Participant 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. Participant has a HAM-D-17 total score of ≥24 at Screening and Day 1 (prior to dosing).
7. Participant is willing to delay start of any antidepressant (except sertraline as per protocol), anxiolytic, anti-insomnia, psychostimulant, prescription opioid regimens, or new psychotherapy (including Cognitive Behavioral Therapy for Insomnia [CBT-I]) until after study completion. Participants receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1 and intend to maintain that schedule for the duration of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence).
9. Female participant who is breastfeeding at Screening or on Day 1 (prior to administration of IP) must be willing to temporarily cease giving breast milk to her child(ren) from just prior to receiving IP on Day 1 until 7 days after the last dose of SAGE-217/placebo.
10. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 5 days after receiving IP, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
11. Male participant is willing to abstain from sperm donation for the treatment period and for 5 days after receiving the last dose of the IP.
12. Participant agrees to refrain from drugs of abuse and alcohol for the duration of the study.

Exclusion Criteria

1. Participant is currently at significant risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of MDD.
2. Participant had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the participant has presented for screening during the 6-month postpartum period.
3. Participant has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eye, ear, nose, and throat disorders, or any other

acute or chronic condition that, in the investigator's opinion, would limit the participant's ability to complete or participate in this clinical study; a BMI ≤18 or ≥45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.

4. Participant 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 2 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. Participant has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Participant is receiving Cognitive Behavioral Therapy for Insomnia (CBT-I) within 28 days prior to Day 1.
7. Participant has a known allergy to SAGE-217, allopregnanolone, sertraline, or related compounds.
8. Participant has been treated with sertraline in the current depressive episode.
9. Participant has taken antidepressants within 30 days prior to Day 1, and/or has taken fluoxetine within 60 days prior to Day 1.
10. Female participant has a positive pregnancy test or confirmed pregnancy.
11. Participant has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
12. Participant has active psychosis per investigator assessment.
13. Participant has a medical history of seizures.
14. Participant has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
15. Participant has a history of mild, moderate, or severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to Screening.
16. Participant has had exposure to another investigational medication or device within 30 days prior to Screening.
17. Participant has previously received brexanolone or participated in a SAGE-217 or SAGE-547 (brexanolone) clinical trial.
18. Participant has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these, within 14 days prior to Day 1.
19. Participant has used any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John’s Wort, within 28 days prior to Day 1.
20. Participant has used any monoamine oxidase inhibitor (MAOI) or pimozide within 14 days prior to Day 1.
21. Participant has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
22. Participant plans to undergo elective surgery before completion of the Day 42 visit.
23. Participant is taking benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Day 1, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Participant is taking any

benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1.

24. Participant is taking non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids), or first or second generation (typical/atypical) antipsychotics within 14 days prior to Day 1. Note that nonsedating antihistamines are permitted.
25. Participant has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
26. Participant has a history of sleep apnea.
27. Participant has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
28. Participant is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as needed, within 28 days prior to Day 1.
29. Participant is a dependent of the sponsor, investigator, investigator's deputy, or study site staff.
30. Participant expects to perform night shift work during the 14-day Treatment Period.

Investigational Product Dosage and Mode of Administration: SAGE-217 will be available as hard gelatin capsules for oral administration; multiple capsules (in 30-mg or 20-mg dose strengths) will be provided to total a 50-mg dose, with option to reduce to 40 mg based on tolerability.

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217, for oral administration.

Sertraline tablets will be administered as per labeled prescribing information, starting with 50 mg each evening during Week 1 and 100 mg each evening during Week 2. During Weeks 3 to 6, sertraline dosing may be increased in 50-mg increments (up to 200 mg per day), as appropriate per the labeled prescribing information and based on individual response.

Duration of Treatment: Blinded SAGE-217 or placebo will be administered once daily for 14 days; open-label sertraline will be administered according to labeled prescribing information for 42 days.

Statistical Methods:

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock and treatment unblinding. Any deviations from or changes to the SAP following database lock will be detailed in the Clinical Study Report.

General Considerations

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

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized participants who receive at least 1 dose of IP and who have a valid baseline as well as at least 1 postbaseline HAM-D evaluation.

The Safety Set is defined as all participants who receive at least 1 dose of IP.

The Randomized Set, defined as all participants who are randomized.

[redacted]

[redacted]

Determination of Sample Size

Using a two-sided alpha level of 0.05, a sample size of 382 total evaluable participants would provide 90% power to detect a treatment difference (between SAGE-217 + sertraline and placebo + sertraline) of approximately 3 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each treatment group, approximately 424 total randomized participants will be required to obtain a total of 382 evaluable participants. Evaluable participants are defined as those randomized participants who receive IP and have valid baseline and at least 1 postbaseline HAM-D assessment.

Analysis of Primary Endpoint

The estimand for the primary analysis is the mean change from baseline in HAM-D total score at Day 15. Using FAS, this will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline time points will be included in the model. The main comparison will be between SAGE-217 + sertraline and placebo + sertraline at the 15-day time point. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p values) will be reported where applicable. An unstructured covariance structure will be used to model the within-participant errors. The Toeplitz compound symmetry, Autoregressive (1) [AR(1)] covariance structure will be used in that sequence if there is a convergence issue with the unstructured covariance model. If convergence is still not achieved, no results will be reported.

Analysis of Secondary Endpoints

Similar to those methods described above for the primary endpoint, an MMRM will be used for the analysis of the change from baseline in other time points in HAM-D total score, MADRS total score, HAM-A total score, CGI-S score, and PHQ-9 total score.

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

A GEE method will also be used for the analysis of CGI-I response including terms for center, treatment, baseline CGI-S score, assessment time point, and time point-by-treatment as explanatory variables.

Safety Analysis

Safety and tolerability of IP will be evaluated by adverse events (AEs)/serious adverse event (SAEs), [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set.

