

Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Gunduz-Bruce H, Silber C, Kaul I, et al. Trial of SAGE-217 in patients with major depressive disorder.
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This supplement contains the following items:

1. Original Protocol (24 October 2016)
2. Final Protocol (12 July 2017)
3. Summary of all Protocol Amendments
4. Original Statistical Analysis Plan (3 February 2017)
5. Final Statistical Analysis Plan (16 November 2017; Summary of changes to the Statistical Analysis Plan is included on pages 14-15 of the protocol under subsection 7.2)

1. TITLE PAGE



PROTOCOL NUMBER: 217-MDD-201

**A PHASE 2, TWO-PART (OPEN-LABEL FOLLOWED BY
DOUBLE-BLIND) STUDY EVALUATING THE SAFETY,
TOLERABILITY, PHARMACOKINETICS, AND
EFFICACY OF SAGE-217 IN THE TREATMENT OF
ADULT SUBJECTS WITH MODERATE TO SEVERE
MAJOR DEPRESSIVE DISORDER**

IND NUMBER: 132,131

Investigational Product	SAGE-217
Clinical Phase	2a
Sponsor	Sage Therapeutics, Inc.
Sponsor Contact	George Nomikos, M.D., Ph.D. Senior Medical Director Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: 617-949-2881 George.Nomikos@sagerx.com
Sponsor Medical Monitor	Handan Gunduz-Bruce, M.D., M.B.A. Medical Director Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: 203-500-9240 Handan.Gunduz-Bruce@sagerx.com
Date of Original Protocol	24 October 2016

Confidentiality Statement

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

PROTOCOL SIGNATURE PAGE

Protocol Number: 217-MDD-201
Product: SAGE-217 Oral Solution
IND No.: 132,131
Study Phase: 2a
Sponsor: Sage Therapeutics
Date of Original Protocol: Version 1.0 24 October 2016

Sponsor Approval

George Nomikos, M.D., Ph.D.
Senior Medical Director
Sage Therapeutics

Date (DD/MMM/YYYY)

Lisa A. Herman, Pharm.D, M.S., R.Ph.
Director of Regulatory Affairs
Sage Therapeutics

Date (DD/MMM/YYYY)

Amanda Moore, M.S.H.S.
Associate Director of Clinical Operations and Development
Sage Therapeutics

Date (DD/MMM/YYYY)

Abdul J. Sankoh, Ph.D.
Vice President of Data Science
Sage Therapeutics

Date (DD/MMM/YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-MDD-201 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

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Research Organization	INC Research	Cincinnati Children's Hospital Medical Center Medical Vigilance Solutions Drug and Poison Information Center 3333 Burnet Avenue, MLC 9004 Cincinnati, OH 45229-3039 1-877-462-0134

2. SYNOPSIS

Name of Sponsor/Company: Sage Therapeutics 215 First Street Cambridge, MA 02142
Name of Investigational Product: SAGE-217 Oral Solution
Name of Active Ingredient: SAGE-217
Title of Study: A Phase 2, Two-Part (Open-Label Followed by Double-Blind) Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Adult Subjects With Moderate to Severe Major Depressive Disorder
Study centers: Approximately 3 sites in Part A and approximately 15 sites in Part B
Phase of development: 2a
Methodology: This study will assess the safety, tolerability, pharmacokinetics (PK), and efficacy of SAGE-217 Oral Solution in adult subjects diagnosed with moderate to severe major depressive disorder (MDD). There are two parts to the study: Part A: Open-label dosing with SAGE-217 Oral Solution (14 days) All subjects will receive a 30 mg SAGE-217 Oral Solution dose administered at 8:00 PM (± 15 minutes) with food on Day 1 to Day 14 as tolerated. Part B: Randomized, double-blind, parallel-group, placebo-controlled (14 days) Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomized within each stratum in a 1:1 fashion to receive SAGE-217 Oral Solution 30 mg or matching placebo for 14 days beginning on Day 1 as tolerated. All doses of study drug will be administered at 8:00 PM (± 15 minutes) with food. Dose adjustments based on tolerability are detailed in Section 9.3 . Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B. Part B may be initiated after termination or completion of Part A if there is a clear signal of activity based on the 17-item Hamilton Rating Scale for Depression (HAM-D) scores and/or other scales being assessed. Both parts of the study will consist of an up to 7-day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 2-week Follow-up Period. During the study Treatment Period, subjects must remain inpatient for the first 7 days at minimum and per Investigator's judgement thereafter. Screening Period: The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit, which can occur on any one calendar day of the 7-day window (from Day -7 through Day -1). The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Axis I Disorders (SCID-I) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the HAM-D, Hamilton Anxiety Rating Scale (HAM-A), Clinical Global Impression - Severity (CGI-S), and Montgomery-Åsberg Depression Rating Scale (MADRS). The Screening Period assessments will be conducted on an outpatient basis. Most eligibility criteria are the same for both parts of the study.

Treatment Period:

Part A – Once subjects are confirmed as eligible, they will receive a 30 mg dose of study drug at 8:00 PM (± 15 minutes) with food for 14 days (Day 1 to Day 14) as tolerated. Subjects who cannot tolerate 30 mg will receive 20 mg for the rest of the Treatment Period. Subjects who cannot tolerate 20 mg will be terminated from the study. The following assessments will be performed: HAM-D, HAM-A, and MADRS total scores and Clinical Global Impression – Improvement (CGI-I).

Part A may be terminated and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed. Alternatively, upon completion of Part A, Part B may begin. The study may be terminated if there is clear lack of activity based on HAM-D scores during Part A. Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B.

Part B - Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomized within each stratum to one of two treatment groups (SAGE-217 Oral Solution 30 mg or matching placebo) in a 1:1 ratio. Subjects will be administered study drug at 8:00 PM (± 15 minutes) with food for 14 days. Subjects who cannot tolerate 30 mg will receive 20 mg for the rest of the Treatment Period. Subjects who cannot tolerate 20 mg will be terminated from the study.

In both parts of the study, subjects may be discharged after a minimum 7-day inpatient stay, following completion of the Day 7 assessments. If their clinical condition does not allow discharge, the Investigator may keep the subjects as inpatients for a longer period of time.

In both parts of the study, subjects discharged from the inpatient unit may receive treatment with study drug for the remainder of the 14-day Treatment Periods as outpatients. The outpatient phase treatment may be provided at the clinical site or, if suitable arrangements can be made, via home administration. Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.

With the exception of subjects permitted to use current stable antidepressant treatment, initiation of psychotropic medications and other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of the Day 15 assessments (Parts A and B). Psychotropic medications, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the Day 15 assessments (Parts A and B).

Efficacy and safety assessments will be performed periodically during the study, and blood samples will be collected for analysis of SAGE-217 as outlined in the Schedule of Events ([Table 2](#) and [Table 3](#)).

Follow-up Period: Follow-up visits will be conducted on an outpatient basis. Follow-up visits for Parts A and B will be conducted at 1 week (21 ± 1 day) and 2 weeks (28 ± 3 days) after the last dose of study drug.

Objectives:

Part A:

Primary:

The primary objective of the study is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg.

Secondary:

The secondary objective of Part A is to determine if treatment with SAGE-217 Oral Solution 30 mg for 14 days reduces depressive symptoms.

Part B:

Primary:

The primary objective of the study is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg.

Secondary:

The secondary efficacy objective for Part B of the study is to determine if treatment with SAGE-217 Oral Solution 30 mg reduces depressive symptoms in subjects with moderate to severe MDD compared to matching placebo.

Endpoints:

Part A:

Primary:

The primary endpoint is the safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); Stanford Sleepiness Scale (SSS) score; physical examination; and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).

Secondary:

Reduction in depressive symptoms as assessed by the following:

- Change from baseline in HAM-D total score at all time points;
- HAM-D response;
- HAM-D remission;
- Change from baseline in the MADRS total score at all time points;
- Change from baseline in HAM-D subscale and individual item scores at all time points; and
- CGI-I response.

Part B:

Primary:

The primary endpoint is the safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS.

Secondary:

Reduction in depressive symptoms, compared to placebo, as assessed by the following:

- Change from baseline in the 17-item HAM-D total score at all time points;
- HAM-D response;
- HAM-D remission;
- Change from baseline in the MADRS total score at all time points;
- Change from baseline in HAM-D subscale and individual item scores at all time points;
- CGI-I response; and
- 36-item short form survey (SF-36) and fatigue associated with depression (FAs-D) patient-reported outcome.

Pharmacokinetic:

The PK objective of Part A and Part B is:

- To assess the PK profile of SAGE-217 Oral Solution in plasma samples.

Number of subjects (planned):

Approximately ten subjects will be enrolled in Part A. Up to 52 subjects may be randomized in Part B.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject has a diagnosis of MDD that has been present for at least a 4-week period as diagnosed by SCID-I.
6. Subject has a HAM-D total score of ≥ 22 at screening and Day 1 (prior to dosing).
7. Subject has a HAM-A total score of ≥ 20 at screening and Day 1 (prior to dosing) (Part B only).
8. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics, during the screening and treatment periods.
9. Subject agrees to practice an acceptable method of highly effective birth control at screening and throughout study participation. Highly effective methods of birth control include sexual abstinence (for males and females); vasectomy; or a condom with spermicide in combination with a highly effective female partner's method (for males); and hormonal methods of contraception (ie, established use of oral, implantable, injectable, or transdermal hormones); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream, or suppository]) (for females).

Exclusion criteria:

1. Subject has a history of suicide attempt.
2. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
3. Subject has a history of treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment).
4. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
5. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration.
6. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV) antibody at screening.
7. Subject has active psychosis per Investigator assessment.
8. Subject has a medical history of seizures.
9. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.

10. Subject has a history of alcohol or drug dependence (including benzodiazepines) in the 12 months prior to screening.
11. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
12. Subject has been treated or randomized in this study (eg, Part A) or any other study employing SAGE-217 previously (ie, subject may not have received study drug and then re-enroll).
13. Subject has had administration of psychotropics that have been initiated within 14 days prior to screening and/or are not being taken at a stable dose.
14. Use of any known strong inhibitors and/or inducers of cytochrome P450 (CYP)3A4 within the 14 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.

Investigational product, dosage and mode of administration:

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% hydroxypropyl- β -cyclodextrin (HP β CD) and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dose.

Duration of participation:

Part A: Up to 38 days (14 days of treatment)

Part B: Up to 38 days (14 days of treatment)

Reference therapy, dosage and mode of administration:

Reference therapy is taste-matched placebo.

Randomization:

Subjects participating in Part A of the study will be administered study drug (SAGE-217 Oral Solution) in an open-label manner. Subjects in Part B will be randomized within each antidepressant treatment stratum to receive SAGE-217 Oral Solution or matching placebo oral solution in a 1:1 ratio. Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist and/or designated pharmacy staff, who will prepare the oral solutions according to the randomization schedule, will be unblinded.

Dose Adjustment for Safety/Tolerability Reasons:

During the Treatment Period, subjects will be able to receive study drug as long as there are no dose-limiting safety/tolerability concerns. Subjects who experience moderate or severe adverse events that according to the clinical judgement of the Investigator are related to study drug while receiving the 30 mg dose of study drug will receive 20 mg for the remaining of the Treatment Period. Subjects who experience moderate or severe related adverse events while receiving the 20 mg dose of study drug may not be able to continue receiving study drug based on the evaluation and clinical judgment of the Investigator, and may be terminated from the study. Dosing may also be modified based on tolerability as assessed with SSS scores.

Part A may be terminated and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed. The study may be terminated if there is clear lack of activity based on HAM-D scores during Part A. A Data Review Team will assess the HAM-D and other data on an ongoing basis during Part A.

Inpatient Length of Stay and Discharge Instructions

The minimum length of inpatient stay in both parts of this study is 7 days. It is the Investigator's responsibility to assess whether the subject can safely be discharged home and continue taking study drug administered by a healthcare professional trained on the protocol and delivery of the study drug for the rest of the treatment days (Days 8 to 14 for Parts A and B) or by returning to the clinic daily. The Investigator may decide to extend the subject's inpatient stay to maximize safety oversight. In making this assessment, the Investigator may consider not only the drug tolerability but also clinical factors including, but not limited to, availability of social support, transportation, severity of symptoms, and suicidality.

Discharge instructions must include warnings about avoiding activities for which sedative effects of the study drug may impair performance, such as driving a motor vehicle and operating machinery.

Criteria for evaluation:**Efficacy:**

Reduction of depressive symptoms will be assessed by the change from baseline at various time points in HAM-D total score; HAM-D response; HAM-D remission; change from baseline in the MADRS total score; CGI-I response; change from baseline in HAM-D subscale and individual item scores; change from baseline in HAM-A total score; change from baseline in SF-36; and change from baseline in FAs-D.

Pharmacokinetics:

Plasma samples will be collected to assay for concentrations of SAGE-217. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC), AUC from time zero to infinity (AUC_{∞}), maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (t_{max}), steady-state drug concentration in the plasma during oral intake (C_{ss}), and in the plasma at steady state during a dosing interval.

Safety:

The safety and tolerability of SAGE-217 Oral Solution will be evaluated by frequency, type, and severity of adverse events; mean changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS during both Part A and Part B.

Statistical methods:**General**

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

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

Analysis Populations and Methods:

The Safety Population (for both Part A and Part B), defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data. Adverse events will be classified by type, incidence, severity, and causality. The overall incidence of adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Data for vital signs, clinical laboratory measurements, ECG, physical examinations, and concomitant medication usage will also be summarized. Safety data will be summarized and examined for possible relationships between subject characteristics and plasma SAGE-217 concentrations, as appropriate. Suicidality data collected using the C-SSRS at baseline and at each visit during the active Treatment Period will be listed for all subjects. The C-SSRS listings will include behavior type and/or category for suicidal ideation and suicidal behavior of the C-SSRS. Out-of-range safety endpoints may be categorized as low or high, where applicable. Subjects will be summarized according to treatment received.

The Efficacy Population (for both Part A and Part B), defined as all subjects in the Safety Population who complete at least 1 day of dosing of study drug and have at least one post-baseline efficacy evaluation, will be used to analyze efficacy data. Efficacy data will be analyzed using appropriate descriptive statistics and pre-specified statistical methods, as well as other data presentation methods where applicable; subject listings will be provided for all efficacy data. For (the open-label) Part A, efficacy data will be summarized descriptively. For Part B, subjects will be analyzed according to randomized treatment.

For Part B, the change from baseline in HAM-D total score will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, antidepressant use strata, assessment time point, and time point-by-treatment as explanatory variables. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 Oral Solution and matching placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means), 95% confidence intervals, and p-values will be reported. An unstructured covariance structure will be used to model the within-subject errors. Continuous variables will be analyzed using similar methods.

Binary efficacy endpoints, including responder and remission endpoints, will be analyzed using logistic regression model.

The PK Population will consist of all subjects in the Safety Population with sufficient plasma concentrations for PK evaluations, and will be used to summarize PK data. PK parameters will be summarized using appropriate descriptive statistics and listed by subject. The PK parameters to be summarized where possible will include AUC_{∞} , C_{max} , t_{max} , $t_{1/2}$, and C_{ss} .

Sample Size Calculation

The sample size of ten subjects for Part A was selected based on clinical and not statistical considerations.

For Part B, assuming a two-sided t-test at an alpha level of 0.10, a sample size of 23 subjects per group would provide 80% power to detect an effect size of 0.75 between the SAGE-217 Oral Solution and matching placebo groups with regard to the secondary efficacy outcome variable of change from baseline in HAM-D total score. An effect size of 0.75 corresponds to a matching placebo-adjusted difference of 7.5 points in the change from baseline in HAM-D total score at 15 days with an assumed SD of 10 points. By including two treatment groups and using a 1:1 randomization, a total of 46 subjects are required. Assuming a non-evaluability rate of 10%, up to 52 subjects will be randomized.

Table 2: Schedule of Events (Part A)

	Screening Period	Open-Label Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D-7 to D-1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)
Study Procedure																		
Informed Consent	X																	
Inclusion/Exclusion	X	X																
Demographics	X																	
Medical/Family History	X																	
SCID-I	X																	
Confinement		X							(X)									
Physical Examination	X								X							X	X	X
Body Weight/Height	X															X (wt only)	X (wt only)	X (wt only)
Clinical Laboratory Assessments ^b	X								X							X	X	X
Drug & Alcohol Screen ^c	X	X																
Pregnancy Test ^d	X	X														X ^e		X
Hepatitis & HIV Screen	X																	
Blood Sample ^f	O																	
Genetic Sample ^g	O																	
Vital Signs ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry		X	X	X	X	X	X	X	X									
12-Lead ECG ⁱ	X	X	X					X							X		X	
C-SSRS ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S ^k	X	X	X	X					X							X	X	X

	Screening Period	Open-Label Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D-7 to D-1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)
Study Procedure																		
CGI-I ^k			X	X					X							X	X	X
HAM-A ^k	X	X	X	X					X							X	X	X
HAM-D ^k	X	X	X	X	X	X	X	X	X							X	X	X
MADRS ^k	X	X	X	X	X	X	X	X	X							X	X	X
SSS ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Plasma PK ^m								X	X						X	X		
Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse Events	X																	
Prior/Concomitant Medications ⁿ	X																	

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ET = early termination; ECG = electrocardiogram; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; MADRS = Montgomery-Åsberg Depression Rating Scale; PK = pharmacokinetic; SCID-I = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Axis I Disorders; SSS = Stanford Sleepiness Scale

*D1 procedures are to be completed prior to dosing

^a Outpatient visits may take place at the subject's residence or in the clinic.

^b Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning on Days 8 and 15 and during the follow-up visits on Day 21 and Day 28.

^c Urine toxicology for selected drugs of abuse and serum or breath test for alcohol.

^d Serum pregnancy test at screening and urine pregnancy test at Day 1 and Day 28.

^e Female subjects who prematurely discontinue will have a pregnancy test performed at the ET visit.

^f An optional blood sample for hormone and exploratory biochemistry testing, where consent is given.

^g An optional genetic sample for biomarker testing, where consent is given.

^h Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ±5 minutes of the scheduled time point through 0.5 hours after dosing and ±30 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between the hours of 23:00 h and 06:00 h. From Day 1 through Day 7, vital signs will be completed at the following time points: predose, 0.25, 0.5, 1, 2, and 12 hours after dosing. During the outpatient treatment period, vital signs will be completed prior to dosing and 1 hour after dosing. Vital signs may be repeated at the discretion of the Investigator or Visiting Home Healthcare Provider as clinically indicated.

ⁱ Will be performed 1 hour ±15 minutes after dosing on Days 1, 2, 7, and 14, and during the follow-up visit on Day 21.

- ^j The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- ^k To be completed to be completed at 8:00 AM (±30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.
- ^l To be completed within ±5 minutes of the scheduled time point through 0.5 hours after dosing and ±15 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between 23:00 h and 06:00 h during the inpatient treatment period. From Day 1 through Day 7, SSS will be completed at the following time points: predose, 0.25, 0.5, 1, and 2 hours after dosing. During the outpatient treatment period, SSS will be completed prior to dosing and 1 hour after dosing.
- ^m Plasma samples for PK analysis in Part A and Part B will be collected predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within ±5 minutes of the scheduled time point through 0.5 hours after dosing and ±15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. Plasma samples for PK analysis will be collected per protocol and subjects may need to be awoken for sample collection.
- ⁿ To include those taken within 30 days prior to informed consent and throughout the study.

Table 3: Schedule of Events (Part B)

	Screening Period	Double-Blind, Placebo-Controlled Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D-7 to D-1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)
Study Procedure																		
Informed Consent	X																	
Inclusion/Exclusion	X	X																
Demographics	X																	
Medical/Family History	X																	
SCID-I	X																	
Randomization		X																
Confinement		X							(X)									
Physical Examination	X								X							X	X	X
Body Weight/Height	X															X (wt only)	X (wt only)	X (wt only)
Clinical Laboratory Assessments ^b	X								X							X	X	X
Drug & Alcohol Screen ^c	X	X																
Pregnancy Test ^d	X	X														X ^e		X
Hepatitis & HIV Screen	X																	
Blood Sample ^f	O																	
Genetic Sample ^g	O																	
Vital Signs ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry		X	X	X	X	X	X	X	X									
12-Lead ECG ⁱ	X	X	X					X							X		X	
C-SSRS ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening Period	Double-Blind, Placebo-Controlled Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D-7 to D-1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)
Study Procedure																		
CGI-S ^k	X	X	X	X					X							X	X	X
CGI-I ^k			X	X					X							X	X	X
HAM-A ^k	X	X	X	X					X							X	X	X
HAM-D ^k	X	X	X	X	X	X	X	X	X							X	X	X
MADRS ^k	X	X	X	X	X	X	X	X	X							X	X	X
SF-36 ^k	X	X							X							X	X	X
FAs-D ^k	X	X							X							X	X	X
SSS ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Plasma PK ^m								X	X						X	X		
Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse Events	X																	
Prior/Concomitant Medications ⁿ	X																	

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ET = early termination; ECG = electrocardiogram; FAs-D = fatigue associated with depression; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; MADRS = Montgomery-Åsberg Depression Rating Scale; PK = pharmacokinetic; SCID-I = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Axis I Disorders; SF-36 = 36-item short form survey; SSS = Stanford Sleepiness Scale

*D1 procedures are to be completed prior to dosing

^a Outpatient visits may take place at the subject's residence or in the clinic.

^b Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning on Days 8 and 15 and during the follow-up visits on Day 21 and Day 28.

^c Urine toxicology for selected drugs of abuse and serum or breath test for alcohol.

^d Serum pregnancy test at screening and urine pregnancy test at Day 1 and Day 28.

^e Female subjects who prematurely discontinue will have a pregnancy test performed at the ET visit.

^f An optional blood sample for hormone and exploratory biochemistry testing, where consent is given.

^g An optional genetic sample for biomarker testing, where consent is given.

- ^h Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ±5 minutes of the scheduled time point through 0.5 hours after dosing and ±30 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between the hours of 23:00 h and 06:00 h. From Day 1 through Day 7, vital signs will be completed at the following time points: predose, 0.25, 0.5, 1, 2, and 12 hours after dosing. During the outpatient treatment period, vital signs will be completed prior to dosing and 1 hour after dosing. Vital signs may be repeated at the discretion of the Investigator or Visiting Home Healthcare Provider as clinically indicated.
- ⁱ Will be performed 1 hour ±15 minutes after dosing on Days 1, 2, 7, and 14, and during the follow-up visit on Day 21.
- ^j The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- ^k To be completed at 8:00 AM (±30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.
- ^l To be completed within ±5 minutes of the scheduled time point through 0.5 hours after dosing and ±15 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between 23:00 h and 06:00 h during the inpatient treatment period. From Day 1 through Day 7, SSS will be completed at the following time points: predose, 0.25, 0.5, 1, and 2 hours after dosing. During the outpatient treatment period, SSS will be completed prior to dosing and 1 hour after dosing.
- ^m Plasma samples for PK analysis in Part A and Part B will be collected predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within ±5 minutes of the scheduled time point through 0.5 hours after dosing and ±15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. Plasma samples for PK analysis will be collected per protocol and subjects may need to be awoken for sample collection.
- ⁿ To include those taken within 30 days prior to informed consent and throughout the study.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AUC	area under the concentration-time curve
AUC _∞	area under the concentration-time curve from time zero to infinity
BMI	body mass index
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
C _{max}	maximum (peak) plasma concentration
CS	clinically significant
C _{ss}	steady-state drug concentration in the plasma during oral intake
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP450	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EP	European Pharmacopeia
FAs-D	fatigue associated with depression
GABA	γ-aminobutyric acid
GABA _A	γ-aminobutyric acid-ligand gated chloride channel
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	17-item Hamilton Rating Scale for Depression
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPβCD	hydroxypropyl-β-cyclodextrin
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
MAD	multiple-ascending dose
MADRS	Montgomery-Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorders
MMRM	mixed effects model for reported measures
MTD	maximum tolerated dose
n	number
NCS	not clinically significant
NF	National Formulary
PK	pharmacokinetic(s)
PPD	postpartum depression
SAD	single-ascending dose
SCID-I	Structured Clinical Interview for DSM-5 Axis I Disorders
SD	standard deviation
SF-36	36-item short form survey
SOC	system organ class
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
TEAE	treatment-emergent adverse event
t _{max}	time at maximum (peak) plasma concentration
USP	United States Pharmacopeia
WHO	World Health Organization
WHO-DD	World Health Organization-Drug Dictionary

5. INTRODUCTION

5.1. Background of Major Depressive Disorders and Unmet Medical Need

World Health Organization (WHO) has identified depression as the leading cause of disability worldwide, and 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 350 million people.