[redacted]

Table 2: Schedule of Assessments

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

Visits	**Screening Period**	**Double-Blind, Placebo-Controlled Treatment Period**					**Sertraline Continuation Period**				
Visit Days	**D-28 to D-1**	**D1**	**D3 (±1d)**	**D8 (+1d)**	**D12 (±1d)**	**D15 (+1d) and/or EOT [a]**	**D18 (±1d)**	**D21 (±1d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d) /ET**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Study Procedure											
Pregnancy Test [h]	X	X				X			X		X
Hepatitis & HIV Screen	X										
[redacted]											
Vital Signs [k]	X	X	X	X	X	X	X		X		X
12-Lead ECG [l]	X	X				X					X
[redacted]											
HAM-D [n, o]	X	X	X	X	X	X		X	X	X	X
MADRS		X		X		X			X		X
HAM-A [o]		X		X		X			X		X
CGI-S	X	X	X	X	X	X		X	X	X	X
CGI-I			X	X	X	X		X	X	X	X
[redacted]											
PHQ-9		X	X	X		X			X		X
[redacted]											
SAGE-217/Placebo Dispensation		X		X							

Visits	Screening Period	Double-Blind, Placebo-Controlled Treatment Period					Sertraline Continuation Period				
Visit Days	**D-28 to D-1**	**D1**	**D3 (±1d)**	**D8 (+1d)**	**D12 (±1d)**	**D15 (+1d) and/or EOT [a]**	**D18 (±1d)**	**D21 (±1d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d) /ET**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Study Procedure											
SAGE-217/Placebo Administration		X (once daily in the evening through Day 14 - inclusive)									
IP Adherence [r]		X									
Sertraline Administration [s]		X									
IP Accountability/Return			X	X		X		X	X	X	X [q]
AEs/SAEs [t]	X										
Prior/Concomitant Medications/Procedures [u]	X										

Abbreviations: AE = adverse event; CGI-I = Clinical Global Impression – Improvement; CGI-S – Clinical Global Impression – Severity; [redacted] D = day; EOT = end of treatment; ET = early termination; ECG = electrocardiogram; FSH = follicle stimulating hormone; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; IP = investigational product; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; PHQ-9 = 9-item Patient Health Questionnaire; [redacted] O = Optional; [redacted] SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Clinical Trials Version; [redacted] V = visit.

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

[b] Participants will be asked to authorize that their unique participant identifiers be entered into a registry (www.subjectregistry.com) with the intent of identifying participants who may meet exclusion criteria for participation in another clinical study.

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

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

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

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

[g] Urine toxicology for selected drugs of abuse (Table 3) and breath test for alcohol.

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

[redacted]

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

[l] Triplicate ECGs will be collected. [redacted]

[redacted]

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

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

[redacted]

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

[r] IP administration will be monitored via a medication adherence monitoring platform used on smartphones to visually confirm IP ingestion.

[s] Sertraline 50 mg each evening during Week 1, and 100 mg each evening during Week 2. May be increased in 50 mg increments up to 200 mg total daily dose, from Weeks 3 to 6, per investigator judgement

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

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

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

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulation
CRO	contract research organization
CSR	clinical study report
IEC	independent ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
IP	investigational product
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PI	principal investigator; the investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
PK	pharmacokinetic
PV	pharmacovigilance
QA	quality assurance
QC	quality control
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SOP	Standard Operating Procedure

Abbreviation	Definition
TEAE	treatment-emergent adverse event
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Major Depressive Disorder and Unmet Medical Need

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

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

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, American Psychiatric Association 2013) provides diagnostic criteria for major depressive disorder (MDD). These include at least 5 of 9 depressive symptoms (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 (SNRI), serotonin norepinephrine reuptake inhibitors (SSRI), tricyclic antidepressants, monoamine oxidase inhibitors (MAOI), 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). Furthermore, these agents can take 4 to 8 weeks to demonstrate full clinical efficacy (Rush 2006; Trivedi 2006), and in the case of the most commonly prescribed classes—SSRIs and SNRIs—common side effects including weight gain, GI symptoms, and sexual dysfunction can prevent titration into an adequate therapeutic range (Sadock and Sadock 2007).

In the largest study to assess the effectiveness of depression treatments in patients with MDD, time to patient remission after treatment was 5.4 to 7.4 weeks; approximately one-half of the patients who ultimately remitted did so after 6 weeks, and 40% of those who achieved remission required 8 or more weeks to do so (Rush 2006; Trivedi 2006). Even following remission, many patients report the presence of residual symptoms, often related to decreased positive affect, such as loss of interest in activities once considered enjoyable, fatigue, loss of energy, as well as sleep and appetite/weight disturbances (Nierenberg 2009; Nierenberg 2015). Thus, patients may remain symptomatic for up to 2 months while waiting for current standard-of-care pharmacotherapy to take full effect. They may also have to contend with undesirable side effects and residual symptoms. These aspects underscore the need for newer, rapid-acting therapies.

SAGE-217 is a synthetic positive allosteric modulator of $GABA_A$ receptors, the major class of inhibitory neurotransmitter receptors in the brain. In pharmacokinetic (PK) studies in mice and

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

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) associated with SAGE-217 (overall) were sedation, somnolence, and dizziness; most adverse events (AEs) were reported as mild or moderate in intensity. Refer to the SAGE-217 Investigator's Brochure for a detailed description of the chemistry, pharmacology, efficacy, and safety of SAGE-217.

This study was designed to target the unmet need of symptom improvement during the latency to SSRI efficacy in the acute phase of a major depressive episode. This study will assess the safety and efficacy of SAGE-217 50 mg plus sertraline, examining if SAGE-217 plus sertraline produces more rapid or more profound reduction in depressive symptoms than sertraline alone.

5.2. Potential Risks and Benefits

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

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

Based on nonclinical findings, embryo-fetal toxicity and withdrawal effects are considered important potential risk for SAGE-217. Risk mitigation measures in this study include monitoring for adverse effects, monitoring for potential withdrawal effects, requiring highly effective contraceptive measures for study participants, and inclusion of dose adjustment criteria and guidance for blinded IP discontinuation (Section 8.4). Finally, due to the sedation/somnolence observed, SAGE-217 is administered in the evening in this study.

Given the outcome of the completed studies of SAGE-217 in participants with MDD and PDD, the current significant unmet need for well-tolerated and rapid-acting depression treatments, and a favorable benefit-risk profile, further investigation of SAGE-217 as a novel rapid response treatment in adults with MDD is justified.

5.3. Dose Justification

Results from a large, multicenter study of SAGE-217 20 and 30 mg in MDD (217-MDD-301) support the need for higher steady-state concentrations of SAGE-217 to allow participants to experience maximum antidepressant and anti-anxiety benefits. SAGE-217 will be administered as a 14-day regimen of an evening dose of 50 mg with reduction to 40 mg as needed based on tolerability. The 50-mg dose of SAGE-217 is expected to exhibit a favorable benefit-risk profile in the context of results from previous SAGE-217 studies utilizing a 30-mg dose, now identified as a minimally effective dose. SAGE-217 is expected to maintain an acceptable tolerability

profile, based on a current safety database of over 2000 participants exposed across different doses/concentrations.

Sertraline is a commercially available SSRI indicated for the treatment of MDD and other psychiatric disorders. Dosage and administration of sertraline as described in the approved US Prescribing Information (PI) recommends a starting dose of 50 mg per day in patients with MDD, with an incremental weekly increase in dose of 25-50 mg per day, if there is an inadequate response to the starting dose, to a maximum dose of 200 mg per day. The dose of sertraline used in this study aligns with the recommended dosing as defined in the PI.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

To evaluate the efficacy of SAGE-217 plus sertraline in the treatment of MDD compared to placebo plus sertraline

6.1.2. Secondary Objectives

- To assess patient-reported outcome (PRO) measures as they relate to depressive symptoms
- To evaluate the safety and tolerability of SAGE-217 plus sertraline

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoint

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

6.2.2. Secondary Endpoints

6.2.2.1. Key Secondary Endpoints

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

6.2.2.2. Other Secondary Endpoints

- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- CGI-I response, defined as “much improved” or “very much improved”, at Day 15
- Change from baseline in MADRS total score at Day 15
- Change from baseline in HAM-A total score at Day 15
- Time to first HAM-D response
- Change from baseline to Day 15 in depressive symptoms, as assessed by the PHQ-9
- Incidence and severity of treatment-emergent AEs

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

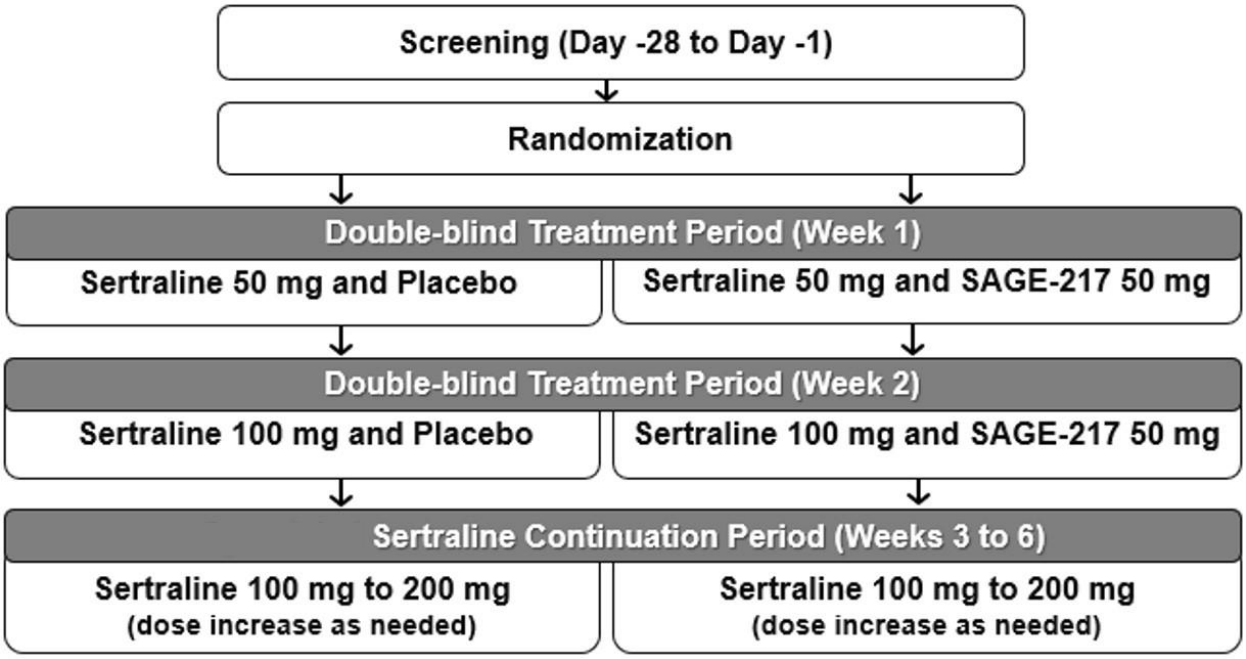
This is a randomized, double-blind, parallel-group, placebo-controlled study in adults with MDD. The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Clinical Trial Version (SCID 5-CT) performed by a qualified healthcare professional. Participants cannot have been treated with sertraline in the current depressive episode.

The study will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day sertraline Continuation Period. The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit. Preliminary screening procedures to determine eligibility include completion of the MGH-ATRQ and HAM-D.

Participants will be randomized to receive blinded SAGE-217 or placebo for administration each evening from Day 1 through 14. In addition, all participants will receive open-label sertraline from Day 1 through the end of the study.

The study design is diagrammed in Figure 1.