In [DSM-5](#), depression refers to an overarching set of diagnoses, including disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder.

In the US, the economic burden of depression, including workplace costs, direct costs and suicide-related costs, was estimated to be \$210.5 billion in 2010 ([Greenberg 2015](#)). As per WHO statistics, over 800,000 people die due to suicide every year, and suicide is the second leading cause of death in 15- to 29-year-olds. In the US, an estimated 10% to 15% of individuals with depression commit suicide ([Angst 1999](#)).

Antidepressants are mainstay of pharmacological treatment for depressive disorders. Selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other compounds that affect monoaminergic neurotransmission, such as mirtazapine and bupropion, represent the major classes of antidepressants. While antidepressants are widely used, large scale studies have demonstrated their limited efficacy. For example, in the STAR*D trial where over 2800 patients were treated in “real world” settings, the HAM-D remission rate was 28% following 14 weeks of treatment with citalopram, a typical selective serotonin reuptake inhibitor ([Trivedi 2006](#)). Recent studies have shown a number of symptoms that remain untreated, such as cognitive impairment, sleep disturbances and anxiety, even in patients that are in remission over a long period of time after treatment ([Conradi 2011](#); [Romera 2013](#)). A close examination of randomized placebo-controlled trials of antidepressants approved by the Food and Drug Administration in the treatment of both major or minor depressive disorders demonstrated Cohen’s *d* effect sizes below 0.2 and high placebo response rates ([Kirsch 2008](#); [Fournier 2010](#)), emphasizing the challenges in assessing antidepressant drug efficacy and the unmet need in the treatment of depression.

Converging preclinical and clinical evidence ([Gerner 1981](#); [Honig 1988](#); [Drugan 1989](#); [Luscher 2011](#); [Mann 2014](#)) implicates deficits in GABAergic neurotransmission in the pathophysiology of depressive disorders including MDD and PPD. Furthermore, several pieces of experimental data implicate deficiencies in the normal regulation of endogenous neuroactive steroids in depressive disorders ([Maguire 2008](#); [Maguire 2009](#)). The neuroactive steroid class of compounds includes the endogenous neuroactive steroid, allopregnanolone. Allopregnanolone is a positive allosteric modulator of both synaptic and extrasynaptic GABA_A receptors – the prominent inhibitory transmitter system in the brain. Depressed patients show low levels of GABA in the brain and of neurosteroids in the CSF and plasma, and antidepressant therapy

restores GABA levels in relevant animal models and neurosteroid concentrations in depressed patients ([Luscher 2011](#); [Schüle 2014](#)).

5.2. SAGE-217 Oral Solution

The intended dosage form for oral administration is SAGE-217 Oral Solution to be compounded at the clinical pharmacy from components supplied by the Sponsor (SAGE-217 Drug Substance Powder in the Bottle, Excipients in the Bottle, and sucralose) and Sterile Water for Injection. SAGE-217 Oral Solution is a clear, colorless, aqueous hydroxypropyl- β -cyclodextrin (HP β CD) solution of SAGE-217 Drug Substance. One concentration, 6 mg/mL, is available for use in clinical studies. In addition to SAGE-217 Drug Substance, SAGE-217 Oral Solution contains HP β CD (Kleptose[®], HPB Parenteral Grade, United States Pharmacopeia/European Pharmacopeia [USP/EP], Roquette) to solubilize the drug substance, sucralose (USP/National Formulary [NF], JK Sucralose, Inc.) to sweeten the solution, and water for injection to be provided by the clinical pharmacy. Refer to [Table 5](#) for the composition of SAGE-217 Oral Solution 6 mg/mL.

The SAGE-217 Oral Solution 6 mg/mL stock solution is compounded at point of use. This stock solution is for oral administration after dilution to the intended dose by the clinical pharmacy.

5.3. Summary of Nonclinical and Clinical Experience with SAGE-217

5.3.1. Nonclinical Studies with SAGE-217

In nonclinical studies of SAGE-217, sedative-hypnotic effects were consistently observed at higher doses in both in vivo pharmacology studies and toxicology studies. The sedative-hypnotic impairments seen with SAGE-217 were typical for GABA_A positive allosteric modulators, ranging from hyperexcitability and ataxia at the lower doses through deep sedation and ultimately anesthesia at higher doses. Depth and duration of sedation demonstrated a clear dose response over the range tested, with evidence of tolerance occurring with continued exposure. Tolerance to the effects of SAGE-217 on motor incoordination was not observed after 7 days of dosing.

The compound has been assessed in 14-day rat and dog toxicology studies with daily administration of SAGE-217 as a solution in HP β CD in dogs and Labrasol[®] in rats. The no-observed-adverse-effect-level was 3 mg/kg (females) and 22.5 mg/kg (males) in rats and 2.5 mg/kg in dogs. There were no adverse effects in dogs or rats in the main toxicology studies. A single observation of mortality occurred in one female rat at the high dose in a toxicokinetic study that was suspected to have been related to exaggerated pharmacology. Additional toxicology and pharmacology information is provided in the [Investigator's Brochure](#).

5.3.2. Clinical Experience

To date, two clinical studies employing SAGE-217 Oral Solution are clinically complete, and final clinical study reports are pending. Discussions of pharmacokinetic (PK) data are limited to the single-ascending dose, food effect, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction cohorts from Study 217-CLP-102. Discussions of safety data are limited to the single-ascending dose cohorts in Study 217-CLP-101 and the multiple-ascending dose cohorts in Study 217-CLP-102.

Study 217-CLP-101 was a first-in-human, four-part study that assessed the effects of a single dose of SAGE-217 Oral Solution. The study was a double-blind, placebo-controlled, single-ascending dose design in healthy adult volunteers, with the objective of identifying the maximum tolerated dose (MTD) and PK profiles of SAGE-217 Oral Solution. Subjects in each of the single-ascending dose cohorts received a single dose of study drug, either SAGE-217 Oral Solution (six subjects) or placebo (two subjects), with SAGE-217 Oral Solution doses of 0.25 mg, 0.75 mg, 2 mg, 5.5 mg, 11 mg, 22 mg, 44 mg, 55 mg, and 66 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the Safety Review Committee (SRC) and agreement reached that it was safe to increase the dose. The MTD was determined to be 55 mg. Two cohorts, six subjects each received SAGE-217 Oral Solution in an open-label manner (one cohort received 50% of the MTD [22 mg] to study the food effects and the other cohort received the MTD [55 mg] to study the effects on subjects with essential tremor). SAGE-217 Oral Solution was orally bioavailable, demonstrated dose-linear PK from the lowest (0.25 mg) through the highest (66 mg) dose, and supported once-daily oral dosing with food. In addition, the pharmacodynamic effects of the SAGE-217 Oral Solution MTD were assessed in placebo-controlled, blinded, crossover electroencephalogram cohorts of eight subjects each; one cohort received 50% of the MTD (22 mg) and the other received the MTD (55 mg).

Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE-217 Oral Solution. The study was a double-blind, placebo-controlled, multiple-ascending dose study in healthy adult volunteers. Subjects in each of the multiple-ascending dose cohorts received study drug, either SAGE-217 Oral Solution (nine subjects) or placebo (three subjects), once daily for 7 days, with SAGE-217 Oral Solution doses of 15 mg, 30 mg, and 35 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the SRC and agreement reached that it was safe to increase the dose. The MTD was determined to be 30 mg. It was observed that subjects receiving the drug in the evening did better in terms of tolerability compared to when they received the drug in the morning. A fourth cohort of 12 subjects received 30 mg of SAGE-217 Oral Solution in an open-label manner to study drug-drug interactions. SAGE-217 Oral Solution is not likely to induce the metabolism of cytochrome P450 (CYP)2B6 or CYP3A4 substrates. SAGE-217 was orally bioavailable and suitable for once-daily oral dosing at nighttime with food.

SAGE-217 Oral Solution was generally well tolerated. In both Phase 1 studies (217-CLP-101 and 217-CLP-102), doses were escalated until the stopping criteria were met. Most adverse events were reported as mild or moderate in intensity, and there were no serious adverse events reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At doses planned for further study, the observed sedation was mild, transient, and associated with daily peak exposure. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, dizziness, euphoric mood, fatigue, tremor, and muscle twitching, reported most frequently in the highest dose group (66 mg). Some changes in mean blood pressure and heart rate were observed after single doses of 44 mg and greater. After multiple doses of 30 mg (AM or PM) or 35 mg (PM) over 7 days, there was no evidence of changes in mean vital sign measures even though Day 7 plasma concentrations approximated that of the highest single dose in the single-ascending dose study. Subjects seemed to tolerate SAGE-217 Oral Solution better when given as nighttime dosing.

There are no clinical efficacy data for SAGE-217 in major depressive disorders (MDD), since the present study is the first study in this indication.

5.4. Potential Risks and Benefits

To date, SAGE-217 Oral Solution has been studied within the context of single-ascending dose (SAD) (217-CLP-101) and multiple-ascending dose (MAD) (217-CLP-102) studies. In addition, the SAD study included a cohort evaluating a 55 mg dose of SAGE-217 Oral Solution in subjects with essential tremor who were otherwise healthy. The most common TEAEs observed across the SAD and MAD studies were sedation, somnolence, dizziness, euphoric mood, and tremor. Most adverse events were reported as mild or moderate in intensity, and there were no serious adverse events reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At predicted efficacious doses in the 20 to 30 mg range, observed sedation was mild, transient, and associated with daily peak exposure. The pharmacokinetic profile obtained from these studies indicates dose linearity over the multiple-dose range studied (15 to 35 mg). SAGE-217 Oral Solution was well-tolerated in the essential tremor subjects.

The safety profile of SAGE-217 Oral Solution based on the SAD, MAD, and limited essential tremor studies thus far suggest that SAGE-217 Oral Solution may also be well tolerated in patients with MDD. The current significant unmet need in the treatment of depression, remaining as a number one cause of disability worldwide, justifies a favorable risk-benefit ratio, and investigation of SAGE-217 Oral Solution in patients with MDD.

5.5. Dose Justification

To date, the pharmacokinetics of SAGE-217 Oral Solution has been investigated in healthy volunteers within the context of the SAD and MAD studies (217-CLP-101 and 217-CLP-102, respectively). The MTD was determined to be 55 mg in the SAD study and 30 mg once daily (either AM or PM dosing) in the MAD study. Thus as a first step, while ensuring tolerability, a 30 mg dose has been chosen to maximize the potential therapeutic benefit in this first clinical study of MDD.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Part A

6.1.1. Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg.

6.1.2. Secondary Objective

The secondary objective of Part A is to determine if treatment with SAGE-217 Oral Solution 30 mg for 14 days reduces depressive symptoms.

6.2. Part B

6.2.1. Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg.

6.2.2. Secondary Objective

The secondary efficacy objective for Part B of the study is to determine if treatment with SAGE-217 Oral Solution 30 mg reduces depressive symptoms in subjects with moderate to severe MDD compared to matching placebo.

6.3. Pharmacokinetic Objective

The PK objective of Part A and Part B is to assess the PK profile of SAGE-217 Oral Solution in plasma samples.

6.4. Endpoints

6.4.1. Part A

6.4.1.1. Primary

The primary endpoint is the safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); Stanford Sleepiness Scale (SSS) score; physical examination; and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).

6.4.1.2. Secondary

Reduction in depressive symptoms as assessed by the following:

- Change from baseline in HAM-D total score at all time points;

- HAM-D response (defined as having a 50% or greater reduction from baseline in HAM-D total score);
- HAM-D remission (defined as having a HAM-D total score of ≤ 7);
- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at all time points;
- Change from baseline in HAM-D subscale and individual item scores at all time points;
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at all time points; and
- Clinical Global Impression – Improvement (CGI-I) response (defined as a CGI-I score of “very much improved” or “much improved”).

6.4.2. Part B

6.4.2.1. Primary

The primary endpoint is the safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS.

6.4.2.2. Secondary

Reduction in depressive symptoms, compared to placebo, as assessed by the following:

- Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at all time points;
- HAM-D response;
- HAM-D remission;
- Change from baseline in the MADRS total score at all time points;
- Change from baseline in HAM-D subscale and individual item scores at all time points;
- Change from baseline in HAM-A total score at all time points;
- CGI-I response; and
- 36-item short form survey (SF-36) and fatigue associated with depression (FAs-D) patient-reported outcome.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study is a two-part, multicenter, Phase 2a study to evaluate the safety, tolerability, PK, and efficacy of SAGE-217 Oral Solution in approximately 62 adult subjects with MDD. Part A of the study is an open-label design with SAGE-217 Oral Solution dosing for 14 days. Part B of the study is a randomized, double-blind, parallel-group, placebo-controlled design with SAGE-217 Oral Solution or matching placebo dosing for 14 days. Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B.

Parts A and B of the study will consist of an up to 7-day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 2-week Follow-up Period (through Day 28).

During the Screening Period (Day -7 to Day -1), after signing the informed consent form (ICF), subjects will be assessed for study eligibility, and the severity of each subject's MDD will be evaluated using HAM-D. The Screening Period assessments will be conducted on an outpatient basis.

If applicable, standard of care data collected prior to obtaining informed consent may also be included as screening data, if appropriate, such as laboratory tests, ECG, physical examination, and vital signs conducted within the preceding 48 hours, as long as the requirement for the screening assessment to be collected retrospectively is met in full. If applicable, to ensure protocol compliance, any standard of care data eligible for inclusion as screening data must include the precise nature and timing of data collection.

During the 14-day study Treatment Period of Parts A and B, subjects must remain inpatient for the first 7 days at minimum and per Investigator's judgement thereafter. The Follow-up Period assessments will be conducted on an outpatient basis.

The study will be conducted in two parts:

- Part A: Beginning on Day 1, subjects will receive open-label SAGE-217 Oral Solution at 8:00 PM (± 15 minutes) with food (as outlined in [Section 9.2.1](#)). Subjects will receive SAGE-217 Oral Solution 30 mg from Day 1 to Day 14 as tolerated.
- Part B: Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomized within each stratum in a 1:1 fashion to receive SAGE-217 Oral Solution or matching placebo for 14 days beginning on Day 1 as tolerated. All doses of study drug will be administered at 8:00 PM (± 15 minutes) with food as outlined in [Section 9.2.2](#).

Part A may be terminated and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed. Alternatively, upon completion of Part A, Part B may begin. The study may be terminated if there is clear lack of activity based on HAM-D scores during Part A.

In Part A and Part B, study drug (SAGE-217 Oral Solution or matching placebo) will be administered at the study center for at least the first 7 days of the Treatment Period, which

includes Day 1 of study drug administration through completion of study drug administration on Day 14. Subjects may be discharged after a minimum 7-day inpatient stay, following completion of the Day 7 assessments. If their clinical condition does not allow discharge, the Investigator may keep the subjects as inpatients for a longer period of time. Subjects discharged from the inpatient unit may receive treatment with study drug for the remainder of the 14-day Treatment Period as outpatients. For the outpatient phase, dosing will be done at the clinical site or, if suitable arrangements can be made, via home administration where local regulations allow. Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.

Subjects will be monitored for safety during the Treatment and Follow-up Periods including monitoring for adverse events/serious adverse events, routine clinical laboratory assessments, physical examination, vital signs, and ECG.

During the Treatment Period, subjects will be able to receive study drug as long as there are no dose-limiting safety/tolerability concerns. Subjects who experience moderate or severe adverse events that according to the clinical judgement of the Investigator are related to study drug while receiving the 30 mg dose of study drug will receive 20 mg for the remaining of the Treatment Period. Subjects who experience moderate or severe related adverse events while receiving the 20 mg dose of study drug may not be able to continue receiving study drug based on the evaluation and clinical judgment of the Investigator, and may be terminated from the study.

Dosing may also be modified based on tolerability as assessed with SSS scores. Any SSS score of ≥ 6 will be reassessed within 10 minutes. If a subject is receiving the 30 mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat assessment during normal waking hours, the dose will be decreased to 20 mg for the rest of the Treatment Period. If a subject is receiving the 20 mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat assessment during normal waking hours, then study drug will be discontinued and the subject will be terminated from the study.

7.2. Blinding and Randomization

Part A is open-label with no control group; therefore, there will be no randomization or blinding.

Part B is a double-blind, placebo-controlled study. Subjects who meet the entrance criteria will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 Oral Solution or taste-matched placebo according to a computer-generated randomization schedule. Once it has been determined that a subject meets eligibility criteria, the subject will be sequentially assigned a subject number from the randomization schedule provided to the unblinded pharmacist. Subject identification numbers will consist of the site number (eg, "01") followed by numbering starting with double zero (eg, 01-001, 01-002, 01-003 through 01-062).

The randomization schedule will be generated using SAS V9.2 or later. Only the clinic pharmacist or designated pharmacy staff, who is responsible for preparing the solutions, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual solution contents to the Investigator, who should also alert Sage of the emergency (see [Section 13.6](#) for more details related to unblinding). In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for

unblinding) must be documented in the subject's records and on the electronic case report form (eCRF). If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study. In addition, an unblinded Monitor will perform drug accountability during the study.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the study.

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject has a diagnosis of MDD that has been present for at least a 4-week period as diagnosed by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Axis I Disorders (SCID-I).
6. Subject has a HAM-D total score of ≥ 22 at screening and Day 1 (prior to dosing).
7. Subject has a HAM-A total score of ≥ 20 at screening and Day 1 (prior to dosing) (Part B only).
8. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics, during the screening and treatment periods.
9. Subject agrees to practice an acceptable method of highly effective birth control at screening and throughout study participation. Highly effective methods of birth control include sexual abstinence (for males and females); vasectomy; or a condom with spermicide in combination with a highly effective female partner's method (for males); and hormonal methods of contraception (ie, established use of oral, implantable, injectable, or transdermal hormones); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream, or suppository]) (for females).

8.2. Subject Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria.

1. Subject has a history of suicide attempt.
2. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.

3. Subject has a history of treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment).
4. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
5. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration.
6. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV) antibody at screening.
7. Subject has active psychosis per Investigator assessment.
8. Subject has a medical history of seizures.
9. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
10. Subject has a history of alcohol or drug dependence (including benzodiazepines) in the 12 months prior to screening.
11. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
12. Subject has been treated or randomized in this study (eg, Part A) or any other study employing SAGE-217 previously (ie, subject may not have received study drug and then re-enroll).
13. Subject has had administration of psychotropics that have been initiated within 14 days prior to screening and/or are not being taken at a stable dose.
14. Use of any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.

8.3. Subject Withdrawal Criteria

If there is an adverse event or medical reason for the withdrawal, the subject should be followed medically until the condition has either resolved or is stable. Details of the reason for withdrawal should be recorded in the subject's eCRF.

Subjects who withdraw should, if possible, have a follow-up examination, including a physical examination, the appropriate investigations, vital signs, and clinical laboratory tests (including pregnancy tests), as outlined for the Day 15 visit ([Table 2](#) and [Table 3](#)). All details of this follow-up examination should be recorded in the subject's medical source documents.

8.3.1. Study Drug Withdrawal

Participation in the study is strictly voluntary. Subjects are free to discontinue the study at any time without giving their reason(s).

A subject must be withdrawn from the study treatment in the event of any of the following:

- Withdrawal of the subject's consent;
- New onset of a condition that would have met exclusion criterion, is clinically relevant and affects the subject's safety, and discontinuation is considered necessary by the Investigators and/Sponsor;
- Occurrence of intolerable adverse events;
- Occurrence of pregnancy;
- Intake of nonpermitted concomitant medication;
- Subject noncompliance;
- Significant protocol deviation determined in consultation with the Medical Monitor.

If a subject failed to attend scheduled assessments during the course of the study, the Investigators must determine the reasons and the circumstances as completely and accurately as possible and document this in the subject's source documents.

Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant. Subjects who withdraw should, if possible, have a follow-up examination, including a physical examination, the appropriate investigations, vital signs, and clinical laboratory tests (including pregnancy tests), as outlined for the Day 15 visit ([Table 2](#) and [Table 3](#)). All details of this follow-up examination should be recorded in the subject's medical source documents.

Subjects who withdraw or are withdrawn from the study will be replaced only if they withdraw prior to dosing. Subjects who are withdrawn from the study, fail to return or are no longer qualified will not be replaced.

8.3.2. 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 adverse events or other findings suggesting unacceptable risk to subjects, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their Institutional Review Board (IRB) and initiate withdrawal procedures for participating subjects.

9. TREATMENT OF SUBJECTS

9.1. Number of Subjects

Approximately ten subjects with MDD will be enrolled into Part A of the study. Up to 52 subjects may be randomized in Part B to ensure at least 46 evaluable subjects for Part B. Evaluable subjects are defined as those subjects receiving study drug with at least one post-baseline HAM-D assessment.

9.2. Treatment Assignment

Study drug will be administered with food in both the inpatient and outpatient treatment periods. Food intake will be standardized as specified by the Sponsor.

9.2.1. Part A

Subjects participating in Part A of the study will take study drug (SAGE-217) in an open-label manner. Subjects will be administered a 30 mg dose of study drug at 8:00 PM (± 15 minutes) with food for 14 days (Day 1 to Day 14) as tolerated.

9.2.2. Part B

Subjects participating in the randomized, double-blind, placebo-controlled portion of the study (Part B) will be randomly assigned to receive SAGE-217 Oral Solution 30 mg or matching placebo solution on a 1:1 basis according to a computer-generated randomization schedule; the randomization schedule will be stratified to allow for treatment balance within each use of antidepressant stratum.

Subjects, clinicians, and study team will be blinded to treatment allocation. The pharmacist, who will prepare the oral solutions according to the randomization schedule, and an unblinded Monitor, who will perform drug accountability during the study, will be unblinded.

9.3. Dose Adjustment Criteria

During the Treatment Period, subjects will be able to receive study drug as long as there are no dose-limiting safety/tolerability concerns.

In both Part A and Part B, subjects who experience moderate or severe adverse events that according to the clinical judgement of the Investigator are related to study drug while receiving the 30 mg dose of study drug will receive 20 mg for the remaining of the Treatment Period. Subjects who experience moderate or severe related adverse events while receiving the 20 mg dose of study drug may not be able to continue receiving study drug based on the evaluation and clinical judgment of the Investigator, and may be terminated from the study.

Dosing may also be modified based on tolerability as assessed with SSS scores. Any SSS score of ≥ 6 will be reassessed within 10 minutes. If a subject is receiving the 30 mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat assessment during normal waking hours, the dose will be decreased to 20 mg for the rest of the Treatment Period. If a subject is receiving the 20 mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat

assessment during normal waking hours, then study drug will be discontinued and the subject will be terminated from the study.

Part A may be terminated and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed. The study may be terminated if there is clear lack of activity based on HAM-D scores during Part A. A Data Review Team will assess the HAM-D and other data on an ongoing basis during Part A.

9.4. Prior/Concomitant Medications

9.4.1. Prior/Concomitant Medications

Subjects will receive standard of care for adult patients diagnosed with moderate to severe MDD. Psychotropic medications, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the Day 15 assessments (Parts A and B).

Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 Oral Solution or taste-matched placebo.

In this study, psychotropic medications refer to central nervous system active medications taken to help depressive symptoms, and include antidepressants, benzodiazepines, and hypnotic agents. Subjects presenting to the study on antidepressants may be eligible to participate if they have been on a stable dose for at least 14 days. Those subjects on benzodiazepines and hypnotic agents may be considered for eligibility based on specific discussions between the Investigator and the Sponsor to ensure safety. Subjects on other psychotropic medications, including stimulants, antipsychotics, and mood stabilizers, are not eligible to participate in this study.

Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study under the guidance outlined in [Section 9.4.2](#). In both Part A and Part B, all medications should be documented throughout the study from 30 days prior to signing the ICF through Day 28 (± 3 days) and recorded on the eCRF. Prior medications (ie, those taken prior to signing of ICF) that required washout for study entry will also be documented.

9.4.2. Restricted Medications

Restrictions on specific classes of medications include the following:

- Initiation of new antidepressant therapy is prohibited upon admission to the study center for those eligible subjects who desire study participation. Those subjects already taking an antidepressant at the time of study entry (and meeting all study inclusion criteria) will be permitted to remain on the pre-existing antidepressant at their current dose if they were on this medication for at least 14 days prior to study enrollment.
- Benzodiazepines are to be avoided as much as possible. Eligible subjects taking a stable dose of benzodiazepine for at least 14 days prior to the study will be discussed on a case-by-case basis with the Sponsor to determine eligibility. Subjects may be permitted to continue to take their current dose of the benzodiazepine (to prevent

acute withdrawal), but no new benzodiazepine use will be permitted during the course of the study.

- The use of hypnotics for sleep/insomnia such as Ambien[®] and trazodone is to be avoided; use of hypnotics will be discussed on a case-by-case basis with the Sponsor.
- Anticonvulsants and atypical antipsychotics are prohibited.

9.5. Treatment Compliance

Investigational product will be prepared by the site pharmacist. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for noncompliance will also be documented, including:

- Missed visits;
- Interruptions in the schedule of administration; and
- Nonpermitted medications.

The time at which study procedures are conducted should follow the protocol timelines as closely as possible.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HP β CD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dose. The 6 mg/mL stock SAGE-217 Oral Solution will be compounded from SAGE-217 Drug Substance Powder in the Bottle and Excipient (s) in the Bottle (manufactured under current Good Manufacturing Practice [GMP] conditions at Pharmatek) and further admixed at the clinical site in preparation for dosing.

A matching placebo oral solution will be prepared for administration without the active ingredient, but including the HP β CD and sucralose, as well as three taste-masking components to preserve the blinding. Detailed instructions for study drug (SAGE-217 Oral Solution 30 mg and matching placebo) preparation will be provided in the Pharmacy Manual.

10.2. Batch Formula for Stock SAGE-217 Oral Solution 6 mg/mL

Each bottle of SAGE-217 Oral Solution 6 mg/mL will be compounded at the clinical pharmacy from components manufactured by Pharmatek and supplied by the Sponsor per the directions provided in the Pharmacy Manual. The batch formula for a 125 mL solution of the 6 mg/mL stock solution is shown in [Table 5](#).

Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL

Ingredient	Compendia Specification	Concentration (mg/mL)	Amount (mg/Bottle)
SAGE-217	not applicable	6	750
HP β CD (Kleptose [®])	USP/EP	457	57,100
Sucralose	USP/NF	0.025	3.124
Water for Injection	USP	not applicable	85,650

Abbreviations: EP = European Pharmacopeia; HP β CD = hydroxypropyl- β -cyclodextrin; NF = National Formulary; USP = United States Pharmacopeia

Additional excipients will be utilized in matching placebo to match the taste of SAGE-217 Oral Solution. They include sucrose octaacetate, tannic acid, and ammonium glycyrrhizate. The quantities of these excipients will vary depending on the dose of SAGE-217 to match the taste of each individual dose.

10.3. Study Drug Packaging and Labeling

The composition and pharmaceutical quality of the investigational product will be maintained according to the current GMP and Good Clinical Practice (GCP) guidelines and available for review in the study medication documentation. Study drug will be provided to the site as powder in the bottle and excipient(s) in the bottle units to be compounded in the pharmacy at a volume of 125 mL of a 6 mg/mL stock solution and then further diluted to approximately 40 mL at the identified doses. The taste-matching excipients will be provided to the clinical pharmacies via suitable suppliers or can be ordered directly by the clinical pharmacies. Study drug labels with

all required information and conforming to all applicable Code of Federal Regulations and GMP/GCP guidelines will be prepared by the clinical research organization.

10.4. Study Drug Storage

Upon receipt of study drug, the Investigator or designee will inspect the materials and complete and return the acknowledgment of receipt form enclosed with the parcel. A copy of the signed receipt will be kept in the study files.

The study drug materials must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 11 days with room temperature excursions allowed for up to 24 hours after preparation), safely and separately from other drugs. The study drug may not be used for any purpose other than the present study. After the study is completed, all unused study drug must be retained, returned as directed, or destroyed on site per the Sponsor's instructions.

The Investigator or designee will be responsible for ensuring appropriate storage, compounding, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the Sponsor or the Sponsor's representatives on request, and must include the information below:

- The identification of the subject to whom the drug was dispensed;
- The date(s) and quantity of the drug dispensed to the subject; and
- The product lot/batch number.

The preparation of the study drugs must be documented on a 'Drug Preparation and Dispensing Log Form' or similar form.

The drug inventory and any clinical supplies that have been destroyed must be documented. This documentation must include at least the information below or as agreed with the Sponsor:

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

10.5. Administration and Study Drug Accountability

Doses will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water that has been used to rinse the dosing bottle. The start time of swallowing the approximately 40 mL oral solution is time zero for all assessments. Subjects may have assistance from the clinic staff when taking the study drug.

10.5.1. Study Drug Administration

While confined in the clinical unit (at least Day 1 through Day 7 of Part A and Part B), subjects will receive study drug at 8:00 PM (± 15 minutes) with food.

Food intake will be standardized as specified by the Sponsor. Subjects who experience moderate or severe related adverse events while receiving study drug may not be able to continue receiving study drug based on the evaluation and clinical judgment of the Investigator, and may be terminated from the study.

Subjects may be discharged after a minimum 7-day inpatient stay, following completion of the Day 7 assessments. If their clinical condition does not allow discharge, the Investigator may keep the subjects as inpatients for a longer period of time.

For non-confinement days (Days 8 through 14 of Parts A and B), dosing will be done at the clinical site or, if suitable arrangements can be made, via home administration where local regulations allow. Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.

10.5.2. Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator or designee must maintain a record of all study drug received, used, and discarded. It must be clear from the records which subject received which dose of active or matching placebo treatment.

The Sponsor will be permitted access to the study supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Only unblinded personnel will be able to access the study drug and accountability documentation from first dosing through database hard lock.

10.6. Study Drug Handling and Disposal

The pharmacist or designee for drug accountability is to document the date and time of initial compounding, subsequent admixture of dosing solutions, administration of test article, and for which subject the study drug was intended (ie, record subject initials and birth date or other unique identifier).

At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions. The disposition of study drug will be documented.

11. ASSESSMENT OF EFFICACY

11.1. Hamilton Rating Scale for Depression (HAM-D)

The primary outcome measure in Part B will be the change from baseline in 17-item HAM-D total score at the end of the Treatment Period (Day 15). The HAM-D will be administered before, during, and after the administration of open-label (Part A) and blinded (Part B) study drug.

The 17-item HAM-D will be used to rate the severity of depression in subjects who are already diagnosed as depressed ([Hamilton 1960](#)). 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 assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28. Every effort should be made for the same rater to perform all HAM-D assessments for an individual subject.

The HAM-D total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (ie, “Not assessed”).

In addition to the primary efficacy endpoint of change from baseline in HAM-D total score (Part B), 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 . A copy of the HAM-D is provided in [Appendix 1](#).

11.2. Montgomery-Åsberg Depression Rating Scale (MADRS)

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

The MADRS assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.

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 ([McDowell 2006](#); [Müller-Thomsen 2005](#)).

The questionnaire includes questions on the following symptoms:

1. Apparent sadness
2. Reported sadness

3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

The MADRS total score will be calculated as the sum of the 10 individual item scores. A copy of the MADRS is provided in [Appendix 2](#).

11.3. Hamilton Anxiety Rating Scale (HAM-A)

The 14-item HAM-A will be used to rate the severity of symptoms of anxiety ([Hamilton 1959](#)). 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 assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28. Every effort should be made for the same rater to perform all HAM-A assessments for an individual subject.

The HAM-A total score will be calculated as the sum of the 14 individual item scores. A copy of the HAM-A is provided in [Appendix 3](#).

11.4. Clinical Global Impression (CGI)

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

The Clinical Global Impression - Severity (CGI-S) uses a 7-point Likert scale to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating as 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=extremely ill. The CGI-S assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.

The CGI-I employs a 7-point Likert scale to measure the overall improvement in the subject's condition posttreatment. The Investigator will rate the subject's total improvement whether or not it is due entirely to drug treatment. Response choices include: 0=not assessed, 1=very much

improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse. 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.” The CGI-I assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28. A copy of the CGI is provided in [Appendix 4](#).

11.5. Short Form-36 (SF-36)

The SF-36[®] Health Survey is a subject-reported 36-item instrument for measuring functional health and well-being in eight dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) ([Ware 2007](#)). Scores are provided for each of the eight dimensions and are totaled into a Physical Component Summary and a Mental Component Summary. Higher SF-36 scores indicate a better state of health. The SF-36 requires approximately 10 minutes to complete, and can be self-administered or completed by interview in person or by telephone. In Part B, the SF-36 assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.

A copy of the SF-36 is provided in [Appendix 5](#).

11.6. The Fatigue Associated With Depression (FAs-D) Patient-Reported Outcome (PRO)

Fatigue is one of the most common symptoms of MDD. The Fatigue Associated with Depression Questionnaire (FAs-D) was developed to assess fatigue and its impact in patients with MDD. The 13-item patient-reported questionnaire was designed to assess fatigue associated with depression in the past week. Three scores are computed: a six-item fatigue experience subscale (fatigued, tired, exhausted, lack of energy, physically weak, and feeling like everything requires too much effort), a seven-item fatigue impact subscale (impact on household chores; family relationships; enjoyable activities; social activities with friends; self-care; intimate relationships; and productivity at work or school), and a total score (all 13 items). Items 12 (impact on intimate relationships) and 13 (impact on productivity at work or school) are not applicable to all subjects, so these items are not answered in some cases. The fatigue experience items are rated on a five-point scale with response options of “never,” “rarely,” “sometimes,” “often,” and “always.” The impact items are rated on a five-point scale with response options of “not at all,” “a little,” “somewhat,” “quite a bit,” and “very much.” The two subscales and the total score are computed as the mean of all answered items within each scale, and each scale score has a possible range of 1 to 5, with higher scores representing greater fatigue. In Part B, the FAs-D assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.

A copy of the FAs-D is provided in [Appendix 6](#).

12. PHARMACOKINETICS

12.1. Blood Sample Collection

Plasma samples for PK analysis in Part A and Part B will be collected predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. The Investigator or designee will arrange to have the plasma samples processed, stored, and transported as directed for bioanalysis.

In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. An additional PK sample may be collected at any time if clinically indicated and at the discretion of the Investigator (eg, for unusual or severe adverse events).

Each sample will be marked with unique identifiers such as the study number, subject number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the CRF or electronically with a bar code or other method.

12.2. Storage and Shipment of Pharmacokinetic Samples

The plasma samples should be kept frozen at approximately -70 to -80°C until analyzed. They should be packed as directed to avoid breakage during transit and with sufficient dry ice to prevent thawing for at least 72 hours. A specimen-identification form must be completed and sent to the laboratory with each set of samples. The clinical site will arrange to have the plasma samples transported as directed for bioanalysis as detailed in the PK instructions.

12.3. Sample Analysis

Bioanalysis of plasma samples for the determination of SAGE-217 will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.

13. ASSESSMENT OF SAFETY

13.1. Safety Parameters

Safety and tolerability of study drug will be evaluated in Parts A and B by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, SSS, and adverse event reporting.

13.1.1. Demographic/Medical History

Age, race, and ethnic origin will be recorded at the Screening visit. The diagnosis of MDD will be determined using the SCID-I.

13.1.2. Vital Signs

Vital signs include respiratory rate, oral temperature, and supine (for at least 5 minutes prior to the measurement) and standing systolic and diastolic blood pressure and heart rate. Vital signs will be obtained within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 30 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between the hours of 23:00 h and 06:00 h.

From Day 1 through Day 7, vital signs and pulse oximetry will be performed at screening (vital signs only) and at the following time points: predose, 0.25, 0.5, 1, 2, and 12 hours after dosing. During the outpatient treatment period, vital signs will be completed prior to dosing and 1 hour after dosing. Vital signs may be repeated at the discretion of the Investigator or Visiting Home Healthcare Provider as clinically indicated.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visit; weight will also be measured on in the morning on Day 15, and during the follow-up visits on Days 21 and 28.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening visit, Day 8, Day 15, and Day 21, with a brief physical examination on Day 28.

13.1.5. Electrocardiogram (ECG)

A 12-lead ECG will be assessed at the Screening visit and 1 hour ± 15 minutes after dosing on Days 1, 2, 7, and 14 and during the follow-up visit on Day 21. All time points are relative to the time of dosing. The standard intervals as well as any abnormalities will be recorded.

13.1.6. Laboratory Assessments

Blood and urine samples will be collected for hematology, serum chemistry, coagulation, select hormone parameters, and urinalysis at the Screening visit, and in the morning on Days 8 and 15 and during the follow-up visits on Days 21 and 28. Where consent is given, an optional blood sample for hormone and exploratory biochemistry testing and optional genetic sample for biomarker testing will be collected at the Screening visit.

Serum and urine samples for pregnancy tests will also be collected. These assessments should be performed as outlined below.

All samples will be analyzed at the central laboratory. Subjects may be considered eligible for the study based on local laboratory results; however, screening samples must also be sent to the central laboratory.

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant (NCS) or abnormal, clinically significant (CS). Screening results considered abnormal, CS recorded at the Screening visit may make the subject ineligible for the study pending review by the Medical Monitor. Clinical laboratory results that are abnormal, CS during the study but within normal range at baseline and/or indicate a worsening from baseline will be considered adverse events, assessed according to [Section 13.2.1](#), and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count, including red blood cells, white blood cells with differentiation, hemoglobin, hematocrit, reticulocytes, and platelets. The coagulation panel will include activated partial thromboplastin time, prothrombin time, and international normalized ratio.

13.1.6.2. Blood Chemistry

Serum chemistry tests will include serum electrolytes; renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide; liver function tests, including total bilirubin, aspartate aminotransferase, and alanine aminotransferase; total protein; and albumin.

13.1.6.3. Urinalysis

Urinalysis will include assessment of protein, blood, glucose, ketones, bile, urobilinogen, hemoglobin, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity.

13.1.6.4. Hormones and Exploratory Biochemistry

Optional blood samples will be collected and may be analyzed for stress hormone levels, kynurenine biochemistry, and markers of inflammation. Future research may suggest other biochemical pathways as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the exploratory biochemistry may involve study of additional unnamed molecular pathways, but only as related to disease susceptibility and drug action.

13.1.6.5. Virus Serology

Subjects will be screened for hepatitis (HBsAg and anti-HCV) and HIV prior to being enrolled in the study.

13.1.6.6. Pregnancy Test

Females of childbearing potential will be tested for pregnancy by serum pregnancy test at the Screening visit and by urine pregnancy test on Day 1 (predose) and at the follow-up visit on

Day 28. In addition, female subjects who prematurely discontinue before Day 28 will have a pregnancy test performed at the early termination visit.

13.1.6.7. Genetic Testing

Where consent is given, an optional genetic sample for biomarker testing will be collected at the Screening visit.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (ie, distribution, safety, tolerability, and efficacy) to SAGE-217. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (eg, cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of SAGE-217 (eg, AKR1C4 [3 α -hydroxysteroid dehydrogenase]), genes associated with the γ -aminobutyric acid (GABA) receptor (eg, GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3), and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

13.1.6.8. Drugs of Abuse and Alcohol

A urine sample for assessment of selected drugs of abuse (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene) and a serum or breath sample for alcohol screen will be collected at screening and predose on Day 1. Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics that have been initiated at least 14 days prior to admission to the study center at a stable dose following discussion with the Sponsor (see [Section 9.3](#)).

13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the study using the C-SSRS ([Posner 2011](#)). This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicidal ideation and behavior, and a post-baseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes ‘yes’ or ‘no’ responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

If, in the opinion of the Investigator, the subject is showing clinically meaningful changes in suicidality, no further study drug will be administered and the subject will be referred to a psychologist or psychiatrist for further evaluation. This information will be tracked.

The “Baseline/Screening” C-SSRS form will be completed at screening (lifetime history and past 24 months). The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points, as outlined in [Table 2](#) and [Table 3](#). The C-SSRS is provided in [Appendix 5](#).

13.1.8. Stanford Sleepiness Scale (SSS)

The SSS is subject-rated scale designed to quickly assess how alert a subject is feeling. Degrees of sleepiness and alertness are rated on a scale of 1 to 7, where the lowest score of '1' indicates the subject is 'feeling active, vital, alert, or wide awake' and the highest score of '7' indicates the subject is 'no longer fighting sleep, sleep onset soon; having dream-like thoughts'.

In both Part A and Part B, from Day 1 through Day 7, SSS will be completed at the following time points: predose, 0.25, 0.5, 1, and 2 after dosing. The scale is to be completed within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between 23:00 h and 06:00 h during the inpatient treatment period. During the outpatient treatment period, SSS will be completed prior to dosing and 1 hour after dosing. All time points are relative to the time of dosing. The SSS is provided in [Appendix 8](#).

13.2. Adverse and Serious Adverse Events

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

13.2.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

13.2.1.3. Serious Adverse Event

A serious adverse event is an adverse event occurring during any study phase and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- It results in death
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- It results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All serious adverse events that occur after any subject has been enrolled, whether or not they are related to the study, must be recorded for the duration of the study on forms provided by Sage Therapeutics or designee.

13.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each adverse event (unrelated, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered “related.”

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

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

13.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as adverse events unless they prompt corrective medical action by the Investigator, constitute a serious adverse event, or lead to discontinuation of administration of study drug.

Information about adverse events will be collected from the signing of the ICF until the final visit of the study for that subject. Adverse events that occur after the first administration of study drug will be denoted TEAEs.

All adverse events will be followed until they are resolved or have reached a clinical plateau with no expectation of future change.

The adverse event term should be reported in standard medical terminology when possible. For each adverse event, the Investigator will evaluate and report the onset (date and time), resolution or clinical plateau (date and time), severity, causality, action taken, outcome, and whether or not it caused the subject to discontinue the study.

Severity will be assessed according to the following scale:

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

13.5. Reporting Adverse Events

All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day 28 follow-up visit. Any serious adverse events considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All serious adverse events must be reported to the Sponsor or Sponsor's designee immediately by phone and in writing within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the serious adverse event pages, verify the accuracy of the information recorded on the serious adverse event pages with the corresponding source documents, and send a copy to Sage Therapeutics or designee.

Additional follow-up information, if required or available, should be sent to Sage Therapeutics or designee within 24 hours of receipt; a follow-up serious adverse event form should be completed and placed with the original serious adverse event information and kept with the appropriate section of the study file.

Sage Therapeutics or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB of all serious adverse events that occur at his or her site if applicable per the IRB's requirements. Investigators will also be notified of all unexpected, serious, drug-related events (7-/15-Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB of these additional serious adverse events.

13.6. Emergency Identification of Study Drug

Part B of the study is double-blind. The pharmacist responsible for preparing the solutions will be unblinded and will retain an official paper copy of the randomization schedule. In addition, an unblinded Monitor will perform drug accountability during the study.

During the study, the blind is to be broken only when the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. Unless a subject is at immediate risk, the Investigator must make diligent attempts to contact the Sponsor prior to unblinding the study treatment administered to a subject. Any request from the Investigator about the treatment administered to study subjects must be discussed with the Sponsor. If the unblinding occurs without the Sponsor's knowledge, the Investigator must notify the Sponsor as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented in the source records. Unless a subject is at immediate risk, any request for the unblinding of individual subjects must be made in writing to the Sponsor and approved by the appropriate Sponsor personnel, according to standard operating procedures. The blinding of the study will be broken after the database has been locked. Electronic copies of the randomization code will be made available to the laboratory performing the bioanalytical analyses in order to allow for limited analysis of samples from subjects receiving matching placebo.

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

14. STATISTICS

14.1. Data Analysis Sets

14.1.1. Analysis Populations and Methods

The Safety Population (for both Part A and Part B), defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Population (for both Part A and Part B), defined as all subjects in the Safety Population who complete at least 1 day of dosing of study drug and have at least one post-baseline efficacy evaluation, will be used to analyze efficacy data.

The PK Population will consist of all subjects in the Safety Population with sufficient plasma concentrations for PK evaluations, and will be used to summarize PK data.

14.2. Handling of Missing Data

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

14.3. General Considerations

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

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

14.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized using the Safety Population.

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

Medical/family history will be listed by subject.

14.5. Efficacy Analyses

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data. For (the open-label) Part A, efficacy data will be summarized descriptively. For Part B, subjects will be analyzed according to randomized treatment.

An analysis of ten subjects completing Part A is planned to inform Part B study conduct.

For Part B of the study, change from baseline to each assessment in HAM-D total score will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include center, treatment, baseline HAM-D total score, antidepressant use strata, assessment time point, and time point-by-treatment as explanatory variables. Center will be treated as a random effect while all other explanatory variables will be treated as fixed effects. All post-baseline time points will be included in the model. The main comparison will be between SAGE-217 Oral Solution and matching placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means), 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. Compound symmetry covariance structure will be used if there is a convergence issue with the unstructured covariance model.

Descriptive statistics for HAM-D total score and change from baseline values will be presented by assessment time point for Part A. Summaries will include n, mean, SD, median, minimum, and maximum.

Similar to those methods described above for Part B, an MMRM will be used for the analysis of the following variables: changes from baseline in MADRS total score and HAM-A total score, and select individual item and subscale scores. For each model, the comparison of interest will be between SAGE-217 Oral Solution and matching placebo at the 15-day time point. Model-based point estimates (ie, LS means), 95% confidence intervals, and p-values will be reported.