Figure 1: Study Schematic



Doses are presented as daily doses. All participants will receive open-label sertraline in addition to blinded IP (SAGE-217/placebo) from Week 1 to Week 2 then continue to receive sertraline alone from Weeks 3 to 6. During Weeks 1 and 2, the blinded IP dose may be reduced to 40 mg, as needed. During Weeks 3 to 6, the sertraline dose may be increased in 50-mg increments each week, as needed, up to a total daily dose of sertraline 200 mg.

Open-label sertraline will be administered as per labeled prescribing information, starting with 50 mg each evening during Week 1 and 100 mg each evening during Week 2.

After the Double-blind Treatment Period, sertraline will be continued each evening for the remainder of the study (sertraline Continuation Period). During this period (Week 3 to 6),

sertraline dosing may be increased in 50-mg increments (up to 200 mg)as appropriate per the labeled prescribing information and based on individual response,.

Initiation of other antidepressants or any other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of assessments at Day 42/end-of-study visit.

Participants will self-administer investigational product (IP) once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. Sertraline and SAGE-217 or placebo will be administered at the same time during the Treatment Period. Participants will return to the study center as outlined in the Schedule of Assessments.

During the Treatment Period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate SAGE-217 or placebo 50 mg will receive 40 mg for the remainder of the Treatment Period. Participants who cannot tolerate the SAGE-217/placebo 40-mg dose may be discontinued from SAGE-217 or placebo at the discretion of the investigator. If blinded IP is discontinued, sertraline may be continued at the discretion of the investigator.

Upon completion of the current study, eligible participants will have the opportunity to enter a long-term open-label study of SAGE-217. Participants that do not enter the open-label study or that terminate the current study early may, per the investigator, receive a supply of sertraline with instructions on how to taper the drug or, if they wish to continue sertraline, a bridge supply to permit them to obtain a prescription from another provider.

7.2. Number of Participants

It is estimated that approximately 424 participants will be randomized and treated to obtain 382 evaluable participants at Day 15 (assuming 10% dropout rate). Additional participants may be randomized if the dropout rate is greater than 10%.

7.3. Treatment Assignment

Participants will be assigned to blinded IP (SAGE-217 or placebo) in accordance with the randomization schedule on Day 1. All participants will also receive open-label sertraline for the study duration; as detailed in Section 9.1 and as per the Schedule of Assessments (Table 2).

Additional details on randomization and blinding are provided in Section 9.5.

7.4. Dose Adjustment Criteria

During the treatment period, participants will be able to receive SAGE-217/placebo as long as there are no dose-limiting safety/tolerability concerns. Participants who cannot tolerate 50 mg (as determined by the investigator) will receive 40 mg for the remainder of the treatment period.

At the discretion of the investigator, participants who cannot tolerate the 40-mg dose at any time may be discontinued from dosing upon completion of an end of treatment (EOT) visit as soon as possible. These participants should be followed and complete assessments as per the Schedule of Assessments (Table 2).

During Weeks 3 to 6, sertraline dosing may be increased, based on individual response, per investigator discretion and per the labeled prescribing information, in 50-mg increments (up to 200 mg).

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 participants, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the investigator. Investigational sites must promptly notify their IRB, where required, and initiate withdrawal procedures for participating participants.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

1. Participant has signed an ICF prior to any study-specific procedures being performed.
2. Participant is a male or female between 18 and 64 years of age, inclusive.
3. Participant is in good physical health and has no clinically significant findings, as determined by the investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Participant agrees to adhere to the study requirements.
5. Participant 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. Participant has a HAM-D-17 total score of ≥24 at Screening and Day 1 (prior to dosing).
7. Participant is willing to delay start of any antidepressant (except sertraline as per protocol), anxiolytic, anti-insomnia, psychostimulant, prescription opioid regimens, or new psychotherapy (including Cognitive Behavioral Therapy for Insomnia [CBT-I]) until after study completion. Participants receiving psychotherapy must have been receiving therapy on a regular schedule for at least 60 days prior to Day 1 and intend to maintain that schedule for the duration of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence).
9. Female participant who is breastfeeding at Screening or on Day 1 (prior to administration of IP) must be willing to temporarily cease giving breast milk to her child(ren) from just prior to receiving IP on Day 1 until 7 days after the last dose of SAGE-217/placebo.
10. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 5 days after receiving IP, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
11. Male participant is willing to abstain from sperm donation for the treatment period and for 5 days after receiving the last dose of the IP.
12. Participant agrees to refrain from drugs of abuse and alcohol for the duration of the study.

8.2. Participant Exclusion Criteria

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

1. Participant is currently at significant risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of MDD.
2. Participant had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the participant has presented for screening during the 6-month postpartum period.
3. Participant 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 participant's ability to complete or participate in this clinical study; a BMI $\leq$18 or $\geq$45 kg/m^2 is exclusionary; a BMI of 40 to 44.9 kg/m^2, inclusive, at Screening is subject to a broader evaluation of medical comorbidities as described above.
4. Participant 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 2 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. Participant has had vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine within the current major depressive episode.
6. Participant is receiving Cognitive Behavioral Therapy for Insomnia (CBT-I) within 28 days prior to Day 1.
7. Participant has a known allergy to SAGE-217, allopregnanolone, sertraline, or related compounds.
8. Participant has been treated with sertraline in the current depressive episode.
9. Participant has taken antidepressants within 30 days prior to Day 1, and/or has taken fluoxetine within 60 days prior to Day 1.
10. Female participant has a positive pregnancy test or confirmed pregnancy.
11. Participant has a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
12. Participant has active psychosis per investigator assessment.
13. Participant has a medical history of seizures.
14. Participant has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.