Logistic regression methods will be used for the analysis of the following binary variables: HAM-D response (defined as $\geq 50\%$ reduction from baseline in HAM-D total score), HAM-D remission (defined as HAM-D total score of ≤ 7.0), and CGI-I response. Logistic regression models will include terms for center, treatment, antidepressant use strata, and baseline score. The comparison of interest will be the difference between SAGE-217 Oral Solution and matching placebo at the 15-day time point in Part B. Model-based point estimates (ie, odds ratios), 95% confidence intervals, and p-values will be reported. For the CGI-I response analysis, baseline CGI-S score will be included in the model.

For all scores, descriptive statistics, change from baseline values, and response variables will be presented by treatment and assessment time point. Summaries will include n, mean, SD, median, minimum, and maximum.

Similar to the main comparison of HAM-D total score in Part B, descriptive summary statistics will be provided and an MMRM model will be used to analyze the change from baseline in SF-36 and FAs-D.

14.6. Safety Analyses

Safety and tolerability of study drug will be evaluated by adverse events, concomitant medication usage, changes from baseline in physical examination, vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Sedation will be assessed using the SSS. Safety data will be listed by subject and summarized by treatment group. All safety summaries will be performed on the Safety Population.

14.6.1. Adverse Events

The analysis of adverse events will be based on the concept of TEAEs. A TEAE is defined as an adverse event with onset after the start of study drug, or any worsening of a pre-existing medical condition/adverse event with onset after the start of study drug and until 7 days after the last dose. The incidence of TEAEs will be summarized overall and by Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or higher System Organ Class (SOC) and preferred term. Incidences will be presented in order of decreasing frequency for the SAGE-217 Oral Solution treatment group. In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see [Section 13.3](#)).

Treatment-emergent adverse events leading to discontinuation and serious adverse events (see [Section 13.2.1.3](#) for definition) with onset after the start of randomized study drug will also be summarized.

All adverse events and serious adverse events (including those with onset or worsening before the start of study drug) through the Day 28 follow-up visit will be listed.

14.6.2. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline in clinical laboratory measures will be summarized.

14.6.3. Physical Examinations

Physical examinations in Parts A and B will be summarized at the Screening visit, Day 8, Day 15, Day 21, and Day 28 visits. Any clinically significant change in physical examination compared to those observed at screening should be noted as an adverse event.

14.6.4. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from randomization in vital signs will be summarized by time point.

14.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, QTc, and QT interval calculated using the Fridericia method (QTcF). Any clinically significant abnormalities or changes in ECGs should be listed as an adverse event. Electrocardiogram findings will be listed by subject and visit.

14.6.6. 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.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken during the 30 days prior to informed consent. Concomitant medications are defined as those with a start date on or after the first dose of study drug, or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug. If medication dates are

incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

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

14.6.7. Columbia Suicide Severity Rating Scale

Suicidality data collected on the C-SSRS at baseline and by visit during the Treatment Period will be listed for all subjects. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

14.6.8. Stanford Sleepiness Scale

Sedation data collected on the SSS will be listed for all subjects. Changes in score over time will be represented graphically, and change from Day 1 will be measured.

14.7. Pharmacokinetic Analyses

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics. Time at maximum (peak) plasma concentration (t_{max}) will be summarized using n, mean, SD, median, minimum, and maximum. All other PK parameters will be summarized using n, geometric mean, coefficient of variation, median, minimum, and maximum and listed by subject.

Plasma concentrations and PK parameters will be listed by subject.

In addition to typical descriptive statistics, summaries should include geometric mean, coefficient of variation, and geometric coefficient of variation.

14.8. Determination of Sample Size

The sample size of ten subjects for Part A was selected based on clinical and not statistical considerations.

For Part B, assuming a two-sided t-test at an alpha level of 0.10, a sample size of 23 subjects per group would provide 80% power to detect an effect size of 0.75 between the SAGE-217 Oral Solution and matching placebo groups with regard to the secondary efficacy outcome variable of change from baseline in HAM-D total score. An effect size of 0.75 corresponds to a matching placebo-adjusted difference of 7.5 points in the change from baseline in HAM-D total score at 15 days with an assumed SD of 10 points. By including two treatment groups and using a 1:1 randomization, a total of 46 subjects are required. Assuming a non-evaluability rate of 10%, up to 52 subjects will be randomized.

14.9. Changes From Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final statistical analysis plan.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Sage Therapeutics or designee will visit the investigational study site to:

- Determine the adequacy of the facilities; and
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sage Therapeutics or designee or its representatives. This will be documented in a Clinical Study Agreement between Sage Therapeutics and the Investigator.

During the study, a monitor from Sage Therapeutics or designee 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 eCRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts);
- Record and report any protocol deviations not previously sent to Sage Therapeutics or designee; and
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to Sage Therapeutics or designee and those serious adverse events that met criteria for reporting have been forwarded to the IRB.

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

15.2. Audits and Inspections

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

15.3. Institutional Review Board (IRB)

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

16. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator and institution will permit study-related monitoring, audits, IRB review, and regulatory inspections as requested by the Food and Drug Administration, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs) in addition to eCRFs.

Quality assurance and quality-control systems with written standard operating procedures will be followed to ensure this study will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality-assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements made by the Sponsor with the Investigator/institution and any other parties involved with the clinical study will be in writing in a separate agreement.

17. ETHICS

17.1. Ethics Review

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

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 subjects 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 with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sage Therapeutics or designee 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.

17.2. 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 its most recent amendment (2008) and are consistent with ICH/GCP and other applicable regulatory requirements.

17.3. Written Informed Consent

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

As additional assessments, the ICF will contain provisions for optional consent for the collection of blood samples for hormone and biomarker testing during screening and the collection of breast milk for biobanking and PK analysis purposes. The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

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

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

18. DATA HANDLING AND RECORDKEEPING

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

Electronic CRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, and subject status.

The Investigator will have access to the electronic data capture system and will receive a copy of the subject eCRF data at the end of the study. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

18.1. Inspection of Records

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

18.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuation of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18.3. Confidentiality

To maintain subject privacy, all eCRFs, study reports, and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

19. 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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21. APPENDICES

APPENDIX 1. HAMILTON RATING SCALE FOR DEPRESSION, 17-ITEM (HAM-D)

Patient Name: _____

Date: _____

Hamilton Rating Scale for Depression (17-items)

Instructions: For each item select the "cue" which best characterizes the patient during the past week.

1. **Depressed Mood**
(sadness, hopeless, helpless, worthless)
 - 0 Absent
 - 1 These feeling states indicated only on questioning
 - 2 These feeling states spontaneously reported verbally
 - 3 Communicates feeling states nonverbally, i.e., through facial expression, posture, voice and tendency to weep
 - 4 Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and nonverbal communication
2. **Feelings of Guilt**
 - 0 Absent
 - 1 Self-reproach, feels he has let people down
 - 2 Ideas of guilt or rumination over past errors or sinful deeds
 - 3 Present illness is a punishment. Delusions of guilt
 - 4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3. **Suicide**
 - 0 Absent
 - 1 Feels life is not worth living
 - 2 Wishes he were dead or any thoughts of possible death to self
 - 3 Suicide ideas or gesture
 - 4 Attempts at suicide (any serious attempt rates 4)
4. **Insomnia - Early**
 - 0 No difficulty falling asleep
 - 1 Complains of occasional difficulty falling asleep i.e., more than ½ hour
 - 2 Complains of nightly difficulty falling asleep
5. **Insomnia - Middle**
 - 0 No difficulty
 - 1 Patient complains of being restless and disturbed during the night
 - 2 Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)
6. **Insomnia - Late**
 - 0 No difficulty
 - 1 Waking in early hours of the morning but goes back to sleep
 - 2 Unable to fall asleep again if gets out of bed
7. **Work and Activities**
 - 0 No difficulty
 - 1 Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
 - 2 Loss of interest in activity; hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
 - 3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores.
 - 4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted.
8. **Retardation**
(slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
 - 0 Normal speech and thought
 - 1 Slight retardation at interview
 - 2 Obvious retardation at interview
 - 3 Interview difficult
 - 4 Complete stupor
9. **Agitation**
 - 0 None
 - 1 "Playing with" hand, hair, etc.
 - 2 Hand-wringing, nail-biting, biting of lips
10. **Anxiety - Psychic**
 - 0 No difficulty
 - 1 Subjective tension and irritability
 - 2 Worrying about minor matters
 - 3 Apprehensive attitude apparent in face or speech
 - 4 Fears expressed without questioning
11. **Anxiety - Somatic**
 - 0 Absent Physiological concomitants of anxiety such as:
 - 1 Mild Gastrointestinal - dry mouth, wind, indigestion,
 - 2 Moderate diarrhea, cramps, belching
 - 3 Severe Cardiovascular – palpitations, headaches
 - 4 Incapacitating Respiratory - hyperventilation, sighing
Urinary frequency
Sweating
12. **Somatic Symptoms - Gastrointestinal**
 - 0 None
 - 1 Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
 - 2 Difficulty eating without staff urging. Requests or requires laxatives or medications for bowels or medication for G.I. symptoms.
13. **Somatic Symptoms - General**
 - 0 None
 - 1 Heaviness in limbs, back or head, backaches, headache, muscle aches, loss of energy and fatigability
 - 2 Any clear-cut symptom rates 2
14. **Genital Symptoms**
 - 0 Absent 0 Not ascertained
 - 1 Mild Symptoms such as: loss of libido,
 - 2 Severe menstrual disturbances
15. **Hypochondriasis**
 - 0 Not present
 - 1 Self-absorption (bodily)
 - 2 Preoccupation with health
 - 3 Frequent complaints, requests for help, etc.
 - 4 Hypochondriacal delusions
16. **Loss of Weight**
 - A. When Rating by History:
 - 0 No weight loss
 - 1 Probable weight loss associated with present illness
 - 2 Definite (according to patient) weight loss
 - B. On Weekly Ratings by Ward Psychiatrist, When Actual Changes are Measured:
 - 0 Less than 1 lb. weight loss in week
 - 1 Greater than 1 lb. weight loss in week
 - 2 Greater than 2 lb. weight loss in week
17. **Insight**
 - 0 Acknowledges being depressed and ill
 - 1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
 - 2 Denies being ill at all

Total Score: _____

APPENDIX 2. MONTGOMERY-ÅSBERG DEPRESSION RATING SCALE (MADRS)

Montgomery-Åsberg Depression Rating Scale (MADRS)

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5) and then report the appropriate number. The items should be rated with regards to how the patient has done over the past week.

1. Apparent sadness

Representing despondency, gloom and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

- 0 = No sadness.
- 2 = Looks dispirited but does brighten up without difficulty.
- 4 = Appears sad and unhappy most of the time.
- 6 = Looks miserable all the time. Extremely despondent

2. Reported sadness

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.

- 0 = Occasional sadness in keeping with the circumstances.
- 2 = Sad or low but brightens up without difficulty.
- 4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
- 6 = Continuous or unvarying sadness, misery or despondency.

3. Inner tension

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

- 0 = Placid. Only fleeting inner tension.
- 2 = Occasional feelings of edginess and ill-defined discomfort.
- 4 = Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
- 6 = Unrelenting dread or anguish. Overwhelming panic.

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

- 0 = Sleeps as normal.
- 2 = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- 4 = Moderate stiffness and resistance
- 6 = Sleep reduced or broken by at least 2 hours.

5. Reduced appetite

Representing the feeling of a loss of appetite compared with when-well. Rate by loss of desire for food or the need to force oneself to eat.

- 0 = Normal or increased appetite.
- 2 = Slightly reduced appetite.
- 4 = No appetite. Food is tasteless.
- 6 = Needs persuasion to eat at all.

6. Concentration difficulties

Representing difficulties in collecting one's thoughts mounting to an incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

- 0 = No difficulties in concentrating.
- 2 = Occasional difficulties in collecting one's thoughts.
- 4 = Difficulties in concentrating and sustaining thought which reduced ability to read or hold a conversation.
- 6 = Unable to read or converse without great difficulty.

7. Lassitude

Representing difficulty in getting started or slowness in initiating and performing everyday activities.

- 0 = Hardly any difficulty in getting started. No sluggishness.
- 2 = Difficulties in starting activities.
- 4 = Difficulties in starting simple routine activities which are carried out with effort.
- 6 = Complete lassitude. Unable to do anything without help.

8. Inability to feel

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- 0 = Normal interest in the surroundings and in other people.
- 2 = Reduced ability to enjoy usual interests.
- 4 = Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- 6 = The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

- 0 = No pessimistic thoughts.
- 2 = Fluctuating ideas of failure, self-reproach or self-depreciation.
- 4 = Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
- 6 = Delusions of ruin, remorse or irredeemable sin. Self-accusations which are absurd and unshakable.

10. Suicidal thoughts

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.

- 0 = Enjoys life or takes it as it comes.
- 2 = Weary of life. Only fleeting suicidal thoughts.
- 4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- 6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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APPENDIX 3. HAMILTON ANXIETY RATING SCALE (HAM-A)

Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

<p>1 Anxious mood <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Worries, anticipation of the worst, fearful anticipation, irritability.</p>	<p>8 Somatic (sensory) <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.</p>
<p>2 Tension <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.</p>	<p>9 Cardiovascular symptoms <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.</p>
<p>3 Fears <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.</p>	<p>10 Respiratory symptoms <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Pressure or constriction in chest, choking feelings, sighing, dyspnea.</p>
<p>4 Insomnia <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.</p>	<p>11 Gastrointestinal symptoms <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.</p>
<p>5 Intellectual <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Difficulty in concentration, poor memory.</p>	<p>12 Genitourinary symptoms <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.</p>
<p>6 Depressed mood <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.</p>	<p>13 Autonomic symptoms <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.</p>
<p>7 Somatic (muscular) <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.</p>	<p>14 Behavior at interview <input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4</p> <p>Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.</p>

APPENDIX 4. CLINICAL GLOBAL IMPRESSION–IMPROVEMENT SCALE (CGI-I) AND SEVERITY SCALE (CGI-S)

1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- | | |
|-----------------------------|---|
| 0 = Not assessed | 4 = Moderately ill |
| 1 = Normal, not at all ill | 5 = Markedly ill |
| 2 = Borderline mentally ill | 6 = Severely ill |
| 3 = Mildly ill | 7 = Among the most extremely ill patients |

2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- | | |
|------------------------|---------------------|
| 0 = Not assessed | 4 = No change |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved | 6 = Much worse |
| 3 = Minimally improved | 7 = Very much worse |

3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

APPENDIX 5. SHORT-FORM 36 (SF-36)

SF-36 QUESTIONNAIRE

Name: _____ Ref. Dr: _____ Date: _____
ID#: _____ Age: _____ Gender: M / F

Please answer the 36 questions of the Health Survey completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

Compared to one year ago, how would you rate your health in general now?

☐ Much better now than one year ago
☐ Somewhat better now than one year ago
☐ About the same
☐ Somewhat worse now than one year ago
☐ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Lifting or carrying groceries

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing several flights of stairs

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing one flight of stairs

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bending, kneeling, or stooping

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking more than a mile

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking several blocks

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking one block

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bathing or dressing yourself

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

☐ Yes ☐ No

Accomplished less than you would like

☐ Yes ☐ No

Were limited in the kind of work or other activities

☐ Yes ☐ No

Had difficulty performing the work or other activities (for example, it took extra effort)

☐ Yes ☐ No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

☐ Yes ☐ No

Accomplished less than you would like

☐ Yes ☐ No

Didn't do work or other activities as carefully as usual

☐ Yes ☐ No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

☐ Not at all ☐ Slightly ☐ Moderately ☐ Severe ☐ Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

☐ None ☐ Very Mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

ENERGY AND EMOTIONS:

These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you been a very nervous person?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you felt so down in the dumps that nothing could cheer you up?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you felt calm and peaceful?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Did you have a lot of energy?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you felt downhearted and blue?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Did you feel worn out?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you been a happy person?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Did you feel tired?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

SOCIAL ACTIVITIES:

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

GENERAL HEALTH:

How true or false is each of the following statements for you?

I seem to get sick a little easier than other people

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

I am as healthy as anybody I know

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

I expect my health to get worse

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

My health is excellent

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

APPENDIX 6. THE FATIGUE ASSOCIATED WITH DEPRESSION (FAs-D) PATIENT-REPORTED OUTCOME (PRO)

Some people experience fatigue when they are depressed. The following items ask you to rate fatigue you have experienced that you think may be related to depression.

In the PAST WEEK, how often have you felt...	<i>Never</i>	<i>Rarely</i>	<i>Sometimes</i>	<i>Often</i>	<i>Always</i>
1. Fatigued	1	2	3	4	5
2. Tired	1	2	3	4	5
3. Exhausted	1	2	3	4	5
4. Like you had no energy	1	2	3	4	5
5. Physically weak	1	2	3	4	5
6. Slowed down	1	2	3	4	5
7. Like everything requires too much effort	1	2	3	4	5

Now think about the impact of this fatigue that is related to depression. The following items ask about the impact of this fatigue on various aspects of your life.

In the PAST WEEK, how much has your fatigue...	<i>Not at all</i>	<i>A little</i>	<i>Somewhat</i>	<i>Quite a bit</i>	<i>Very much</i>
8. Limited your ability to complete daily household chores	1	2	3	4	5
9. Interfered with family activities or relationships	1	2	3	4	5
10. Interfered with doing things you enjoy	1	2	3	4	5
11. Interfered with social activities, like spending time with friends	1	2	3	4	5
12. Interfered with taking care of yourself (e.g., bathing, dressing, brushing your teeth)	1	2	3	4	5
13. Kept you from getting out of bed	1	2	3	4	5

Do you have a spouse or significant other? ☐ Yes ☐ No

If no, leave item 14 blank.

If yes, please answer item 14.

In the PAST WEEK, how much has your fatigue...	<i>Not at all</i>	<i>A little</i>	<i>Somewhat</i>	<i>Quite a bit</i>	<i>Very much</i>
14. Interfered with your intimate relationship (i.e., with a spouse or significant other)	1	2	3	4	5

Do you have a job or go to school? ☐ Yes ☐ No

If no, leave items 15 and 16 blank.

If yes, please answer items 15 and 16.

In the past week, how much has your fatigue...	<i>Not at all</i>	<i>A little</i>	<i>Somewhat</i>	<i>Quite a bit</i>	<i>Very much</i>
15. Prevented you from going to work or school	1	2	3	4	5
16. Limited your productivity at work or school	1	2	3	4	5

APPENDIX 7. COLUMBIA - SUICIDE SEVERITY RATING SCALE (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

***Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;
Burke, A.; Oquendo, M.; Mann, J.***

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION			
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.		Lifetime: Time He/She Felt Most Suicidal	Past ___ Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i> If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i> If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <i>Have you been thinking about how you might do this?</i> If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i> If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i> If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
INTENSITY OF IDEATION			
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.			
Lifetime - Most Severe Ideation: _____ Type # (1-5) Description of Ideation		Most Severe	Most Severe
Past X Months - Most Severe Ideation: _____ Type # (1-5) Description of Ideation			
Frequency <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		_____	_____
Duration <i>When you have the thoughts how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time		_____	_____
Controllability <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (6) Does not attempt to control thoughts		_____	_____
Deterrents <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (6) Does not apply		_____	_____
Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (6) Does not apply		_____	_____

SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)		Lifetime	Past __ Years
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i> . Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <i>any</i> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <i>There does not have to be any injury or harm</i> , just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? What did you do? Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to end your life when you _____? Or Did you think it was possible you could have died from _____? Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of Attempts _____	Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior? Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of interrupted _____	Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of aborted _____	Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
Suicidal Behavior: Suicidal behavior was present during the assessment period?		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
Answer for Actual Attempts Only		Most Recent Attempt Date:	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death		Enter Code _____	Enter Code _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care		Enter Code _____	Enter Code _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

***Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;
Burke, A.; Oquendo, M.; Mann, J.***

Disclaimer:

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*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

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SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.		Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <i>Have you been thinking about how you might do this?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).		Most Severe
Most Severe Ideation: _____ <div style="display: flex; justify-content: space-between;"> Type # (1-5) Description of Ideation </div>		
Frequency <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		_____
Duration <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time		_____
Controllability <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (6) Does not attempt to control thoughts		_____
Deterrents <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (6) Does not apply		_____
Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (6) Does not apply		_____

SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)		Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i> . Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm , just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? <i>What did you do?</i> <i>Did you _____ as a way to end your life?</i> <i>Did you want to die (even a little) when you _____?</i> <i>Were you trying to end your life when you _____?</i> <i>Or did you think it was possible you could have died from _____?</i> Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of Attempts _____ Yes No <input type="checkbox"/> <input type="checkbox"/>	
Has subject engaged in Non-Suicidal Self-Injurious Behavior? Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of interrupted _____	
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of aborted _____	
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No <input type="checkbox"/> <input type="checkbox"/>	
Suicide:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
Answer for Actual Attempts Only		Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	Enter Code _____	
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with on coming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	Enter Code _____	

APPENDIX 8. STANFORD SLEEPINESS SCALE (SSS)

Stanford Sleepiness Scale

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	Scale Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X



PROTOCOL NUMBER: 217-MDD-201
A PHASE 2, TWO-PART (OPEN-LABEL FOLLOWED BY
DOUBLE-BLIND) STUDY EVALUATING THE SAFETY,
TOLERABILITY, PHARMACOKINETICS, AND
EFFICACY OF SAGE-217 IN THE TREATMENT OF
ADULT SUBJECTS WITH MODERATE TO SEVERE
MAJOR DEPRESSIVE DISORDER

IND NUMBER: 132,131

Investigational Product	SAGE-217
Clinical Phase	2a
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	George Nomikos, M.D., Ph.D. Senior Medical Director Phone: 617-949-2881 George.Nomikos@sagerx.com
Sponsor Medical Monitor	Handan Gunduz-Bruce, M.D., M.B.A. Medical Director Phone: 203-500-9240 Handan.Gunduz-Bruce@sagerx.com
Date of Original Protocol	Version 1.0, 24 October 2016
Date of Amendment One	Version 2.0, 13 January 2017
Date of Amendment Two	Version 3.0, 09 March 2017
Date of Amendment Three	Version 4.0, 06 June 2017
Date of Amendment Four	Version 5.0, 12 July 2017

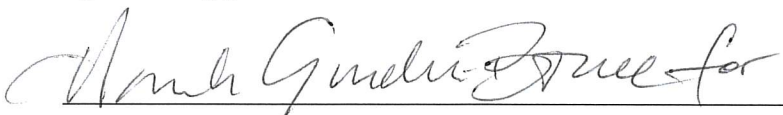
Confidentiality Statement

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

PROTOCOL SIGNATURE PAGE

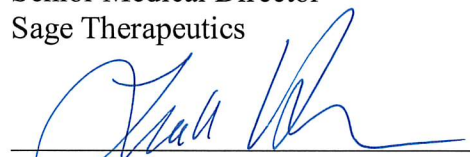
Protocol Number: 217-MDD-201
Product: SAGE-217 Oral Solution (Part A)
SAGE-217 Capsules (Part B)
IND No.: 132,131
Study Phase: 2a
Sponsor: Sage Therapeutics
Date of Amendment Four: Version 5.0 12 July 2017

Sponsor Approval

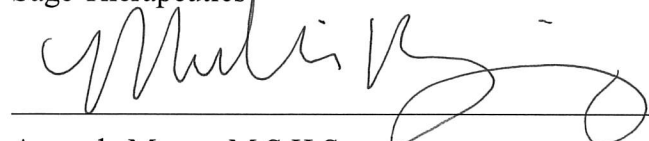
 12 July 2017

George Nomikos, M.D., Ph.D.
Senior Medical Director
Sage Therapeutics


Date (DD/MMM/YYYY)


Lisa A. Herman, Pharm.D, M.S., R.Ph.
Director of Regulatory Affairs
Sage Therapeutics

12 July 2017
Date (DD/MMM/YYYY)

 for
Amanda Moore, M.S.H.S.
Associate Director of Clinical Operations and Development
Sage Therapeutics

12 July 2017
Date (DD/MMM/YYYY)

 for
Haihong Li, Ph.D.
Director, Biostatistics
Sage Therapeutics

12 July 2017
Date (DD/MMM/YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-MDD-201 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

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Research Organization	INC Research	INC Research 3201 Beechleaf Ct., Suite 600 Raleigh, NC 27604 USA 1-877-462-0134

2. SYNOPSIS

Name of Sponsor/Company: Sage Therapeutics 215 First Street Cambridge, MA 02142
Name of Investigational Product: SAGE-217 Oral Solution (Part A) SAGE-217 Capsules (Part B)
Name of Active Ingredient: SAGE-217
Title of Study: A Phase 2, Two-Part (Open-Label Followed by Double-Blind) Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Adult Subjects with Moderate to Severe Major Depressive Disorder
Study centers: Approximately 3 sites in Part A and approximately 15 sites in Part B
Phase of development: 2a
Methodology: <p>This study will assess the safety, tolerability, pharmacokinetics (PK), and efficacy of SAGE-217 Oral Solution (Part A) and SAGE-217 Capsules (Part B) in adult subjects diagnosed with moderate to severe major depressive disorder (MDD).</p> <p>There are two parts to the study:</p> <ul style="list-style-type: none">• Part A: Open-label dosing with SAGE-217 Oral Solution (14 days). All subjects will receive a 30-mg dose of SAGE-217 Oral Solution administered at 8:00 PM (± 15 minutes) with food on Day 1 to Day 14, as tolerated. Part A will consist of an up to 7-day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 2-week Follow-up Period.• Part B: Randomized, double-blind, parallel-group, placebo-controlled (14 days). Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomized within each stratum in a 1:1 ratio to receive SAGE-217 Capsules (30 mg) or matching placebo for 14 days beginning on Day 1, as tolerated. All doses of study drug will be administered at 8:00 PM (± 15 minutes) with food. Part B will consist of an up to 14-day Screening Period (Days -14 to -1), a 14-day Treatment Period, and a 4-week Follow-up Period. <p>Dose adjustments based on tolerability are detailed in Section 9.3.</p> <p>Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B. Part B may be initiated and enrollment into Part A stopped if there is a clear signal of activity based on the 17-item Hamilton Rating Scale for Depression (HAM-D) scores and/or other scales being assessed.</p> <p>During the 14-day study Treatment Period, subjects must remain inpatient for the first 7 days at minimum and per Investigator's judgement thereafter.</p> <p>Screening Period: The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit, which can occur on any two consecutive calendar days of the 7-day (Part A) or 14-day (Part B) window (from Day -7 or -14, respectively, through Day -1). The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Axis I Disorders (SCID-I) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the HAM-D, Hamilton Anxiety Rating Scale</p>

(HAM-A), Clinical Global Impression - Severity (CGI-S), and Montgomery-Åsberg Depression Rating Scale (MADRS). The Screening Period assessments will be conducted on an outpatient basis.

Treatment Period:

Part A – Once subjects are confirmed as eligible, they will receive a 30-mg dose of study drug at 8:00 PM (± 15 minutes) with food for 14 days (Day 1 to Day 14) as tolerated. Subjects who cannot tolerate 30 mg will receive 20 mg for the rest of the Treatment Period. Subjects who cannot tolerate 20 mg may be terminated from the study at the discretion of the Investigator. The following assessments will be performed: HAM-D, HAM-A, and MADRS total scores and Clinical Global Impression – Improvement (CGI-I).

Enrollment into Part A may be stopped and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed. Alternatively, upon completion of Part A, Part B may begin. The study may be terminated if there is clear lack of activity based on HAM-D scores during Part A.

Part B - Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomized within each stratum to one of two treatment groups (SAGE-217 Capsules [30 mg dose] or matching placebo) in a 1:1 ratio. Subjects will be administered study drug at 8:00 PM (± 15 minutes) with food for 14 days. Subjects who cannot tolerate 30 mg will receive 20 mg for the rest of the Treatment Period. Subjects who experience intolerable AEs at the 20 mg dose level may be terminated from the study at the discretion of the Investigator.

In both parts of the study, subjects may be discharged after a minimum 7-day inpatient stay, following completion of the Day 7 assessments. If their clinical condition does not allow discharge, the Investigator may keep the subjects as inpatients for a longer period of time.

In both parts of the study, subjects discharged from the inpatient unit may receive treatment with study drug for the remainder of the 14-day Treatment Periods as outpatients. The outpatient treatment may be provided at the clinical site or, if suitable arrangements can be made, via home administration. All dosing will be observed, either in the clinical unit or by a healthcare professional at home. Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.

With the exception of subjects permitted to use current stable antidepressant treatment, initiation of psychotropic medications and other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of the Day 15 assessments (Parts A and B). Psychotropic medications, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the Day 15 assessments (Part A).

Psychotropic medications that are used with the intent to treat depressive symptoms such as antidepressants, atypical antipsychotics, etc., must have been initiated at least 30 days prior to screening and must remain at a stable dose until completion of the Day 15 assessments (Part B).

Follow-up Period: Follow-up visits will be conducted on an outpatient basis. Follow-up visits will be conducted weekly for 2 weeks after completion of the Treatment Period in Part A (Day 28 ± 1 day) and weekly for 4 weeks after completion of the Treatment Period in Part B (Day 42 ± 3 days).

Efficacy, safety, and PK assessments will be performed periodically during the study, as outlined in the Schedule of Events (Table 2 and Table 3).

Objectives:

Part A:

Primary:

The primary objective of Part A is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg.

Secondary:

The secondary objective of Part A is to determine if treatment with SAGE-217 Oral Solution 30 mg for 14 days reduces depressive symptoms.

Pharmacokinetic:

The PK objective of Part A is to assess the PK profile of SAGE-217 Oral Solution in plasma samples.

Part B:

Primary:

The primary efficacy objective for Part B of the study is to determine if treatment with SAGE-217 Capsules (30 mg) reduces depressive symptoms in subjects with moderate to severe MDD compared to matching placebo.

Secondary:

The secondary objective of Part B is to evaluate the safety, tolerability, and efficacy of SAGE-217 Capsule (30 mg).

Exploratory:

The exploratory objective for Part B of the study is to assess the patient-reported outcome (PRO) measures as they relate to quality of life, work function, productivity, and depressive symptoms.

Pharmacokinetic:

The PK objective of Part B is to assess the PK profile of SAGE-217 Capsules in plasma samples.

Endpoints:

Part A:

Primary:

The primary endpoint for Part A is the safety and tolerability of SAGE-217 Oral Solution as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); Stanford Sleepiness Scale (SSS) score; physical examination; and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).

Secondary:

Reduction in depressive symptoms as assessed by the following:

- Change from baseline in HAM-D total score at Day 15 (ET) and all other time points;
- HAM-D response;
- HAM-D remission;
- Change from baseline in the MADRS total score at Day 15 (ET) and all other time points;
- Change from baseline in HAM-D subscale and individual item scores at Day 15 (ET) and all other time points;
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at all time points; and
- CGI-I response (defined as a CGI-I score of “very much improved” or “much improved”).

Pharmacokinetic:

- Maximum (peak) plasma concentration (C_{\max}), time at maximum (peak) plasma concentration (t_{\max}), plasma elimination half-life ($t_{1/2}$), area under the curve from zero to infinity (AUC_{∞}), and steady-state drug concentration in the plasma during oral intake (C_{ss}).

Part B:

Primary:

The primary endpoint for Part B is the reduction in depressive symptoms, compared to placebo, as assessed by the change in the 17-item HAM-D total score from baseline to Day 15.

Secondary:

- Reduction in depressive symptoms, compared to placebo, as assessed by the following:
 - Change in the 17-item HAM-D total score from baseline at all time points;
 - HAM-D response;
 - HAM-D remission;
 - Change from baseline in the MADRS total score at Day 15 (ET) and all other time points;
 - Change from baseline in HAM-D subscale and individual item scores at all time points;
 - Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at Day 15 (ET) and all other time points; and
 - CGI-I response.
- The safety and tolerability of SAGE-217 Capsules as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS.

Exploratory

Responses to the 36-item short form survey (SF-36), fatigue associated with depression (FAs-D), Remission in Depression Questionnaire (RDQ), and the Health-Related Productivity Questionnaire (HRPQ) will be summarized as exploratory endpoints for Part B.

Pharmacokinetic:

- C_{\max} , t_{\max} , $t_{1/2}$, AUC_{∞} , and C_{ss} .

Number of subjects (planned):

Approximately ten subjects will be enrolled in Part A. Approximately 88 subjects may be randomized in Part B.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject has a diagnosis of MDD that has been present for at least a 4-week period as diagnosed by SCID-I.

6. Subject has a HAM-D total score of ≥ 22 at screening and Day 1 (prior to dosing).
7. Removed per Amendment #2.
8. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics, during the screening and treatment periods.
9. **Part A:** Subject agrees to practice an acceptable method of highly effective birth control at screening and throughout study participation. Highly effective methods of birth control include sexual abstinence (for males and females); vasectomy; or a condom with spermicide in combination with a highly effective female partner's method (for males); and hormonal methods of contraception (ie, established use of oral, implantable, injectable, or transdermal hormones); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream, or suppository]) (for females).

Part B: Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause) and/or surgically sterile:

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

Exclusion criteria:

1. Subject has a history of suicide attempt.
2. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
3. Subject has a history of treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment).
4. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
5. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration.
6. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV) antibody at screening (except if the subject has a documented Hepatitis C antigen test (HCV RNA) with a negative result in their recent medical history).
7. Subject has active psychosis per Investigator assessment.

8. Subject has a medical history of seizures.
9. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
10. Subject has a history of alcohol or drug dependence (including benzodiazepines) in the 12 months prior to screening.
11. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
12. Subject has been treated or randomized in this study (eg, Part A) or any other study employing SAGE-217 previously (ie, subject may not have received study drug and then re-enroll).
13. Subject has had administration of psychotropics that have been initiated within 14 days prior to screening and/or are not being taken at a stable dose in Part A. Subject has had administration of psychotropic medications that are used with the intent to treat depressive symptoms such as antidepressants, atypical antipsychotics, etc., which have been initiated within 30 days prior to screening and/or are not being taken at a stable dose in Part B.
14. Use of any known strong inhibitors and/or inducers of cytochrome P450 (CYP)3A4 within the 14 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.
15. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.

Investigational product, dosage and mode of administration:

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% hydroxypropyl- β -cyclodextrin (HP β CD) and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dose. In Part A, doses will be prepared as an approximate 40 mL oral solution (containing 20 mg or 30 mg SAGE-217) to be swallowed all at once, followed by approximately 200 mL of water that has been used to rinse the dosing bottle.

SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients. For Part B, capsules will be available in 10-mg and 20-mg dose strengths. Subjects will be administered two capsules per dose (either two 10-mg capsules for the 20-mg dose, or one 10-mg plus one 20-mg capsule for the 30-mg dose).

Duration of participation:

Part A: Up to 38 days (up to 7 days for screening; 14 days of treatment; 14 -17 days for follow-up)

Part B: Up to 59 days (up to 14 days for screening; 14 days of treatment; 28-31 days for follow-up)

Reference therapy, dosage and mode of administration:

Part A: None

Part B: Placebo for Part B is hard gelatin capsules for oral administration containing only the excipients listed above for the active capsule treatment. Subjects will receive two placebo capsules per dose.

Randomization:

Subjects participating in Part A of the study will be administered study drug (SAGE-217 Oral Solution) in an open-label manner. Subjects in Part B will be randomized within each antidepressant treatment stratum to receive SAGE-217 Capsules or matching placebo capsules in a 1:1 ratio. Subjects, clinicians, and the study team will be blinded to treatment assignment. The pharmacist and/or designated pharmacy staff, who will prepare the study drug according to the randomization schedule, will be unblinded.

Dose Adjustment for Safety/Tolerability Reasons:

During the Treatment Period, subjects will be able to receive study drug as long as there are no dose-limiting safety/tolerability concerns. Subjects who cannot tolerate 30 mg will receive 20 mg for the remaining of the Treatment Period. Subjects who experience intolerable AEs at the 20-mg dose level may be terminated from the study at the discretion of the Investigator. Dosing may also be modified based on tolerability as assessed with SSS scores.

Inpatient Length of Stay and Discharge Instructions

The minimum length of inpatient stay in both parts of this study is 7 days. It is the Investigator's responsibility to assess whether the subject can safely be discharged home and continue taking study drug administered by a healthcare professional trained on the protocol and delivery of the study drug for the remaining treatment days (Days 8 to 14 for Parts A and B) or by returning to the clinic daily. The Investigator may decide to extend the subject's inpatient stay to maximize safety oversight. In making this assessment, the Investigator may consider not only the drug tolerability but also clinical factors including, but not limited to, availability of social support, transportation, severity of symptoms, and suicidality.

Discharge instructions must include warnings about avoiding activities for which sedative effects of the study drug may impair performance, such as driving a motor vehicle and operating machinery.

Criteria for evaluation:**Efficacy:**

Reduction of depressive symptoms will be assessed by the change from baseline at various post-baseline time points in HAM-D total score; HAM-D response; HAM-D remission; change from baseline in the MADRS total score; CGI-I response; change from baseline in HAM-D subscale and individual item scores; and change from baseline in HAM-A total score.

Pharmacokinetics:

Plasma samples will be collected to assay for concentrations of SAGE-217. The following PK parameters will be derived from the plasma concentrations (where evaluable): AUC, AUC_{∞} , C_{max} , t_{max} , steady-state drug concentration in the plasma during oral intake (C_{ss}), and in the plasma at steady state during a dosing interval.

Safety:

The safety and tolerability of SAGE-217 Oral Solution or SAGE-217 Capsules will be evaluated by frequency, type, and severity of adverse events; mean changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS during both Part A and Part B.

Statistical methods:**General**

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

Continuous endpoints will be summarized with 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 and Methods:

The Safety Set (for both Part A and Part B), defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data. Adverse events will be classified by type, incidence, severity, and causality. The overall incidence of adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Data for vital signs, clinical laboratory measurements, ECG, and concomitant medication usage will also be summarized. Safety data will be summarized and examined for possible relationships between subject characteristics and plasma SAGE-217 concentrations, as appropriate. Suicidality data collected using the C-SSRS at baseline and at each visit during the active Treatment Period will be listed for all subjects. The C-SSRS listings will include behavior type and/or category for suicidal ideation and suicidal behavior of the C-SSRS. Out-of-range safety endpoints may be categorized as low or high, where applicable. Subjects will be summarized according to treatment received.

The Efficacy Set (for both Part A and Part B), defined as all subjects in the Safety Set who complete at least 1 day of dosing of study drug and have at least one post-baseline efficacy evaluation, will be used to analyze efficacy data. Efficacy data will be analyzed using appropriate descriptive statistics and pre-specified statistical methods, as well as other data presentation methods where applicable; subject listings will be provided for all efficacy data. For (the open-label) Part A, efficacy data will be summarized descriptively. For Part B, subjects will be analyzed according to randomized treatment.

For Part B, the change from baseline in HAM-D total score will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include center, treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. Center will be treated as random and all other explanatory variables as fixed effects. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 Capsules and matching placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means), 95% confidence intervals, and p-values will be reported. An unstructured covariance structure will be used to model the within-subject errors. Other continuous endpoints will be analyzed using similar methods.

Binary efficacy endpoints, including responder and remission endpoints, will be analyzed using generalized estimating equation (GEE) models.

The PK Set will consist of all subjects in the Safety Set with sufficient plasma concentrations for PK evaluations, and will be used to summarize PK data. PK parameters will be summarized using appropriate descriptive statistics and listed by subject. The PK parameters to be summarized where possible will include AUC_{∞} , C_{max} , t_{max} , $t_{1/2}$, and C_{ss} .

Sample Size Calculation

The sample size of ten subjects for Part A was selected based on clinical and not statistical considerations.

For Part B, assuming a two-sided t-test at an alpha level of 0.05, a sample size of 40 subjects per group would provide 90% power to detect an effect size of 0.75 between the SAGE-217 Capsules and matching placebo groups with regard to the efficacy outcome variable of change from baseline in HAM-D total score. An effect size of 0.75 corresponds to a matching placebo-adjusted difference of 7.5 points in the change from baseline in HAM-D total score at 15 days with an assumed SD of 10 points. By including two treatment groups and using a 1:1 randomization, a total of 80 subjects are required. Assuming a non-evaluability rate of 10%, approximately 88 subjects will be randomized. Additional subjects may be enrolled if the drop-out rate is higher than 10%.

Table 2: Schedule of Events (Part A)

	Screening Period	Open-Label Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D-7 to D-1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)
Study Procedure																		
Informed Consent	X																	
Inclusion/Exclusion	X	X																
Demographics	X																	
Medical/Family History	X																	
SCID-I	X																	
Confinement		X							(X)									
Physical Examination	X								X							X	X	X
Body Weight/Height	X															X (wt only)	X (wt only)	X (wt only)
Clinical Laboratory Assessments ^b	X								X							X	X	X
Drug & Alcohol Screen ^c	X	X																
Pregnancy Test ^d	X	X														X ^e		X
Hepatitis & HIV Screen	X																	
Blood Sample ^f	O								O							O		
Genetic Sample ^g	O																	
Vital Signs ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry		X	X	X	X	X	X	X	X									
12-Lead ECG ⁱ	X	X	X					X							X		X	
C-SSRS ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S ^k	X	X	X	X					X							X	X	X

	Screening Period	Open-Label Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D-7 to D-1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)
Study Procedure																		
CGI-Ik			X	X					X							X	X	X
HAM-Ak	X	X	X	X					X							X	X	X
HAM-Dk	X	X	X	X	X	X	X	X	X							X	X	X
MADRSk	X	X	X	X	X	X	X	X	X							X	X	X
SSSi	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Plasma PK _m			X	X	X	X	X	X	X						X	X		
Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse Events	X																	
Prior/Concomitant Medications _n	X																	

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ET = early termination; ECG = electrocardiogram; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; MADRS = Montgomery-Åsberg Depression Rating Scale; PK = pharmacokinetic; SCID-I = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Axis I Disorders; SSS = Stanford Sleepiness Scale; wt = weight

*D1 procedures are to be completed prior to dosing

^a Outpatient visits may take place at the subject's residence or in the clinic.

^b Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning on Days 8 and 15 and during the follow-up visits on Day 21 and Day 28.

^c Urine toxicology for selected drugs of abuse and serum or breath test for alcohol.

^d Serum pregnancy test at screening and urine pregnancy test at Day 1 and Day 28.

^e Female subjects who prematurely discontinue will have a pregnancy test performed at the ET visit.

^f An optional blood sample for hormone and exploratory biochemistry testing, where consent is given.

^g An optional genetic sample for biomarker testing, where consent is given.

^h Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ±5 minutes of the scheduled time point through 0.5 hours after dosing and ±30 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between the hours of 11:00 PM and 06:00 AM. From Day 1 through Day 7, vital signs will be completed at the following time points: predose, 0.25, 0.5, 1, 2, and 12 hours after dosing. During the outpatient treatment period, vital signs will be completed prior to dosing and 1 hour after dosing. Vital signs may be repeated at the discretion of the Investigator or Visiting Home Healthcare Provider as clinically indicated.

- ⁱ Will be performed 1 hour \pm 15 minutes after dosing on Days 1, 2, 7, and 14, and during the follow-up visit on Day 21.
- ^j The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- ^k To be completed to be completed at 8:00 AM (\pm 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28. The assessment timeframe for HAM-D and HAM-A scales will refer to the past 7 days (1 week) on Screening, Day 1, Day 15/ET, Day 21, and Day 28 visits, and the past 24 hours on visits occurring on Days 2 through 8.
- ^l To be completed within \pm 5 minutes of the scheduled time point through 0.5 hours after dosing and \pm 15 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between 11:00 PM and 06:00 AM during the inpatient treatment period. From Day 1 through Day 7, SSS will be completed at the following time points: predose, 0.25, 0.5, 1, and 2 hours after dosing. During the outpatient treatment period, SSS will be completed prior to dosing and 1 hour after dosing.
- ^m Plasma samples for PK analysis in Part A and Part B will be collected predose on Days 2, 3, 4, 5, and 6, predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within \pm 5 minutes of the scheduled time point through 0.5 hours after dosing and \pm 15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. Plasma samples for PK analysis will be collected per protocol and subjects may need to be awoken for sample collection.
- ⁿ To include those taken within 30 days prior to informed consent and throughout the study.