15. Participant has a history of mild, moderate, or severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to Screening.
16. Participant has had exposure to another investigational medication or device within 30 days prior to Screening.
17. Participant has previously received brexanolone or participated in a SAGE-217 or SAGE-547 (brexanolone) clinical trial.
18. Participant has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to Day 1.
19. Participant has used any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort, within 28 days prior to Day 1.
20. Participant has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
21. Participant has used any monoamine oxidase inhibitor (MAOI) or pimozide within 14 days prior to Day 1.
22. Participant plans to undergo elective surgery before completion of the Day 42 visit.
23. Participant is taking benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) within 28 days prior to Day 1, or has been using these agents daily or near-daily (≥4 times per week) for more than 1 year. Participant is taking any benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1.
24. Participant 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 within 14 days prior to Day 1. Note that nonsedating antihistamines are permitted.
25. Participant has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
26. Participant has a history of sleep apnea.
27. Participant has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
28. Participant is taking psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as needed, within 28 days prior to Day 1.
29. Participant is a dependent of the sponsor, investigator, investigator's deputy, or study site staff.
30. Participant expects to perform night shift work during the 14-day treatment period.

8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study intervention. A minimal set of screen failure information

will be collected, including demography, screen failure details, eligibility criteria, and any AE/serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

8.4. Investigational Product Discontinuation and Early Termination from the Study

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

Based on known withdrawal symptoms with other GABAergic drugs and nonclinical 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 blinded IP discontinuation or dose reduction are presented to support participant safety:

1. Any participant reporting a confirmed or suspected seizure at any time will be discontinued from blinded IP but will continue to be followed in the study.
2. The investigator should monitor the course of CNS-based signs and symptoms suggestive of a seizure which are not accounted for by comorbid psychiatric or medical conditions. Examples of reported serious or severe events which may reflect an oncoming and/or increased risk for seizure may include temporary confusion, tremors, involuntary muscle fasciculations or jerking movements of arms or legs, or paresthesia. Should such symptoms occur, the investigator should consider decreasing the dose of SAGE-217 or placebo to 40 mg, stopping treatment to assess the effect on the symptom(s) (eg, resolution, improvement), or discontinuing the participant from treatment. A participant who discontinues treatment should remain in the study and continue protocol-required assessments until the end of the study.

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

8.4.1. Investigational Product Discontinuation

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

Participants who discontinue treatment early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place as scheduled relative to the last dose of treatment (eg, if a participant's last dose is on Day 13, their first follow-up visit, Visit 7, should occur 4 days later), and will continue safety and efficacy assessments as scheduled for 6 weeks following the final dose.

Participants that discontinue blinded IP early may, per the investigator, receive a supply of sertraline with instructions on how to taper the drug or, if they wish to continue sertraline, a bridge supply to permit them to obtain a prescription from another provider.

8.4.2. Early Termination from the Study

If a participant decides to terminate the study, the participant should return for an early termination (ET) visit, if possible. The primary reason for early termination from the study must be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF). If a participant discontinues IP and terminates the study on the same day during a clinic visit, the EOT and ET visits can be on the same day; in this case, all EOT visit assessments should be conducted in addition to an abbreviated physical examination

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

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

Participants who terminate from the study early may, per the investigator, receive a supply of sertraline with instructions on how to taper the drug or, if they wish to continue sertraline, a bridge supply to permit them to obtain a prescription from another provider.

8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after 3 attempts at contacting the participant have been unsuccessful.

8.4.4. Replacement of Participants

Participants will not be replaced.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Products

SAGE-217 will be available as hard gelatin capsules for oral administration; 2 capsules (one 30 mg and one 20 mg) will be provided to total a 50-mg dose, with option to reduce to 40 mg based on tolerability, as per criteria described in Section 7.4. If the dose is reduced to 40 mg, it will be administered as 2 20-mg capsules.

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217, for oral administration.

All participants will self-administer blinded and open-label IP orally once daily at approximately 8 PM with fat-containing food for 14 days.

Sertraline tablets will be administered as per labeled prescribing information, starting with 50 mg each evening during Week 1 and 100 mg each evening during Week 2. During Weeks 3 to 6, sertraline dosing may be increased in 50-mg increments (up to 200 mg per day), based on individual response per Investigator discretion and the labeled prescribing information.

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

9.2.1. Prior and Concomitant Medications and/or Supplements

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

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

9.2.2. Prohibited Medications

The following specific classes of medications are prohibited:

- Initiation of new psychotropic medications through the Day 42 visit
- Initiation of new antidepressant therapy from 30 days (60 days for fluoxetine) prior to Day 1 through the Day 42 visit
- Use of any benzodiazepines, barbiturates, $GABA_A$ modulators, GABA-containing agents from Day -28 through the Day 42 visit (from Day -60 for benzodiazepines or GABA modulators with a half-life ≥48 hours)
- Chronic or as-needed psychostimulants (eg, methylphenidate, amphetamine) or opioids from Day -28 through the Day 42 visit
- First generation (typical) antipsychotics (eg, haloperidol, perphenazine) and second generation (atypical) antipsychotics (eg, aripiprazole, quetiapine) from Day -14 through the Day 42 visit

- Use of any non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids) from Day -14 to Day 1. Note that nonsedating antihistamines are permitted.
- Exposure to another investigational medication or device from 30 days prior to Screening through the Day 42 visit
- Any known strong inhibitors of CYP3A4 from Day -28 or 5 half-lives prior to Day 1 (whichever is longer) through the Treatment Period
- Use of any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort from Day -28 through the Treatment Period
- Use of any monoamine oxidase inhibitor from Day -14 to Day 1
- Use of pimozide from Day -14 through the Day 42 visit

9.2.3. Other Restrictions

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

The concomitant use of sertraline with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate; therefore, decrease the dosage of a CYP2D6 substrate if needed.

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

Female participants who are lactating or actively breastfeeding must stop giving breast milk to the baby(ies) starting on Day 1 until 7 days after the last dose of SAGE-217/placebo.

Elective surgeries or procedures are prohibited through the Day 42 visit.

Participants must not participate in night shift work during the Treatment Period.

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

Participants receiving psychotherapy on a regular schedule for at least 60 days prior to Day 1 are permitted if the participant intends to continue that schedule through the Follow-up Period (Day 42). Initiation of new psychotherapy is prohibited until after study completion.