Table 3: Schedule of Events (Part B)

	Screening Period	Double-Blind, Placebo-Controlled Treatment Period														Follow-up Period				
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT				
Visit Days	D-14 to D-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)	D35 (±3d)	D42 (±3d)
Study Procedure																				
Informed Consent	X																			
Inclusion/Exclusion	X	X*																		
Demographics	X																			
Medical/Family History	X																			
SCID-I	X																			
Randomization		X*																		
Confinement		X							(X)											
Physical Examination	X								X							X				X
Body Weight/Height	X															X (wt only)	X (wt only)	X (wt only)	X (wt only)	X (wt only)
Clinical Laboratory Assessments ^b	X								X							X	X	X	X	X
Drug & Alcohol Screen ^c	X	X*																		
Pregnancy Test ^d	X	X*														X ^e				X
Hepatitis & HIV Screen	X																			
Blood Sampler	O								O							O				
Genetic Sample ^g	O																			
Vital Signs ^h	X	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry		X*	X	X	X	X	X	X	X											

	Screening Period	Double-Blind, Placebo-Controlled Treatment Period														Follow-up Period				
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT				
Visit Days	D-14 to D-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)	D35 (±3d)	D42 (±3d)
Study Procedure																				
12-Lead ECG ⁱ	X	X	X					X							X		X			
C-SSRS ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S ^k	X	X*	X	X					X							X	X	X	X	X
CGI-I ^k			X	X					X							X	X	X	X	X
HAM-A ^k	X	X*	X	X					X							X	X	X	X	X
HAM-D ^k	X	X*	X	X	X	X	X	X	X							X	X	X	X	X
MADRS ^k	X	X*	X	X	X	X	X	X	X							X	X	X	X	X
SF-36 ^k		X*							X							X				X
FAs-D ^k		X*							X							X				X
RDQ ^k		X*														X				X
HRPQ ^k		X*														X				X
SSS ^l	X	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Plasma PK ^m			X	X	X	X	X	X	X						X	X				
Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Adverse Events	X																			
Prior/Concomitant Medications ⁿ	X																			

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ET = early termination; ECG = electrocardiogram; FAs-D = fatigue associated with depression; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; HRPQ = Health-Related Productivity Questionnaire; MADRS = Montgomery-Åsberg Depression Rating Scale; PK = pharmacokinetic; RDQ = Remission in Depression Questionnaire; SCID-I = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Axis I Disorders; SF-36 = 36-item short form survey; SSS = Stanford Sleepiness Scale; wt = weight

*D1 procedures are to be completed prior to dosing

- ^a Outpatient visits may take place at the subject's residence or in the clinic.
- ^b Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning on Days 8 and 15 and during the follow-up visits on Day 21, Day 28, Day 35, and Day 42.
- ^c Urine or serum toxicology for selected drugs of abuse (as per the lab manual) and serum or breath test for alcohol (as per the standard procedures at each site).
- ^d Serum pregnancy test at screening and urine pregnancy test at Day 1 and Day 42.
- ^e Female subjects who prematurely discontinue will have a pregnancy test performed at the ET visit.
- ^f An optional blood sample for hormone and exploratory biochemistry testing, where consent is given.
- ^g An optional genetic sample for biomarker testing, where consent is given.
- ^h Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 30 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between the hours of 11:00 PM and 06:00 AM. From Day 1 through Day 7, vital signs will be completed at the following time points: predose, 0.25, 0.5, 1, 2, and 12 hours after dosing. During the outpatient treatment period, vital signs will be completed prior to dosing and 1 hour after dosing. Vital signs may be repeated at the discretion of the Investigator or Visiting Home Healthcare Provider as clinically indicated.
- ⁱ Will be performed 1 hour ± 15 minutes after dosing on Days 1, 2, 7, and 14, and during the follow-up visit on Day 21.
- ^j The "Baseline/Screening" C-SSRS form will be completed at screening. The "Since Last Visit" C-SSRS form will be completed at any time of day at all subsequent time points.
- ^k To be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period. The assessment timeframe for HAM-D and HAM-A scales will refer to the past 7 days (1 week) on Screening, Day 1, Day 15/ET, Day 21, Day 28, Day 35, and Day 42 visits, and the past 24 hours on visits occurring on Days 2 through 8.
- ^l To be completed within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between 11:00 PM and 06:00 AM during the inpatient treatment period. From Day 1 through Day 7, SSS will be completed at the following time points: predose, 0.25, 0.5, 1, and 2 hours after dosing. During the outpatient treatment period, SSS will be completed prior to dosing and 1 hour after dosing.
- ^m Plasma samples for PK analysis in Part A and Part B will be collected predose on Days 2, 3, 4, 5, and 6, predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. Plasma samples for PK analysis will be collected per protocol and subjects may need to be awoken for sample collection.
- ⁿ To include those taken within 30 days prior to informed consent and throughout the study.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AUC	area under the concentration-time curve
AUC _∞	area under the concentration-time curve from time zero to infinity
BMI	body mass index
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
C _{max}	maximum (peak) plasma concentration
CS	clinically significant
C _{ss}	steady-state drug concentration in the plasma during oral intake
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP450	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EP	European Pharmacopeia
ET	early termination
FAs-D	fatigue associated with depression
GABA	γ-aminobutyric acid
GABA _A	γ-aminobutyric acid-ligand gated chloride channel
GCP	Good Clinical Practice
GEE	generalized estimating equation
GMP	Good Manufacturing Practice
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	17-item Hamilton Rating Scale for Depression
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPβCD	hydroxypropyl-β-cyclodextrin

Abbreviation or Specialist Term	Explanation
HRPQ	Health-Related Productivity Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAD	multiple-ascending dose
MADRS	Montgomery-Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorders
MMRM	mixed effects model for reported measures
MTD	maximum tolerated dose
n	number
NCS	not clinically significant
NF	National Formulary
PK	pharmacokinetic(s)
PPD	postpartum depression
RDQ	Remission in Depression Questionnaire
SAD	single-ascending dose
SCID-I	Structured Clinical Interview for DSM-5 Axis I Disorders
SD	standard deviation
SF-36	36-item short form survey
SOC	system organ class
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
$t_{1/2}$	plasma elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time at maximum (peak) plasma concentration
USP	United States Pharmacopeia
WHO	World Health Organization
WHO-DD	World Health Organization-Drug Dictionary

5. INTRODUCTION

5.1. Background of Major Depressive Disorders and Unmet Medical Need

World Health Organization (WHO) has identified depression as the leading cause of disability worldwide, and 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 350 million people.

In [DSM-5](#), depression refers to an overarching set of diagnoses, including disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder.

In the US, the economic burden of depression, including workplace costs, direct costs and suicide-related costs, was estimated to be \$210.5 billion in 2010 ([Greenberg 2015](#)). As per WHO statistics, over 800,000 people die due to suicide every year, and suicide is the second leading cause of death in 15- to 29-year-olds. In the US, an estimated 10% to 15% of individuals with depression commit suicide ([Angst 1999](#)).

Antidepressants are mainstay of pharmacological treatment for depressive disorders. Selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other compounds that affect monoaminergic neurotransmission, such as mirtazapine and bupropion, represent the major classes of antidepressants. While antidepressants are widely used, large scale studies have demonstrated their limited efficacy. For example, in the STAR*D trial where over 2800 patients were treated in “real world” settings, the HAM-D remission rate was 28% following 14 weeks of treatment with citalopram, a typical selective serotonin reuptake inhibitor ([Trivedi 2006](#)). Recent studies have shown a number of symptoms that remain untreated, such as cognitive impairment, sleep disturbances and anxiety, even in patients that are in remission over a long period of time after treatment ([Conradi 2011](#); [Romera 2013](#)). A close examination of randomized placebo-controlled trials of antidepressants approved by the Food and Drug Administration in the treatment of both major or minor depressive disorders demonstrated Cohen’s *d* effect sizes below 0.2 and high placebo response rates ([Kirsch 2008](#); [Fournier 2010](#)), emphasizing the challenges in assessing antidepressant drug efficacy and the unmet need in the treatment of depression.

Converging preclinical and clinical evidence ([Gerner 1981](#); [Honig 1988](#); [Drugan 1989](#); [Luscher 2011](#); [Mann 2014](#)) implicates deficits in GABAergic neurotransmission in the pathophysiology of depressive disorders including MDD and PPD. Furthermore, several pieces of experimental data implicate deficiencies in the normal regulation of endogenous neuroactive steroids in depressive disorders ([Maguire 2008](#); [Maguire 2009](#)). The neuroactive steroid class of compounds includes the endogenous neuroactive steroid, allopregnanolone. Allopregnanolone is a positive allosteric modulator of both synaptic and extrasynaptic GABA_A receptors – the prominent inhibitory transmitter system in the brain. Depressed patients show low levels of GABA in the brain and of neurosteroids in the CSF and plasma, and antidepressant therapy

restores GABA levels in relevant animal models and neurosteroid concentrations in depressed patients ([Luscher 2011](#); [Schüle 2014](#)).

5.2. SAGE-217

Two dosage forms of SAGE-217 for oral administration will be used in this study (Oral Solution and Capsules). For Part A, SAGE-217 Oral Solution is to be compounded at the clinical pharmacy from components supplied by the Sponsor (SAGE-217 Drug Substance Powder in the Bottle, Excipients in the Bottle, and sucralose) and Sterile Water for Injection. SAGE-217 Oral Solution is a clear, colorless, aqueous hydroxypropyl- β -cyclodextrin (HP β CD) solution of SAGE-217 Drug Substance. One concentration, 6 mg/mL, is available for use in clinical studies. In addition to SAGE-217 Drug Substance, SAGE-217 Oral Solution contains HP β CD (Kleptose[®], HPB Parenteral Grade, United States Pharmacopeia/European Pharmacopeia [USP/EP], Roquette) to solubilize the drug substance, sucralose (USP/National Formulary [NF], JK Sucralose, Inc.) to sweeten the solution, and water for injection to be provided by the clinical pharmacy. Refer to [Table 5](#) for the composition of SAGE-217 Oral Solution 6 mg/mL.

The SAGE-217 Oral Solution 6 mg/mL stock solution is compounded at point of use. This stock solution is for oral administration after dilution to the intended dose by the clinical pharmacy.

For Part B, SAGE-217 Capsules will be administered orally. SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the active, SAGE-217 capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients. Placebo capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate.

5.3. Summary of Nonclinical and Clinical Experience with SAGE-217

5.3.1. Nonclinical Studies with SAGE-217

In nonclinical studies of SAGE-217, sedative-hypnotic effects were consistently observed at higher doses in both in vivo pharmacology studies and toxicology studies. The sedative-hypnotic impairments seen with SAGE-217 were typical for GABA_A positive allosteric modulators, ranging from hyperexcitability and ataxia at the lower doses through deep sedation and ultimately anesthesia at higher doses. Depth and duration of sedation demonstrated a clear dose response over the range tested, with evidence of tolerance occurring with continued exposure. Tolerance to the effects of SAGE-217 on motor incoordination was not observed after 7 days of dosing.

The compound has been assessed in 14-day rat and dog toxicology studies with daily administration of SAGE-217 as a solution in HP β CD in dogs and Labrasol[®] in rats. The no-observed-adverse-effect-level was 3 mg/kg (females) and 22.5 mg/kg (males) in rats and 2.5 mg/kg in dogs. There were no adverse effects in dogs or rats in the main toxicology studies. A single observation of mortality occurred in one female rat at the high dose in a toxicokinetic study that was suspected to have been related to exaggerated pharmacology. Additional toxicology and pharmacology information is provided in the [Investigator's Brochure](#).

5.3.2. Clinical Experience

To date, two clinical studies employing SAGE-217 Oral Solution are clinically complete, and final clinical study reports are pending; in addition, a clinical study of SAGE-217 Capsules is clinically completed with the final report in progress. Discussions of pharmacokinetic (PK) data for the Oral Solution are limited to the single-ascending dose, food effect, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction cohorts from Study 217-CLP-102. Discussions of safety data for the Oral Solution are limited to the single-ascending dose cohorts in Study 217-CLP-101 and the multiple-ascending dose cohorts in Study 217-CLP-102. Safety and PK data for the Capsules are derived from Study 217-CLP-103.

Study 217-CLP-101 was a first-in-human, four-part study that assessed the effects of a single dose of SAGE-217 Oral Solution. The study was a double-blind, placebo-controlled, single-ascending dose design in healthy adult volunteers, with the objective of identifying the maximum tolerated dose (MTD) and PK profiles of SAGE-217 Oral Solution. Subjects in each of the single-ascending dose cohorts received a single dose of study drug, either SAGE-217 Oral Solution (six subjects) or placebo (two subjects), with SAGE-217 Oral Solution doses of 0.25 mg, 0.75 mg, 2 mg, 5.5 mg, 11 mg, 22 mg, 44 mg, 55 mg, and 66 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the Safety Review Committee (SRC) and agreement reached that it was safe to increase the dose. The MTD was determined to be 55 mg. Two cohorts, six subjects each received SAGE-217 Oral Solution in an open-label manner (one cohort received 50% of the MTD [22 mg] to study the food effects and the other cohort received the MTD [55 mg] to study the effects on subjects with essential tremor). SAGE-217 Oral Solution was orally bioavailable, demonstrated dose-linear PK from the lowest (0.25 mg) through the highest (66 mg) dose, and supported once-daily oral dosing with food. In addition, the pharmacodynamic effects of the SAGE-217 Oral Solution MTD were assessed in placebo controlled-, blinded, crossover electroencephalogram cohorts of eight subjects each; one cohort received 50% of the MTD (22 mg) and the other received the MTD (55 mg).

Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE-217 Oral Solution. The study was a double-blind, placebo-controlled, multiple-ascending dose study in healthy adult volunteers. Subjects in each of the multiple-ascending dose cohorts received study drug, either SAGE-217 Oral Solution (nine subjects) or placebo (three subjects), once daily for 7 days, with SAGE-217 Oral Solution doses of 15 mg, 30 mg, and 35 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the SRC and agreement reached that it was safe to increase the dose. The MTD was determined to be 30 mg. It was observed that subjects receiving the drug in the evening did better in terms of tolerability compared to when they received the drug in the morning. A fourth cohort of 12 subjects received 30 mg of SAGE-217 Oral Solution in an open-label manner to study drug-drug interactions. SAGE-217 Oral Solution is not likely to induce the metabolism of cytochrome P450 (CYP)2B6 or CYP3A4 substrates. SAGE-217 was orally bioavailable and suitable for once-daily oral dosing at nighttime with food.

SAGE-217 Oral Solution was generally well tolerated. In both Phase 1 studies (217-CLP-101 and 217-CLP-102), doses were escalated until the stopping criteria were met. Most adverse events were reported as mild or moderate in intensity, and there were no serious adverse events

reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At doses planned for further study, the observed sedation was mild, transient, and associated with daily peak exposure. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, dizziness, euphoric mood, fatigue, tremor, and muscle twitching, reported most frequently in the highest dose group (66 mg). Some changes in mean blood pressure and heart rate were observed after single doses of 44 mg and greater. After multiple doses of 30 mg (AM or PM) or 35 mg (PM) over 7 days, there was no evidence of changes in mean vital sign measures even though Day 7 plasma concentrations approximated that of the highest single dose in the single-ascending dose study. Subjects seemed to tolerate SAGE-217 Oral Solution better when given as nighttime dosing.

The safety, tolerability, PK, and relative bioavailability of the SAGE-217 Capsules were assessed in a Phase 1 randomized, open-label, cross-over study (Study 217-CLP-103). In the fasted state, SAGE-217 Capsules demonstrated reduced exposure in terms of maximum (peak) plasma concentration (C_{max}) and area under the curve from zero to the time of the last quantifiable concentration (AUC_{last}) compared to SAGE-217 Oral Solution. SAGE-217 Capsules administered in the fed state (with standard and high fat meal) showed increased exposure compared to the fasted state and approximately equivalent exposure in terms of geometric mean AUC_{last} compared to SAGE-217 Oral Solution; however, the C_{max} for SAGE-217 Capsules was reduced by approximately 50% when compared with SAGE-217 Oral Solution. Based on these study results, exposures with SAGE-217 Capsules are anticipated to be equal to or less than exposures observed at the same dose with SAGE-217 Oral Solution.

There are no clinical efficacy data for SAGE-217 in major depressive disorders (MDD), since the present study is the first study in this indication.

5.4. Potential Risks and Benefits

To date, SAGE-217 Oral Solution has been studied within the context of single-ascending dose (SAD) (217-CLP-101) and multiple-ascending dose (MAD) (217-CLP-102) studies. In addition, the SAD study included a cohort evaluating a 55 mg dose of SAGE-217 Oral Solution in subjects with essential tremor who were otherwise healthy. The most common TEAEs observed across the SAD and MAD studies were sedation, somnolence, dizziness, euphoric mood, and tremor. Most adverse events were reported as mild or moderate in intensity, and there were no serious adverse events reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At predicted efficacious doses in the 20 to 30 mg range, observed sedation was mild, transient, and associated with daily peak exposure. The pharmacokinetic profile obtained from these studies indicates dose linearity over the multiple-dose range studied (15 to 35 mg). SAGE-217 Oral Solution was well-tolerated in the essential tremor subjects.

The safety profile of SAGE-217 Oral Solution based on the SAD, MAD, and in a limited number of subjects with essential tremor suggest that SAGE-217 Oral Solution may also be well tolerated in patients with MDD. In addition, the safety, tolerability, PK, and relative bioavailability of SAGE-217 Capsules were evaluated in a Phase 1 study. In this study, SAGE-217 Capsules were found to be generally well-tolerated with no serious adverse events reported during the Treatment and Follow-up periods. The most frequent adverse event

observed was mild sedation; sedation was transient, occurred between 1-4 hours, and generally dissipated by 8 hours. The current significant unmet need in the treatment of depression, remaining as a number one cause of disability worldwide, justifies a favorable risk-benefit ratio, and investigation of SAGE-217 Oral Solution in patients with MDD.

5.5. Dose Justification

To date, the pharmacokinetics of SAGE-217 Oral Solution has been investigated in healthy volunteers within the context of the SAD and MAD studies (217-CLP-101 and 217-CLP-102, respectively). The MTD was determined to be 55 mg in the SAD study and 30 mg once daily (either AM or PM dosing) in the MAD study. Thus, as a first step, while ensuring tolerability, a 30 mg dose has been chosen to maximize the potential therapeutic benefit in this first clinical study of MDD.

The safety, tolerability, pharmacokinetics, and relative bioavailability of the SAGE-217 Capsules were assessed in a Phase 1 randomized, open-label, cross-over study (Study 217-CLP-103). Based on the results of this study (see [Section 5.3.2](#) and [Section 5.4](#)), the SAGE-217 Capsules were deemed appropriate for use in further clinical trials.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Part A

6.1.1. Primary Objective

The primary objective of Part A is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg.

6.1.2. Secondary Objective

The secondary objective of Part A is to determine if treatment with SAGE-217 Oral Solution 30 mg for 14 days reduces depressive symptoms.

6.1.3. Pharmacokinetic Objective

The PK objective of Part A is to assess the PK profile of SAGE-217 Oral Solution in plasma samples.

6.2. Part B

6.2.1. Primary Objective

The primary efficacy objective for Part B of the study is to determine if treatment with SAGE-217 Capsules (30 mg) reduces depressive symptoms in subjects with moderate to severe MDD compared to matching placebo.

6.2.2. Secondary Objective

The secondary objective of Part B is to evaluate the safety and tolerability of SAGE-217 Capsules (30 mg).

6.2.3. Exploratory

The exploratory objective for Part B of the study is to assess the patient-reported outcome (PRO) measures as they relate to quality of life, work function, productivity, and depressive symptoms.

6.2.4. Pharmacokinetic Objective

The PK objective of Part B is to assess the PK profile of SAGE-217 Capsules in plasma samples.

6.3. Endpoints

6.3.1. Part A

6.3.1.1. Primary

The primary endpoint for Part A is the safety and tolerability of SAGE-217 Oral Solution as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); Stanford Sleepiness Scale

(SSS) score; physical examination; and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).

6.3.1.2. Secondary

Reduction in depressive symptoms as assessed by the following:

- Change from baseline in HAM-D total score at Day 15 (ET) and all other time points;
- HAM-D response (defined as having a 50% or greater reduction from baseline in HAM-D total score);
- HAM-D remission (defined as having a HAM-D total score of ≤ 7);
- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15 (ET) and all other time points;
- Change from baseline in HAM-D subscale and individual item scores at Day 15 (ET) and all other time points;
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at all time points; and
- Clinical Global Impression – Improvement (CGI-I) response (defined as a CGI-I score of “very much improved” or “much improved”).

6.3.1.3. Pharmacokinetic

The following PK endpoints will be assessed in Part A:

- C_{\max} , time at maximum (peak) plasma concentration (t_{\max}), plasma elimination half-life ($t_{1/2}$), area under the curve from zero to infinity (AUC_{∞}), and steady-state drug concentration in the plasma during oral intake (C_{ss}).

6.3.2. Part B

6.3.2.1. Primary

The primary endpoint for Part B is the reduction in depressive symptoms, compared to placebo, as assessed by the change in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score from baseline to Day 15.

6.3.2.2. Secondary

- Reduction in depressive symptoms, compared to placebo, as assessed by the following:
 - Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at all time points;
 - HAM-D response;
 - HAM-D remission;

- Change from baseline in the MADRS total score at Day 15 (ET) and all other time points;
 - Change from baseline in HAM-D subscale and individual item scores at all time points;
 - Change from baseline in HAM-A total score at Day 15 (ET) and all other time points; and
 - CGI-I response.
- The safety and tolerability of SAGE-217 Capsules as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS.

6.3.2.3. Exploratory

Responses to the 36-item short form survey (SF-36), fatigue associated with depression (FAs-D), Remission in Depression Questionnaire (RDQ), and the Health-Related Productivity Questionnaire (HRPQ) will be summarized as exploratory endpoints for Part B.

6.3.2.4. Pharmacokinetic

The following PK endpoints will be assessed in Part B:

- C_{\max} , t_{\max} , $t_{1/2}$, AUC_{∞} , and C_{ss} .

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study is a two-part, multicenter, Phase 2a study to evaluate the safety, tolerability, PK, and efficacy of SAGE-217 Oral Solution (Part A) and SAGE-217 Capsules (Part B) in approximately 76 adult subjects with MDD. Part A of the study is an open-label design with SAGE-217 Oral Solution dosing for 14 days. Part A will consist of an up to 7-day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 2-week Follow-up Period. Part B of the study is a randomized, double-blind, parallel-group, placebo-controlled design with SAGE-217 Capsule or matching placebo dosing for 14 days. Part B will consist of an up to 14-day Screening Period (Days -14 to -1), a 14-day Treatment Period, and a 4-week Follow-up Period. Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B.

During the Screening Period, after signing the informed consent form (ICF), subjects will be assessed for study eligibility, and the severity of each subject's MDD will be evaluated using HAM-D. The Screening Period assessments will be conducted on an outpatient basis.

If applicable, standard of care data collected prior to obtaining informed consent may also be included as screening data, if appropriate, such as laboratory tests, ECG, physical examination, and vital signs conducted within the preceding 48 hours, as long as the requirement for the screening assessment to be collected retrospectively is met in full. If applicable, to ensure protocol compliance, any standard of care data eligible for inclusion as screening data must include the precise nature and timing of data collection.

During the 14-day study Treatment Period of Parts A and B, subjects must remain inpatient for the first 7 days at minimum and per Investigator's judgement thereafter. The Follow-up Period assessments will be conducted on an outpatient basis.

The study will be conducted in two parts:

- Part A: Beginning on Day 1, subjects will receive a 30-mg dose of open-label SAGE-217 Oral Solution at 8:00 PM (± 15 minutes) with food (as outlined in [Section 9.2.1](#)). Subjects will receive SAGE-217 Oral Solution 30 mg from Day 1 to Day 14, as tolerated.
- Part B: Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomized within each stratum in a 1:1 ratio to receive SAGE-217 Capsules (30 mg) or matching placebo for 14 days beginning on Day 1, as tolerated. All doses of study drug will be administered at 8:00 PM (± 15 minutes) with food as outlined in [Section 9.2.2](#).

Enrollment into Part A may be stopped and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed. Alternatively, upon completion of Part A, Part B may begin. The study may be terminated if there is clear lack of activity based on HAM-D scores during Part A.

In Part A and Part B, study drug (SAGE-217 Oral Solution in Part A; SAGE-217 Capsule or matching placebo in Part B) will be administered at the study center for at least the first 7 days of the Treatment Period, which includes Day 1 of study drug administration through completion of study drug administration on Day 14. Subjects may be discharged after a minimum 7-day inpatient stay, following completion of the Day 7 assessments. If their clinical condition does not allow discharge, the Investigator may keep the subjects as inpatients for a longer period of time. Subjects discharged from the inpatient unit may receive treatment with study drug for the remainder of the 14-day Treatment Period as outpatients. For the outpatient phase, dosing will be done at the clinical site or, if suitable arrangements can be made, via home administration where local regulations allow. All dosing will be observed, either in the clinical unit or by a healthcare professional at home. Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.

Subjects will be monitored for safety during the Treatment and Follow-up Periods including monitoring for adverse events/serious adverse events, routine clinical laboratory assessments, physical examination, vital signs, and ECG (only Day 15 during Follow-up).

During the Treatment Period, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects cannot tolerate 30 mg will receive 20 mg for the remaining of the Treatment Period. Subjects who experience intolerable AEs at the 20-mg dose level may be terminated from the study at the discretion of the Investigator.

Dosing may also be modified based on tolerability as assessed with SSS scores. Any SSS score of ≥ 6 will be reassessed within 10 minutes. If a subject is receiving the 30 mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat assessment during normal waking hours, the dose will be decreased to 20 mg for the rest of the Treatment Period. If a subject is receiving the 20 mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat assessment during normal waking hours, then study drug will be discontinued and the subject will be terminated from the study.

Follow-up visits will be conducted on an outpatient basis. Follow-up visits will be conducted weekly for 2 weeks after completion of the Treatment Period in Part A (Day 28 \pm 1 day) and weekly for 4 weeks after completion of the Treatment Period in Part B (Day 42 \pm 3 days).

7.2. Blinding and Randomization

Part A is open-label with no control group; therefore, there will be no randomization or blinding.

Part B is a double-blind, placebo-controlled study. Subjects who meet the entrance criteria will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 Capsules or matched placebo according to a computer-generated randomization schedule. Once it has been determined that a subject meets eligibility criteria, the subject will be sequentially assigned a subject number from the randomization schedule provided to the unblinded pharmacist and/or designated pharmacy staff. Subject identification numbers will consist of the site number (eg, "01") followed by numbering starting with double zero (eg, 01-001, 01-002, 01-003 through 01-062).

The randomization schedule will be generated using SAS V9.2 or later. Only the clinic pharmacist and/or designated pharmacy staff, who is responsible for preparing the study drug, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist and/or designated pharmacy staff may reveal actual study drug contents to the Investigator, who should also alert Sage of the emergency (see [Section 13.6](#) for more details related to unblinding). In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the electronic case report form (eCRF). If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study. In addition, an unblinded Monitor will perform drug accountability during the study.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the study.

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject has a diagnosis of MDD that has been present for at least a 4-week period as diagnosed by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Axis I Disorders (SCID-I).
6. Subject has a HAM-D total score of ≥ 22 at screening and Day 1 (prior to dosing).
7. Removed per Amendment #2.
8. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics, during the screening and treatment periods.
9. **Part A:** Subject agrees to practice an acceptable method of highly effective birth control at screening and throughout study participation. Highly effective methods of birth control include sexual abstinence (for males and females); vasectomy; or a condom with spermicide in combination with a highly effective female partner's method (for males); and hormonal methods of contraception (ie, established use of oral, implantable, injectable, or transdermal hormones); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream, or suppository]) (for females).

Part B: Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause) and/or surgically sterile:

- 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 occlusion.

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

8.2. Subject Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria.

1. Subject has a history of suicide attempt.
2. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
3. Subject has a history of treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment).
4. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
5. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration.
6. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV) antibody at screening (except if the subject has a documented Hepatitis C antigen test (HCV RNA) with a negative result in their recent medical history).
7. Subject has active psychosis per Investigator assessment.
8. Subject has a medical history of seizures.
9. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
10. Subject has a history of alcohol or drug dependence (including benzodiazepines) in the 12 months prior to screening.
11. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
12. Subject has been treated or randomized in this study (eg, Part A) or any other study employing SAGE-217 previously (ie, subject may not have received study drug and then re-enroll).
13. Subject has had administration of psychotropics that have been initiated within 14 days prior to screening and/or are not being taken at a stable dose in Part A. Subject has had administration of psychotropic medications that are used with the intent to treat depressive symptoms such as antidepressants, atypical antipsychotics, etc., which have been initiated within 30 days prior to screening and/or are not being taken at a stable dose in Part B.

14. Use of any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.
15. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.

8.3. Subject Withdrawal Criteria

If there is an adverse event or medical reason for the withdrawal, the subject should be followed medically until the condition has either resolved or is stable. Details of the reason for withdrawal should be recorded in the subject's eCRF.

Subjects who withdraw should, if possible, have a follow-up examination, including a physical examination, the appropriate investigations, vital signs, and clinical laboratory tests (including pregnancy tests), as outlined for the Day 15 visit ([Table 2](#) and [Table 3](#)). All details of this follow-up examination should be recorded in the subject's medical source documents.

8.3.1. Study Drug Withdrawal

Participation in the study is strictly voluntary. Subjects are free to discontinue the study at any time without giving their reason(s).

A subject must be withdrawn from the study treatment in the event of any of the following:

- Withdrawal of the subject's consent;
- New onset of a condition that would have met exclusion criterion, is clinically relevant and affects the subject's safety, and discontinuation is considered necessary by the Investigators and/Sponsor;
- Occurrence of intolerable adverse events;
- Occurrence of pregnancy;
- Intake of nonpermitted concomitant medication;
- Subject noncompliance;
- Significant protocol deviation determined in consultation with the Medical Monitor.

If a subject failed to attend scheduled assessments during the course of the study, the Investigators must determine the reasons and the circumstances as completely and accurately as possible and document this in the subject's source documents.

Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant. Subjects who withdraw should, if possible, have a follow-up examination, including a physical examination, the appropriate investigations, vital signs, and clinical laboratory tests (including pregnancy tests), as outlined for the Day 15 visit ([Table 2](#) and [Table 3](#)). All details of this follow-up examination should be recorded in the subject's medical source documents.

Subjects who withdraw or are withdrawn from the study will be replaced only if they withdraw prior to dosing. Subjects who are withdrawn from the study, fail to return or are no longer qualified will not be replaced. Additional subjects may be enrolled if the drop-out rate is higher than 10%.

8.3.2. 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 adverse events or other findings suggesting unacceptable risk to subjects, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their Institutional Review Board (IRB) and initiate withdrawal procedures for participating subjects.

9. TREATMENT OF SUBJECTS

9.1. Number of Subjects

Approximately ten subjects with MDD will be enrolled into Part A of the study. Approximately 88 subjects may be randomized in Part B to ensure at least 80 evaluable subjects for Part B. Evaluable subjects are defined as those subjects receiving study drug with at least one post-baseline HAM-D assessment. Additional subjects may be enrolled if the drop-out rate is higher than 10%.

9.2. Treatment Assignment

Study drug will be administered with food in both the inpatient and outpatient treatment periods. Food intake will be standardized as specified by the Sponsor.

9.2.1. Part A

Subjects participating in Part A of the study will take study drug (SAGE-217 Oral Solution) in an open-label manner. Subjects will be administered a 30 mg dose of study drug at 8:00 PM (± 15 minutes) with food for 14 days (Day 1 to Day 14) as tolerated.

9.2.2. Part B

Subjects participating in the randomized, double-blind, placebo-controlled portion of the study (Part B) will be randomly assigned to receive SAGE-217 Capsules (30 mg) or matching placebo capsules in a 1:1 ratio according to a computer-generated randomization schedule; the randomization schedule will be stratified to allow for treatment balance within each use of antidepressant stratum.

Subjects, clinicians, and study team will be blinded to treatment allocation. The pharmacist and/or designated pharmacy staff, who will prepare the study drug according to the randomization schedule, and a Monitor, who will perform drug accountability during the study, will be unblinded.

9.3. Dose Adjustment Criteria

During the Treatment Period, subjects will be able to receive study drug as long as there are no dose-limiting safety/tolerability concerns.

In Part A, subjects who experience moderate or severe adverse events that according to the clinical judgement of the Investigator are related to study drug while receiving the 30 mg dose of study drug will receive 20 mg for the remaining of the Treatment Period. Subjects who experience moderate or severe related adverse events while receiving the 20 mg dose of study drug may not be able to continue receiving study drug based on the evaluation and clinical judgment of the Investigator, and may be terminated from the study.

In Part B, subjects who cannot tolerate 30 mg will receive 20 mg for the rest of the Treatment Period. Subjects who experience intolerable AEs at the 20 mg dose level may be terminated from the study at the discretion of the Investigator.

Dosing may also be modified based on tolerability as assessed with SSS scores. Any SSS score of ≥ 6 will be reassessed within 10 minutes. If a subject is receiving the 30 mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat assessment during normal waking hours, the dose will be decreased to 20 mg for the rest of the Treatment Period. If a subject is receiving the 20 mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat assessment during normal waking hours, then study drug will be discontinued and the subject will be terminated from the study.

9.4. Prior/Concomitant Medications

9.4.1. Prior/Concomitant Medications

Subjects will receive standard of care for adult patients diagnosed with moderate to severe MDD. Psychotropic medications, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the Day 15 assessments (Part A).

Eligible subjects in Part B will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 Capsules or matched placebo.

In this study, psychotropic medications refer to central nervous system active medications taken to help depressive symptoms, and include antidepressants, benzodiazepines, and hypnotic agents. Subjects presenting to the study on psychotropic medications may be eligible to participate if they have been on a stable dose for at least 14 days (Part A) or if the medications have been initiated at least 30 days prior to screening (Part B); the subject must remain at a stable dose until completion of the Day 15 assessments (Part B). Those subjects on benzodiazepines and hypnotic agents may be considered for eligibility based on specific discussions between the Investigator and the Sponsor to ensure safety. Subjects on other psychotropic medications, including stimulants, and mood stabilizers, are not eligible to participate in this study. Subjects who have been receiving atypical antipsychotics with the intent of treatment of depressive symptoms, but not psychotic symptoms, may be eligible.

Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study under the guidance outlined in [Section 9.4.2](#). In both Part A and Part B, all medications should be documented throughout the study from 30 days prior to signing the ICF through Day 28/42 (± 3 days) and recorded on the eCRF. Prior medications (ie, those taken prior to signing of ICF) that required washout for study entry will also be documented.

9.4.2. Restricted Medications

Restrictions on specific classes of medications include the following:

- Initiation of new antidepressant therapy is prohibited upon admission to the study center for those eligible subjects who desire study participation. Those subjects already taking an antidepressant at the time of study entry (and meeting all study inclusion criteria) will be permitted to remain on the pre-existing antidepressant at their current dose if they were on this medication for at least 30 days prior to study enrollment (Part B).

- Benzodiazepines are to be avoided as much as possible. Eligible subjects taking a stable dose of benzodiazepine for at least 30 days prior to enrollment in Part B will be discussed on a case-by-case basis with the Sponsor to determine eligibility. Subjects may be permitted to continue to take their current dose of the benzodiazepine (to prevent acute withdrawal), but no new benzodiazepine use will be permitted during the course of the study.
- The use of hypnotics for sleep/insomnia such as Ambien[®] and trazodone is to be avoided; use of hypnotics will be discussed on a case-by-case basis with the Sponsor.
- Anticonvulsants are prohibited. Atypical antipsychotics are allowed only if the indication has been for the treatment of the depressive episode and not for treatment of psychotic symptoms.

9.5. Treatment Compliance

Investigational product will be prepared by the site pharmacist and/or designated pharmacy staff. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for noncompliance will also be documented, including:

- Missed visits;
- Interruptions in the schedule of administration; and
- Nonpermitted medications.

The time at which study procedures are conducted should follow the protocol timelines as closely as possible.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HP β CD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dose. The 6 mg/mL stock SAGE-217 Oral Solution will be compounded from SAGE-217 Drug Substance Powder in the Bottle and Excipient (s) in the Bottle (manufactured under current Good Manufacturing Practice [GMP] conditions at Pharmatek) and further admixed at the clinical site in preparation for dosing. In Part A, doses will be prepared as an approximate 40 mL oral solution (containing 20 mg or 30 mg SAGE-217) to be swallowed all at once, followed by approximately 200 mL of water that has been used to rinse the dosing bottle.

SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients. For Part B, capsules will be available in 10-mg and 20-mg dose strengths. Subjects will be administered 2 capsules per dose (either two 10-mg capsules for the 20-mg dose, or one 10-mg plus one 20-mg capsule for the 30-mg dose).

Matching placebo capsules are hard gelatin capsules for oral administration containing only the excipients listed above for the active capsule treatment. Subjects will receive two placebo capsules per dose.

Detailed instructions for SAGE-217 Oral Solution preparation will be provided in the Pharmacy Manual.

10.2. Batch Formula for Stock SAGE-217 Oral Solution 6 mg/mL

For Part A, each bottle of SAGE-217 Oral Solution 6 mg/mL will be compounded at the clinical pharmacy from components manufactured by Pharmatek and supplied by the Sponsor per the directions provided in the Pharmacy Manual. The batch formula for a 125 mL solution of the 6 mg/mL stock solution is shown in [Table 5](#).

Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL

Ingredient	Compendia Specification	Concentration (mg/mL)	Amount (mg/Bottle)
SAGE-217	not applicable	6	750
HP β CD (Kleptose [®])	USP/EP	457	57,100
Sucralose	USP/NF	0.025	3.124
Water for Injection	USP	not applicable	85,650

Abbreviations: EP = European Pharmacopeia; HP β CD = hydroxypropyl- β -cyclodextrin; NF = National Formulary; USP = United States Pharmacopeia

10.3. Batch Formula for SAGE-217 Capsules

For Part B, SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients.

Placebo for Part B is hard gelatin capsules for oral administration containing only the excipients listed above for the active capsule treatment.

10.4. Study Drug Packaging and Labeling

The composition and pharmaceutical quality of the investigational product will be maintained according to the current GMP and Good Clinical Practice (GCP) guidelines and available for review in the study medication documentation. SAGE-217 Oral Solution for Part A will be provided to the site as powder in the bottle and excipient(s) in the bottle units to be compounded in the pharmacy at a volume of 125 mL of a 6 mg/mL stock solution and then further diluted to approximately 40 mL at the identified doses. SAGE-217 Capsules and matched placebo capsules for Part B will be provided to the sites in appropriately labeled bottles.

Study drug labels with all required information and conforming to all applicable Code of Federal Regulations and GMP/GCP guidelines will be prepared by the clinical research organization.

10.5. Study Drug Storage

Upon receipt of study drug, the Investigator or designee will inspect the materials and complete and return the acknowledgment of receipt form enclosed with the parcel. A copy of the signed receipt will be kept in the study files.

The SAGE-217 Oral Solution must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 11 days with room temperature excursions allowed for up to 24 hours after preparation), safely and separately from other drugs. SAGE-217 Capsules may be stored at room temperature. The study drug may not be used for any purpose other than the present study. After the study is completed, all unused study drug must be retained, returned as directed, or destroyed on site per the Sponsor's instructions.

The Investigator or designee will be responsible for ensuring appropriate storage, compounding, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the Sponsor or the Sponsor's representatives on request, and must include the information below:

- The identification of the subject to whom the drug was dispensed;
- The date(s) and quantity of the drug dispensed to the subject; and
- The product lot/batch number.

The preparation of the study drugs must be documented on a 'Drug Preparation and Dispensing Log Form' or similar form.

The drug inventory and any clinical supplies that have been destroyed must be documented. This documentation must include at least the information below or as agreed with the Sponsor:

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

10.6. Administration and Study Drug Accountability

Doses for Part A will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water that has been used to rinse the dosing bottle. The start time of swallowing the approximately 40 mL oral solution is time zero for all assessments. Subjects may have assistance from the clinic staff when taking the study drug.

For Part B, subjects will swallow two capsules per dose (either two 10-mg capsules for the 20-mg dose, or one 10-mg plus one 20-mg capsule for the 30-mg dose).

10.6.1. Study Drug Administration

While confined in the clinical unit (at least Day 1 through Day 7 of Part A and Part B), subjects will receive study drug at 8:00 PM (± 15 minutes) with food.

Food intake will be standardized as specified by the Sponsor. Subjects who cannot tolerate 30 mg will receive 20 mg for the rest of the Treatment Period. Subjects who experience intolerable AEs at the 20 mg dose level may be terminated from the study at the discretion of the Investigator.

Subjects may be discharged after a minimum 7-day inpatient stay, following completion of the Day 7 assessments. If their clinical condition does not allow discharge, the Investigator may keep the subjects as inpatients for a longer period of time.

For non-confinement days (Days 8 through 14 of Parts A and B), dosing will be done at the clinical site or, if suitable arrangements can be made, via home administration where local regulations allow. All dosing will be observed, either in the clinical unit or by a healthcare professional at home. Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.

10.6.2. Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator or designee must maintain a record of all study drug received, used, and discarded. It must be clear from the records which subject received which dose of active or matching placebo treatment.

The Sponsor will be permitted access to the study supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug

accountability reconciliation. Only unblinded personnel will be able to access the study drug and accountability documentation from first dosing through database hard lock.

10.7. Study Drug Handling and Disposal

The pharmacist or designee for drug accountability is to document the date and time of initial compounding (Part A only), subsequent admixture of dosing solutions (Part A only), administration of test article, and for which subject the study drug was intended (ie, record subject initials and birth date or other unique identifier).

At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions. The disposition of study drug will be documented.

11. ASSESSMENT OF EFFICACY

11.1. Hamilton Rating Scale for Depression (HAM-D)

The primary outcome measure in Part B will be the change from baseline in 17-item HAM-D total score at the end of the Treatment Period (Day 15). The HAM-D will be administered before, during, and after the administration of open-label (Part A) and blinded (Part B) study drug.

The 17-item HAM-D will be used to rate the severity of depression in subjects who are already diagnosed as depressed ([Williams 2013a](#); [Williams 2013b](#)). The 17-item HAM-D comprises individual ratings related to the following symptoms: depressed mood (sadness, hopeless, helpless, worthless), feelings of guilt, suicide, insomnia (early, middle, late), work and activities, retardation (slowness of thought and speech; impaired ability to concentrate; decreased motor activity), agitation, anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis, loss of weight, and insight. The HAM-D assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15, Day 21, and Day 28 for Part A and Day 15, Day 21, Day 28, Day 35, and Day 42 in Part B). Every effort should be made for the same rater to perform all HAM-D assessments for an individual subject.

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 (Part B), 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 . A copy of the HAM-D is provided in [Appendix 1](#).

11.2. Montgomery-Åsberg Depression Rating Scale (MADRS)

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

The MADRS assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15, Day 21, and Day 28 for Part A and Day 15, Day 21, Day 28, Day 35, and Day 42 in Part B).

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 questionnaire includes questions on the following symptoms:

1. Apparent sadness
2. Reported sadness
3. Inner tension

4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

The MADRS total score will be calculated as the sum of the ten individual item scores. A copy of the MADRS is provided in [Appendix 2](#).

11.3. Hamilton Anxiety Rating Scale (HAM-A)

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

The HAM-A assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15, Day 21, and Day 28 for Part A and Day 15, Day 21, Day 28, Day 35, and Day 42 in Part B). Every effort should be made for the same rater to perform all HAM-A assessments for an individual subject.

The HAM-A total score will be calculated as the sum of the 14 individual item scores. A copy of the HAM-A is provided in [Appendix 3](#).

11.4. Clinical Global Impression (CGI)

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

The Clinical Global Impression - Severity (CGI-S) uses a 7-point Likert scale to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating as 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=extremely ill ([Busner 2007a](#)). The CGI-S assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15, Day 21, and Day 28 for Part A and Day 15, Day 21, Day 28, Day 35, and Day 42 in Part B).

The CGI-I employs a 7-point Likert scale to measure the overall improvement in the subject's condition posttreatment. The Investigator will rate the subject's total improvement whether or

not it is due entirely to drug treatment. Response choices include: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse ([Busner 2007b](#)). The CGI-I is only rated at posttreatment assessments. By definition, all CGI-I assessments are evaluated against baseline conditions. CGI-I response will be defined as having a CGI-I score of “very much improved” or “much improved.” The CGI-I assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15, Day 21, and Day 28 for Part A and Day 15, Day 21, Day 35, and Day 42 in Part B). A copy of the CGI is provided in [Appendix 4](#).

11.5. Short Form-36 (SF-36)

The Medical Outcomes Study Short Form-36 (SF-36v2) is a 36-item measure of health status that has undergone validation in many different disease states ([Ware 2007](#)). The SF-36 covers eight health dimensions including four physical health status domains (physical functioning, role participation with physical health problems [role-physical], bodily pain, and general health) and four mental health status domains (vitality, social functioning, role participation with emotional health problems [role-emotional], and mental health). In addition, two summary scores, physical component summary (PCS) and mental component summary (MCS), are produced by taking a weighted linear combination of the eight individual domains. The SF-36v2 is available with two recall periods: the standard recall period is 4 weeks and the acute recall period is 1 week. This study will use the acute version, which asks patients to respond to questions as they pertain to the past week. Higher SF-36 scores indicate a better state of health. The SF-36 requires approximately 10 minutes to complete, and can be self-administered or completed by interview in person or by telephone. In Part B, the SF-36 assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15 and Day 42).

A copy of the SF-36 is provided in [Appendix 5](#).

11.6. The Fatigue Associated with Depression (FAs-D) Patient-Reported Outcome (PRO)

Fatigue is one of the most common symptoms of MDD. The Fatigue Associated with Depression Questionnaire (FAs-D) was developed to assess fatigue and its impact in patients with MDD. The 13-item patient-reported questionnaire was designed to assess fatigue associated with depression in the past week. Three scores are computed: a six-item fatigue experience subscale (fatigued, tired, exhausted, lack of energy, physically weak, and feeling like everything requires too much effort), a seven-item fatigue impact subscale (impact on household chores; family relationships; enjoyable activities; social activities with friends; self-care; intimate relationships; and productivity at work or school), and a total score (all 13 items) ([Matza 2015](#)). Items 12 (impact on intimate relationships) and 13 (impact on productivity at work or school) are not applicable to all subjects, so these items are not answered in some cases. The fatigue experience items are rated on a five-point scale with response options of “never,” “rarely,” “sometimes,” “often,” and “always.” The impact items are rated on a five-point scale with response options of “not at all,” “a little,” “somewhat,” “quite a bit,” and “very much.” The two subscales and the total score are computed as the mean of all answered items within each scale,

and each scale score has a possible range of 1 to 5, with higher scores representing greater fatigue. In Part B, the FAs-D assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15 and Day 42).

A copy of the FAs-D is provided in [Appendix 6](#).

11.7. Remission in Depression Questionnaire (RDQ)

Recent research suggests that the symptom-based definitions of remission used in efficacy studies do not adequately reflect the perspective of depressed patients receiving treatment in routine clinical settings. The Remission from Depression Questionnaire (RDQ) was developed to capture the broader array of domains considered by patients to be relevant to the construct of remission symptoms of depression, non-depressive symptoms, features of positive mental health, coping ability, functioning, life satisfaction, and a general sense of well-being. The RDQ is a reliable and valid measure that evaluates the multiple domains that depressed patients consider important in determining remission. The RDQ demonstrated excellent internal consistency, with a Cronbach's alpha of 0.97 for the total scale and above 0.80 for each of the seven subscales. The test-retest reliability of the total scale was 0.85 and above 0.60 for each subscale ([Zimmerman 2013](#); [Zimmerman 2014](#)). In Part B, the RDQ is to be completed at 8:00 AM (± 30 minutes) at each scheduled time point on Day 1, and in the morning during the Follow-up Period (Day 15 and Day 42).

A copy of the RDQ is located in [Appendix 9](#).

11.8. Health-Related Productivity Questionnaire (HRPQ)

The Health-Related Productivity Questionnaire (HRPQ) is a generic measure developed to measure health-related work productivity in patients with a particular disease and/or being treated for the disease. The instrument collects productivity data in terms of absenteeism, presenteeism, and combined lost productivity for three work venues: work outside home, housework, and classes/homework ([Kumar 2003](#)). In Part B, the HRPQ is to be completed at 8:00 AM (± 30 minutes) at each scheduled time point on Day 1, and in the morning during the Follow-up Period (Day 15 and Day 42).