9.2.4. Acceptable Forms of Contraception

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

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

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

Acceptable forms of contraception for male participants include:

- History of vasectomy (performed at least 3 months prior to screening)
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

9.3. Intervention after the End of the Study

Upon completion of the current study, eligible participants will have the opportunity to enter an open-label, long-term study of SAGE-217 in which additional treatment with SAGE-217 will be offered. Participants that do not enter the open-label study or that terminate the current study early may continue to receive sertraline as prescribed by the investigator either to taper the drug appropriately or—if the participant wishes to continue sertraline—to bridge the participant until he or she receives a new prescription.

9.4. Treatment Adherence

Investigational products will be self-administered by participants (see Section 10.5).

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

In addition, participants will be instructed to bring their SAGE-217 or placebo dosing kit and sertraline to the site as outlined in Table 2, at which time the investigator or designee will be responsible for ensuring the kit contains sufficient doses for the duration of the treatment period.

All participants should be reinstructed about the dosing requirements during study contacts. The authorized study personnel conducting the reeducation must document the process in the participant source records.

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

9.5. Randomization and Blinding

Participants will be randomized in a 1:1 ratio to receive SAGE-217 or matched placebo. Participants, site staff, and the sponsor will be blinded to treatment allocation. All participants will also receive open-label sertraline. Randomization will be performed centrally via an interactive response technology (IRT) system. Randomization schedules will be generated by an independent statistician. The allocation to blinded treatment (SAGE-217or placebo) will be based on the randomization schedule. The randomization schedules will be kept strictly

confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

9.5.1. Emergency Unblinding

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

In all cases where the IP allocation for a participant is unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's records and on the eCRF.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Products

10.1.1. Blinded Investigational Products

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

Blinded placebo will be provided as hard gelatin capsules matched in appearance to SAGE-217.

10.1.2. Open-label Investigational Product

Sertraline tablets, packaged and labeled by the commercial manufacturer, will be supplied by a third-party vendor. Sertraline is to be stored and administered according to the package insert. Sertraline during this study is for use only as directed in this protocol.

10.2. Blinded Investigational Product Packaging and Labeling

SAGE-217 and placebo will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the blinded IP in appropriately labeled, participant-specific kits containing sealed unit doses. Each unit dose for 40-mg and 50-mg dose levels consists of 2 capsules. Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Labels with all required information and conforming to all applicable FDA Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices guidelines will be prepared by the sponsor for SAGE-217 and placebo.

10.3. Blinded Investigational Product Storage

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

10.4. Blinded Investigational Product Preparation

Not applicable.

10.5. Blinded and Open-label Investigational Product Administration

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

If a participant misses a dose of blinded IP or open-label sertraline, the participant should skip that dose (ie, they should not take the dose in the morning) and take the next scheduled dose the next evening.

10.6. Blinded Investigational Product Accountability, Handling, and Disposal

Upon receipt of blinded IP dosing kits, the investigator(s), or the responsible pharmacist or designee, will inspect the kits and complete and follow the instructions regarding receipt and storage in the SAGE-217 Investigator's Brochure and (where applicable) in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the participant-specific kits to participants at the planned dispensation visit intervals outlined in Table 2. Site staff will access the IRT at the Screening Visit to obtain a participant identification (ID) number for each participant that has signed an informed consent form. On Day 1, site staff will access the IRT and provide the necessary participant-identifying information, including the participant ID number assigned at Screening, to randomize the eligible participant into the study and obtain the medication ID number for the blinded IP to be dispensed to that participant. The medication ID number and the number of blinded capsules dispensed must be recorded.

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

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

The blinded IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all blinded IP received, used and returned/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.

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

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

10.7. Blinded Investigational 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 provided in Table 1. Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

11. EFFICACY AND CLINICAL PHARMACOLOGY ASSESSMENTS

11.1. Efficacy Assessments

11.1.1. Hamilton Rating Scale for Depression

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

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

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

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

11.1.2. Montgomery-Åsberg Depression Rating Scale

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

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

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

11.1.3. Hamilton Anxiety Rating Scale

The 14-item HAM-A will be used to rate the severity of symptoms of anxiety (Williams 2013c; Williams 2013d). Each of the 14 items is defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Scoring for HAM-A is calculated by assigning scores of 0 (not present) to 4 (very severe), with a total score range of 0 to 56, where <17 indicates mild severity, 18 to 24, mild to moderate severity, and 25 to 30, moderate to severe severity. The HAM-A total score will be calculated as the sum of the 14 individual item scores.

11.1.4. Clinical Global Impressions

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

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

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

[redacted]

11.1.6. Patient Health Questionnaire

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

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

[redacted]

[redacted]

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

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

12.1.1. Demographic/Medical History

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including: family psychiatric history, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, persistent depressive disorder, postpartum depression, substance use disorder, alcohol use disorder, MDD with seasonal pattern, MDD with psychotic features, premenstrual dysphoric disorder, MDD with atypical features, schizophrenia; or schizoaffective disorder will be documented. The diagnosis of MDD will be determined using the SCID-5-CT. If available, the disease code associated with the diagnosis of MDD based on the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) will be used to determine whether the participant has treatment-resistant depression, defined as persistent depressive symptoms despite treatment during the current major depressive episode with adequate doses of antidepressants from 2 different classes for at least 4 weeks of treatment.

12.1.2. Weight and Height

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

12.1.3. Physical Examination

Physical examinations assessing body systems (eg, head, eyes, ears, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Thereafter, abbreviated physical examinations will include brief assessments of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical examination as needed. Unscheduled, symptom-directed physical examinations may also be conducted at the investigator's discretion. Whenever possible, the same individual is to perform all physical examinations for a given participant. Unscheduled brief, symptom-driven physical examinations may also be conducted per the investigator's discretion.

Any abnormality in physical examinations will be interpreted by the investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.

12.1.4. Vital Signs

Vital signs comprise both supine and standing for systolic and diastolic blood pressure and heart rate measurements. Heart rate and blood pressure are to be collected in supine position after the participant has been resting for 5 minutes and then after approximately 3 minutes in the standing

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

Any abnormality in vital signs will be interpreted by the investigator as abnormal, NCS or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1.

12.1.5. Electrocardiogram (ECG)

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

12.1.6. Laboratory Assessments

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

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

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

All clinical laboratory test results outside the central laboratory's reference range will be interpreted by the investigator as abnormal, NCS; or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.1. A clinically significant laboratory abnormality following participant randomization will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

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

Table 3: Clinical Laboratory Tests

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

Red Blood Cell Indices (MCV, MCH, MCHC) Reflex to Red blood cell morphology if indices are abnormal	Total protein Creatinine Blood urea nitrogen Creatine kinase Gamma-glutamyl transferase Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphorus Triglycerides Thyroid stimulating hormone (TSH) Reflex to free T3/T4 if TSH is abnormal	Leukocyte esterase Ketones Bilirubin Urobilinogen	
Diagnostic			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C Reflex HCV RNA HIV-1 and -2 Female participants that are not surgically sterile and do not meet the protocol-defined criteria for being postmenopausal: serum hCG Female participants, if menopause is suspected and not surgically sterile: FSH	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine Female participants that are not surgically sterile and do not meet the protocol-defined criteria for being postmenopausal: urine hCG	Alcohol	

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

A serum follicle stimulating hormone test will be conducted at Screening to confirm whether a female participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal (Section 8.1).

12.1.6.1. Drugs of Abuse and Alcohol

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

12.1.6.2. Pregnancy Screen

For female participants that are not surgically sterile, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at all other scheduled time points thereafter, including the ET visit for participants who prematurely discontinue.

[redacted]

12.2. Adverse and Serious Adverse Events

12.2.1. Adverse Event Definition

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

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

[redacted] are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for an SAE should be reported in an expedited manner. [redacted] that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

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

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

12.2.2. Serious Adverse Event Definition

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

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

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

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

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

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

12.2.3. Relationship to Investigational Product

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

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

12.2.4. Recording Adverse Events

Adverse events spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the

investigational site. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, outcome and seriousness (if applicable), and whether or not it caused the participant to discontinue the IP or withdraw early from the study.

Intensity will be assessed according to the following scale:

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

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

12.2.5. Reporting Serious Adverse Events

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

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

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

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

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

12.3. Pregnancy

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

Overdoses, regardless of presence of associated clinical manifestation(s) (eg, headache, abnormal laboratory value) will be considered an AE and recorded as such on the eCRF. Any clinical manifestation(s) of overdose must also be recorded as an AE on the eCRF. In addition, all overdoses must be recorded on an Overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose.

13. STATISTICS

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

13.1. Data Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized participants in the Safety Set who have a valid baseline as well as at least 1 postbaseline HAM-D evaluation.

The Randomized Set is defined as all participants who are randomized.

The Safety Set is defined as all participants who receive at least 1 dose of IP.

[redacted]

13.2. Handling of Missing Data

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

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in a participant data listing, some may be presented with a corresponding table or figure; these will be indicated in relevant sections below. All summaries will be provided by treatment – either by randomized treatment or actual treatment received. Actual treatment is defined as SAGE-217 if the participant received any SAGE-217 (50 mg or 40 mg) at any time; otherwise, it is placebo.

If a participant takes any dose of SAGE-217, the participant's actual treatment is considered as SAGE-217 regardless of the treatment to which the participant has been randomized.

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

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

13.4. Demographics and Baseline Characteristics

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

13.5. Efficacy Analysis

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

The estimand for the primary efficacy analysis is the mean change from baseline in HAM-D total score at Day 15. Using the FAS, this will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline time points will be included in the model. The main comparison will be between SAGE-217 + sertraline and placebo + sertraline at the Day 15 time point. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p values) will be reported where applicable. An unstructured covariance structure will be used to model the within-participant errors. The Toeplitz compound symmetry, Autoregressive (1) [AR(1)] covariance structure will be used in that sequence if there is a convergence issue with the unstructured covariance model. If convergence is still not achieved, no results will be reported.

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

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

A GEE method will also be used for the analysis of CGI-I response, including terms for treatment, baseline CGI-S score, assessment time point, and time point-by-treatment as explanatory variables.

13.6. Safety Analyses

Safety and tolerability of SAGE-217 will be evaluated by TEAEs, changes from baseline in [redacted]. [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be presented for the Safety Set using actual treatment received. Where applicable, ranges of potentially clinically significant values will be provided in the SAP.

13.6.1. Adverse Events

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

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

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

[redacted]

13.6.3. Physical Examinations

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

[redacted]

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each of the triplicate ECGs for each participant: heart rate, PR, QRS, QT, and QTcF. The derived mean of each parameter will also be listed. Mean ECG data will be summarized by visit. Potentially clinically significant values of QTcF will be summarized by treatment. Electrocardiogram findings will be listed by participant and visit.

13.6.6. Prior and Concomitant Medications

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

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

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

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

[redacted]

[redacted]

13.6.9. Other Safety Analysis

[redacted]

13.8. Sample Size and Power

Using a 2-sided alpha level of 0.05, a sample size of 382 total evaluable participants would provide 90% power to detect a treatment difference (between SAGE-217 + sertraline and placebo + sertraline) of approximately 3 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation of 9 points. Assuming a 10% dropout rate and a 1:1 randomization ratio within each treatment group, approximately 424 total randomized participants will be required to obtain a total of 382 evaluable participants. Evaluable participants are defined as those randomized participants who receive IP and have valid baseline and at least 1 postbaseline HAM-D assessment.

13.8.1. Interim and Data Monitoring Committee Analyses

No interim analyses or data monitoring committee analyses will be conducted.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage 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 IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or independent ethics committee.

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

14.2. Audits and Inspections

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

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

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

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

16.3. Written Informed Consent

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

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

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

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

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

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

17.2. Retention of Records

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

18. PUBLICATION POLICY

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

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Protocol 217-MDD-305, Amendment 3

Date of Draft Amendment: 10 January 2022

A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY COMPARING THE EFFICACY AND SAFETY OF SAGE-217 PLUS AN ANTIDEPRESSANT VERSUS PLACEBO PLUS AN ANTIDEPRESSANT IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to revise the primary endpoint to change from baseline in HAM-D total score at Day 3 (instead of Day 15). In line with the objectives of this study as a rapid response therapy in the treatment paradigm of co-initiation, an earlier time point in the treatment period will characterize the rapid onset of effect while awaiting the efficacy of a standard antidepressant. Additional changes are outlined below:

Study Endpoints

- The change from baseline in HAM-D total score over the blinded treatment period (using equal weights for the scheduled visits – Day 3, Day 8, Day 12, Day 15) has been added as the key secondary endpoint
- The change from baseline in CGI-S at Day 15 has been designated as an 'other secondary' endpoint (previously key secondary endpoint)
- The change from baseline in HAM-D total score at Day 3, Day 8, and Day 42 (previously key secondary endpoint) has been removed
- The change from baseline in HAM-D total score at Day 15 and Day 42 has been designated as an 'other secondary' endpoint
- Added the following as new 'other secondary' endpoints:
    - CGI-I response at Day 3
    - The change from baseline in the HAM-D total score around end of blinded treatment (using equal weights for the scheduled visits – Day 12, Day 15, Day 18)
    - MADRS response at Day 15
    - MADRS remission at Day 15

Statistics

- Expanded the Full Analysis Set definition to include participants who have data from other efficacy endpoints in addition to HAM-D total score
- Modified the condition of the sensitivity analyses to assess the impact of missing data to be performed regardless of missing data rate
- Clarified the estimand for the primary and key secondary endpoints

- Updated methods of the covariance structure for the MMRM model for the primary and key secondary endpoints to be consistent with recent FDA feedback for a Phase 1 SAGE-217 study
- Updated the method of the multiplicity adjustment to align with the change in key secondary endpoint

Other

- Removed score of '0 (not assessed)' as a choice for the Clinical Global Impression Scale
- Corrected the PHQ-9 category of "minimal depression" to start at '0' instead of '1'

Protocol 217-MDD-305, Amendment 2

Date of Amendment: 22 January 2021

A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY COMPARING THE EFFICACY AND SAFETY OF SAGE-217 PLUS AN ANTIDEPRESSANT VERSUS PLACEBO PLUS AN ANTIDEPRESSANT IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

Rationale for Protocol Amendment

The primary purpose for this protocol amendment in response to FDA feedback is to update the visit schedule for participants that discontinue any treatment early: these participants will now complete remaining study visits as scheduled through Day 42 (ie, relative to Day 1), unless the participant withdraws consent. Additional changes to incorporate FDA feedback or clarify the study design are outlined below:

Schedule of Assessments

- Subsequent to the primary purpose for this amendment, the End of Treatment (EOT) visit is no longer needed and has been removed

Investigational Products

- Updated the recommended starting dose options for duloxetine to better align with its labeled prescribing information

Inclusion/Exclusion Criteria

- Corrected Exclusion Criterion #7, which incorrectly specified sertraline
- Specified the types of bilateral tubal occlusion procedures that are considered to be acceptable forms of contraception, including a minimum time for which hysteroscopic bilateral tubal occlusion procedures may have been performed prior to Screening

Statistical Analysis:

- Specified separate Safety Sets for those participants that administered blinded IP and those that administered open-label antidepressant therapy only; subsequently updated the Full Analysis Set definition to specify this set includes participants who administered blinded IP
- Removed the statement that no imputation process will be used to estimate missing data and replaced with a statement that missing data for particular visits may be imputed using the visit window and available data, as described in the statistical analysis plan (SAP)
- Specified the 2 treatment regimens as part of the estimand definition and re-formatted the estimand definition
- Added a reference to the SAP for the definition and details of the Per Protocol Set

Other

- Updated the study medical monitors

- Specified that any restriction(s) for the assigned SSRI/SNRI with concomitant medications per the labeled prescribing information should be considered; subsequently removed a restriction specific only to sertraline
- Specified that the treatment adherence monitoring application will only record details of IP ingestion that has been visually confirmed
- Updated the emergency unblinding procedure to specify that if the blind is to be broken, it should be done by the investigator via the IRT system, removed the statement that the investigator should discuss requests about treatment with the Sage medical monitor, and specified that the responsibility to break treatment code resides solely with the investigator

Protocol 217-MDD-305, Amendment 1

Date of Amendment: 11 September 2020

A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY COMPARING THE EFFICACY AND SAFETY OF SAGE-217 PLUS AN ANTIDEPRESSANT VERSUS PLACEBO PLUS AN ANTIDEPRESSANT IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

Rationale for Protocol Amendment

The primary purpose for this protocol amendment in response to FDA feedback is to include a panel of commonly used antidepressants of more than one class, including an antidepressants that do not require titration to reach the preferred effective dose, to administer with SAGE-217, with stratification of randomization by class. Additional changes to incorporate FDA feedback or clarify the study design are outlined below:

Schedule of Assessments:

- Added a HAM-D assessment at Day 18 to evaluate any acute discontinuation effect on MDD symptoms (in response to FDA feedback)
- [redacted]
- Added COVID-19 Questions

Inclusion/Exclusion Criteria:

- Added inclusion criteria #13 due to the updated study design
- Removed previous exclusion criteria #8 and #21 as they pertained only to sertraline in the previous protocol version
- Modified exclusion criteria #14 to allow participants with a history of mild or moderate substance use disorder in sustained remission for at least 6 months prior to Screening, as depressed patients with such diagnoses are liable to be prescribed this medication should it be approved for marketing (in response to FDA feedback)
- Added exclusion criterion #29 to exclude participants with detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at Screening

Statistical Analysis:

- Added detailed description of the estimand of the primary efficacy endpoint (in response to FDA feedback)
- Added the multiplicity adjustment for key secondary endpoints (in response to FDA feedback)