A copy of the HRPQ is located in [Appendix 10](#).

12. PHARMACOKINETICS

12.1. Blood Sample Collection

Plasma samples for PK analysis in Part A and Part B will be collected predose on Days 2, 3, 4, 5, and 6, predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. The Investigator or designee will arrange to have the plasma samples processed, stored, and transported as directed for bioanalysis.

In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. An additional PK sample may be collected at any time if clinically indicated and at the discretion of the Investigator (eg, for unusual or severe adverse events).

Each sample will be marked with unique identifiers such as the study number, subject number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the CRF or electronically with a bar code or other method.

12.2. Storage and Shipment of Pharmacokinetic Samples

The plasma samples should be kept frozen at approximately -70 to -80°C until analyzed. They should be packed as directed to avoid breakage during transit and with sufficient dry ice to prevent thawing for at least 72 hours. A specimen-identification form must be completed and sent to the laboratory with each set of samples. The clinical site will arrange to have the plasma samples transported as directed for bioanalysis as detailed in the PK instructions.

12.3. Sample Analysis

Bioanalysis of plasma samples for the determination of SAGE-217 will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.

13. ASSESSMENT OF SAFETY

13.1. Safety Parameters

Safety and tolerability of study drug will be evaluated in Parts A and B by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, SSS, and adverse event reporting.

13.1.1. Demographic/Medical History

Age, race, and ethnic origin will be recorded at the Screening visit. The diagnosis of MDD will be determined using the SCID-I.

13.1.2. Vital Signs

Vital signs include respiratory rate, oral temperature, and supine (for at least 5 minutes prior to the measurement) and standing systolic and diastolic blood pressure and heart rate. Vital signs will be obtained within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 30 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between the hours of 11:00 PM and 06:00 AM.

From Day 1 through Day 7, vital signs and pulse oximetry will be performed at screening (vital signs only) and at the following time points: predose, 0.25, 0.5, 1, 2, and 12 hours after dosing. During the outpatient treatment period, vital signs will be completed prior to dosing and 1 hour after dosing. Vital signs may be repeated at the discretion of the Investigator or Visiting Home Healthcare Provider as clinically indicated.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visit; weight will also be measured on in the morning on Day 15, and during the follow-up visits on Days 21 and 28 for Part A and Days 21, 28, 35, and 42 in Part B.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening visit, Day 8, Day 15, and Day 21, with a brief physical examination on Day 28 in Part A; in Part B, a physical examination will be undertaken and recorded at the Screening visit, Day 8, and Day 15, with a brief physical examination on Day 42.

13.1.5. Electrocardiogram (ECG)

A 12-lead ECG will be assessed at the Screening visit and 1 hour ± 15 minutes after dosing on Days 1, 2, 7, and 14 and during the follow-up visit on Day 21. All time points are relative to the time of dosing. The standard intervals as well as any abnormalities will be recorded.

13.1.6. Laboratory Assessments

Blood and urine samples will be collected for hematology, serum chemistry, coagulation, select hormone parameters, and urinalysis at the Screening visit, and in the morning on Days 8 and 15 and during the follow-up visits (Days 21 and 28 for Part A and Days 21, 28, 35, and 42 for

Part B). Where consent is given, an optional blood sample for hormone and exploratory biochemistry testing will be collected at the Screening visit, Day 8 and Day 15 and an optional genetic sample for biomarker testing will be collected at the Screening visit.

Serum and urine samples for pregnancy tests will also be collected. These assessments should be performed as outlined below.

All required samples in Part A will be analyzed at local laboratories. All samples in Part B will be analyzed at the central laboratory. Subjects may be considered eligible for the study based on local laboratory results; however, screening samples in Part B must also be sent to the central laboratory. Both local and central screening labs must adhere to the visit window provided in the Schedule of Events.

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant (NCS) or abnormal, clinically significant (CS). Screening results considered abnormal, CS recorded at the Screening visit may make the subject ineligible for the study pending review by the Medical Monitor. Clinical laboratory results that are abnormal, CS during the study but within normal range at baseline and/or indicate a worsening from baseline will be considered adverse events, assessed according to [Section 13.2.1](#), and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count, including red blood cells, white blood cells with differentiation, hemoglobin, hematocrit, reticulocytes, and platelets. The coagulation panel will include activated partial thromboplastin time, prothrombin time, and international normalized ratio.

13.1.6.2. Blood Chemistry

Serum chemistry tests will include serum electrolytes; renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide; liver function tests, including alkaline phosphatase, total bilirubin, aspartate aminotransferase, and alanine aminotransferase; total protein; albumin; and thyroid stimulating hormone.

13.1.6.3. Urinalysis

Urinalysis will include assessment of protein, blood, glucose, ketones, bilirubin, urobilinogen, hemoglobin, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity.

13.1.6.4. Hormones and Exploratory Biochemistry

Optional blood samples will be collected and may be analyzed for stress hormone levels, kynurenine biochemistry, and markers of inflammation. Future research may suggest other biochemical pathways as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the exploratory biochemistry may involve study of additional unnamed molecular pathways, but only as related to disease susceptibility and drug action.

13.1.6.5. Virus Serology

Subjects will be screened for hepatitis (HBsAg and anti-HCV) and HIV prior to being enrolled in the study.

13.1.6.6. Pregnancy Test

Females of childbearing potential will be tested for pregnancy by serum pregnancy test at the Screening visit and by urine pregnancy test on Day 1 (predose) and at the follow-up visit on Day 28 for Part A or Day 42 for Part B. In addition, female subjects who prematurely discontinue before Day 28/42 will have a pregnancy test performed at the early termination visit.

13.1.6.7. Genetic Testing

Where consent is given, an optional genetic sample for biomarker testing will be collected at the Screening visit.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (ie, distribution, safety, tolerability, and efficacy) to SAGE-217. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (eg, cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of SAGE-217 (eg, AKR1C4 [3 α -hydroxysteroid dehydrogenase]), genes associated with the γ -aminobutyric acid (GABA) receptor (eg, GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3), and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

13.1.6.8. Drugs of Abuse and Alcohol

Part A: A urine sample for assessment of selected drugs of abuse (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene) and a serum or breath sample for alcohol screen will be collected at screening and predose on Day 1. Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics that have been initiated at least 14 days prior to admission to the study center at a stable dose following discussion with the Sponsor (see [Section 9.3](#)).

Part B: A urine and/or serum sample (as per the lab manual) for assessment of selected drugs of abuse (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene) will be collected at screening; a urine sample will be collected for assessment of drugs of abuse predose on Day 1. A serum or breath sample for alcohol screen (as per the standard procedures at each site) will be collected at screening and predose on Day 1. Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics that have been initiated at least 30 days prior to admission to the study center at a stable dose following discussion with the Sponsor (see [Section 9.3](#)).

13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the study using the C-SSRS. This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicidal ideation and behavior (Posner 2008a), and a post-baseline evaluation that focuses on suicidality since the last study visit (Posner 2008b). The C-SSRS includes ‘yes’ or ‘no’ responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

If, in the opinion of the Investigator, the subject is showing clinically meaningful changes in suicidality, no further study drug will be administered and the subject will be referred to a psychologist or psychiatrist for further evaluation. This information will be tracked.

The “Baseline/Screening” C-SSRS form will be completed at screening (lifetime history and past 24 months). The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points, as outlined in Table 2 and Table 3.

The C-SSRS is provided in Appendix 7.

13.1.8. Stanford Sleepiness Scale (SSS)

The SSS is subject-rated scale designed to quickly assess how alert a subject is feeling. Degrees of sleepiness and alertness are rated on a scale of 1 to 7, where the lowest score of ‘1’ indicates the subject is ‘feeling active, vital, alert, or wide awake’ and the highest score of ‘7’ indicates the subject is ‘no longer fighting sleep, sleep onset soon; having dream-like thoughts’ (Hoddes 1973).

In both Part A and Part B, from Day 1 through Day 7, SSS will be completed at the following time points: predose, 0.25, 0.5, 1, and 2 after dosing. The scale is to be completed within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between 11:00 PM and 06:00 AM during the inpatient treatment period. During the outpatient treatment period, SSS will be completed prior to dosing and 1 hour after dosing. All time points are relative to the time of dosing.

The SSS is provided in Appendix 8.

13.2. Adverse and Serious Adverse Events

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

13.2.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

13.2.1.3. Serious Adverse Event

A serious adverse event is an adverse event occurring during any study phase and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- It results in death
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- It results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All serious adverse events that occur after any subject has been enrolled, whether or not they are related to the study, must be recorded for the duration of the study on forms provided by Sage Therapeutics or designee.

13.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each adverse event (unrelated, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered “related.”

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

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

13.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as adverse events unless they prompt corrective medical action by the Investigator, constitute a serious adverse event, or lead to discontinuation of administration of study drug.

Information about adverse events will be collected from the signing of the ICF until the final visit of the study for that subject. Adverse events that occur after the first administration of study drug will be denoted TEAEs.

All adverse events, regardless of Investigator-determined causality, should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant.

The adverse event term should be reported in standard medical terminology when possible. For each adverse event, the Investigator will evaluate and report the onset (date and time), resolution or clinical plateau (date and time), severity, causality, action taken, outcome, and whether or not it caused the subject to discontinue the study.

Severity will be assessed according to the following scale:

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

13.5. Reporting Adverse Events

All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day 28 follow-up visit (Part A) or the Day 42 follow-up visit (Part B). Any serious adverse events considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All serious adverse events must be reported to the Sponsor or Sponsor’s designee immediately by phone and in writing within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the serious adverse event pages, verify the accuracy of the information recorded on the serious adverse event pages with the corresponding source documents, and send a copy to Sage Therapeutics or designee.

Additional follow-up information, if required or available, should be sent to Sage Therapeutics or designee within 24 hours of receipt; a follow-up serious adverse event form should be completed and placed with the original serious adverse event information and kept with the appropriate section of the study file.

Sage Therapeutics or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB of all serious adverse events that occur at his or her site if applicable per the IRB's requirements. Investigators will also be notified of all unexpected, serious, drug-related events (7-/15-Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB of these additional serious adverse events.

13.6. Emergency Identification of Study Drug

Part B of the study is double-blind. The pharmacist and/or designated pharmacy staff responsible for preparing the study drug will be unblinded and will retain an official paper copy of the randomization schedule. In addition, an unblinded Monitor will perform drug accountability during the study.

During the study, the blind is to be broken only when the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. Unless a subject is at immediate risk, the Investigator must make diligent attempts to contact the Sponsor prior to unblinding the study treatment administered to a subject. Any request from the Investigator about the treatment administered to study subjects must be discussed with the Sponsor. If the unblinding occurs without the Sponsor's knowledge, the Investigator must notify the Sponsor as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented in the source records. Unless a subject is at immediate risk, any request for the unblinding of individual subjects must be made in writing to the Sponsor and approved by the appropriate Sponsor personnel, according to standard operating procedures. The blinding of the study will be broken after the database has been locked. Electronic copies of the randomization code will be made available to the laboratory performing the bioanalytical analyses in order to allow for limited analysis of samples from subjects receiving matching placebo.

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

13.7. Pregnancy

In the event either the subject or their partner becomes pregnant, the pregnancy will be followed. By enrolling in this study, all subjects are consenting to pregnancies being followed to conclusion either by the site if the study is still active or through Sage standard pharmacovigilance services if the study is no longer active.

14. STATISTICS

14.1. Analysis Sets and Methods

14.1.1. Data Analysis Sets

The Safety Set (for both Part A and Part B), defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set (for both Part A and Part B), defined as all subjects in the Safety Set who complete at least 1 day of dosing of study drug and have at least one post-baseline efficacy evaluation, will be used to analyze efficacy data.

The PK Set will consist of all subjects in the Safety Set with sufficient plasma concentrations for PK evaluations, and will be used to summarize PK data.

14.2. Handling of Missing Data

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

14.3. General Considerations

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

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

14.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized using the Safety Set.

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

Medical/family history will be listed by subject.

14.5. Efficacy Analyses

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data. For (the open-label) Part A, efficacy data will be summarized descriptively. For Part B, subjects will be analyzed according to randomized treatment.

An analysis of ten subjects completing Part A is planned to inform Part B study conduct.

For Part B of the study, change from baseline to each assessment in HAM-D total score will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include center, treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. Center will be treated as a random effect while all other explanatory variables will be treated as fixed effects. All post-baseline time points will be included in the model. The main comparison will be between SAGE-217 Capsules and matching placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means), 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. Compound symmetry covariance structure will be used if there is a convergence issue with the unstructured covariance model.

Descriptive statistics for HAM-D total score and change from baseline values will be presented by assessment time point for Part A. Summaries will include n, mean, SD, median, minimum, and maximum.

Similar to those methods described above for Part B, an MMRM will be used for the analysis of the following variables: changes from baseline in MADRS total score and HAM-A total score, and select individual item and subscale scores. For each model, the comparison of interest will be between SAGE-217 Capsules and matching placebo at the 15-day time point. Model-based point estimates (ie, LS means), 95% confidence intervals, and p-values will be reported.

Generalized estimating equation (GEE) methods will be used for the analysis of the following binary variables: HAM-D response (defined as $\geq 50\%$ reduction from baseline in HAM-D total score), HAM-D remission (defined as HAM-D total score of ≤ 7.0), and CGI-I response. GEE models will include terms for center, treatment, baseline score, antidepressant use strata, assessment time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 Capsule and matching placebo at the 15-day time point in Part B. Model-based point estimates (ie, odds ratios), 95% confidence intervals, and p-values will be reported. For the CGI-I response analysis, baseline CGI-S score will be included in the model.

For all scores, descriptive statistics, change from baseline values, and response variables will be presented by treatment and assessment time point. Summaries will include n, mean, SD, median, minimum, and maximum.

Descriptive summary statistics will be provided for SF-36, FAs-D, RDQ, and HRPQ.

14.6. Safety Analyses

Safety and tolerability of study drug will be evaluated by adverse events, concomitant medication usage, changes from baseline in physical examination, vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Sedation will be assessed using the SSS. Safety data will be listed by subject and summarized by treatment group. All safety summaries will be performed on the Safety Population.

14.6.1. Adverse Events

The analysis of adverse events will be based on the concept of TEAEs. A TEAE is defined as an adverse event with onset after the start of study drug, or any worsening of a pre-existing medical

condition/adverse event with onset after the start of study drug and until 7 days after the last dose. The incidence of TEAEs will be summarized overall and by Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or higher System Organ Class (SOC) and preferred term. Incidences will be presented in order of decreasing frequency for the SAGE-217 treatment group (Oral Solution for Part A and Capsules for Part B). In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see [Section 13.3](#)).

Treatment-emergent adverse events leading to discontinuation and serious adverse events (see [Section 13.2.1.3](#) for definition) with onset after the start of randomized study drug will also be summarized.

All adverse events and serious adverse events (including those with onset or worsening before the start of study drug) through the Day 28 follow-up visit (Part A) or Day 42 follow-up visit (Part B) will be listed.

14.6.2. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline in clinical laboratory measures will be summarized.

14.6.3. Physical Examinations

Any clinically significant change in physical examination compared to those observed at screening should be noted as an adverse event.

14.6.4. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from randomization in vital signs will be summarized by time point.

14.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, QTc, and QT interval calculated using the Fridericia method (QTcF). Any clinically significant abnormalities or changes in ECGs should be listed as an adverse event. Electrocardiogram findings will be listed by subject and visit.

14.6.6. 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 2016, or later.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken prior to the first dose of study drug. Concomitant medications are defined as those with a start date on or after the first dose of study drug, or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

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

14.6.7. Columbia Suicide Severity Rating Scale

Suicidality data collected on the C-SSRS at baseline and by visit during the Treatment Period will be listed for all subjects. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

14.6.8. Stanford Sleepiness Scale

Sedation data collected on the SSS will be listed for all subjects. Changes in score over time will be represented graphically, and change from Day 1 will be measured.

14.7. Pharmacokinetic Analyses

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics. The PK parameters to be summarized where possible will include AUC_{∞} , C_{max} , t_{max} , $t_{1/2}$, and C_{ss} . Time at maximum (peak) plasma concentration (t_{max}) will be summarized using n, mean, SD, median, minimum, and maximum. All other PK parameters will be summarized using n, geometric mean, coefficient of variation, median, minimum, and maximum and listed by subject.

Plasma concentrations and PK parameters will be listed by subject.

In addition to typical descriptive statistics, summaries should include geometric mean, coefficient of variation, and geometric coefficient of variation.

14.8. Determination of Sample Size

The sample size of ten subjects for Part A was selected based on clinical and not statistical considerations.

For Part B, assuming a two-sided t-test at an alpha level of 0.05, a sample size of 40 subjects per group would provide 90% power to detect an effect size of 0.75 between the SAGE-217 Capsules and matching placebo groups with regard to the efficacy outcome variable of change from baseline in HAM-D total score. An effect size of 0.75 corresponds to a matching placebo-adjusted difference of 7.5 points in the change from baseline in HAM-D total score at 15 days with an assumed SD of 10 points. By including two treatment groups and using a 1:1 randomization, a total of 80 subjects are required. Assuming a non-evaluability rate of 10%, approximately 88 subjects will be randomized. Additional subjects may be enrolled if the drop-out rate is higher than 10%.

14.9. Changes From Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final statistical analysis plan.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Sage Therapeutics or designee will visit the investigational study site to:

- Determine the adequacy of the facilities; and
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sage Therapeutics or designee or its representatives. This will be documented in a Clinical Study Agreement between Sage Therapeutics and the Investigator.

During the study, a monitor from Sage Therapeutics or designee 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 eCRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts);
- Record and report any protocol deviations not previously sent to Sage Therapeutics or designee; and
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to Sage Therapeutics or designee and those serious adverse events that met criteria for reporting have been forwarded to the IRB.

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

15.2. Audits and Inspections

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

15.3. Institutional Review Board (IRB)

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

16. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator and institution will permit study-related monitoring, audits, IRB review, and regulatory inspections as requested by the Food and Drug Administration, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs) in addition to eCRFs.

Quality assurance and quality-control systems with written standard operating procedures will be followed to ensure this study will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality-assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements made by the Sponsor with the Investigator/institution and any other parties involved with the clinical study will be in writing in a separate agreement.

17. ETHICS

17.1. Ethics Review

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

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 subjects 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 with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sage Therapeutics or designee 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.

17.2. 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 its most recent amendment (2008) and are consistent with ICH/GCP and other applicable regulatory requirements.

17.3. Written Informed Consent

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

As additional assessments, the ICF will contain provisions for optional consent for the collection of blood samples for biochemistry during screening, Day 8, and Day 15 and biomarker testing during screening. The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

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

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

18. DATA HANDLING AND RECORDKEEPING

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

Electronic CRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, and subject status.

The Investigator will have access to the electronic data capture system and will receive a copy of the subject eCRF data at the end of the study. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

18.1. Inspection of Records

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

18.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuation of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18.3. Confidentiality

To maintain subject privacy, all eCRFs, study reports, and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

19. 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.

20. LIST OF REFERENCES

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21. APPENDICES

APPENDIX 1. HAMILTON RATING SCALE FOR DEPRESSION, 17-ITEM (HAM-D)

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON DEPRESSION RATING SCALE – 17 ITEM VERSION (SIGH-D-17) – 24 HR TWENTY-FOUR HOUR ASSESSMENT VERSION

Janet B.W. Williams, PhD

INTERVIEWER

The first question for each item, in bold type, should be asked exactly as written. Often this question will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information. You should ask for examples for any symptoms acknowledged as present (e.g., "Can you give me an example of that?"). For some of the HAM-D items, you may find you have already asked about some of the symptoms (for a previous item). You do not need to repeat questions about these symptoms unless you need additional information to rate their severity.

Time period. In this 24 hour version, the interview questions indicate that the ratings should be based on the subject's condition over the past 24 hours.

Referent of "usual" or "normal" condition. In the HAM-D, most items are rated positive only if they represent a change from usual functioning. In most cases, this version of the SIGH-D will be used at some time after the original Past Week version of the scale, during which a euthymic baseline (the most recent 2-month period of non-depressed functioning) was established. This euthymic baseline should be the referent for determining change. When no clear euthymic baseline can be established, one should rate symptomatic behavior as one sees it, even if it is not a change from the patient's usual dysphoric self.

Administration method. This version includes interview questions to help the clinician rate psychomotor agitation and psychomotor retardation when the interview is administered by telephone. Several research studies have demonstrated that depression scale scores are equivalent whether the scale is administered face-to-face, by telephone, or by video (Williams JBW and Kobak KA: Development and Reliability of a Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale. Br J Psychiatry 192, 52-58, 2008; Kobak KA: A comparison of face-to-face and remote administration of the Hamilton Depression Rating Scale via videoconferencing. J Telemed Telecare 10, 231-235, 2004).

This instrument provides an interview guide for the Hamilton Depression Scale (Hamilton, Max: A rating scale for depression. J Neurol Neurosurg Psychiatr 23:56-61, 1960). The anchor point descriptions for all items except Helplessness, Hopelessness, and Worthlessness, in the 25-item version with very minor modifications, have been taken from the ECDEU Assessment Manual (Guy, William, ECDEU Assessment Manual for Psychopharmacology, Revised 1976, DHEW Publication No. (ADM) 76-338). The loss of weight item has been simplified to eliminate the section for ratings by ward staff and the "Not assessed" anchor point. A reliability study of the SIGH-D (interview guide for the HAM-D alone) was published in the Archives of General Psychiatry (1988;45:742-747). Additional designators were added in parentheses to the anchor points by Kobak, Lipsitz and Williams to further standardize ratings.

For further information and permission to use or translate the SIGH-D, contact Dr. Williams at jbw@nyu.edu.

STRUCTURED INTERVIEW GUIDE FOR THE
HAMILTON DEPRESSION RATING SCALE – 17 ITEM VERSION (SIGH-D-17) – 24 HR
TWENTY-FOUR HOUR ASSESSMENT VERSION

PT'S INITIALS: _____ TIME BEGAN SIGH-D: _____ INTERVIEWER: _____

DATE TODAY: ____/____/____ DATE OF LAST EVALUATION: ____/____/____

OVERVIEW: How have you been feeling since yesterday at this time? IF OUTPATIENT: Have you been working? IF NOT: Why not?

What's your mood been like since this time yesterday (compared to when you feel okay)?

Have you been feeling down or depressed?

IF YES: Can you describe what this feeling has been like for you? How bad is the feeling?

Does the feeling lift at all if something good happens?

How are you feeling about the future?

IF UNKNOWN: Have you been feeling discouraged or pessimistic since this time yesterday?

IF YES: What have your thoughts been?

Since this time yesterday, how often have you felt (OWN EQUIVALENT FOR DEPRESSED MOOD)? For how much of the time?

Have you been crying at all? How often?

1. DEPRESSED MOOD (sadness, hopeless, helpless, worthless):

0	Absent
1	Indicated only on questioning (<i>occasional, mild depression</i>)
2	Spontaneously reported verbally (<i>persistent, mild to moderate depression</i>)
3	Communicated non-verbally, i.e., facial expression, posture, voice, tendency to weep (<i>persistent, moderate to severe depression</i>)
4	VIRTUALLY ONLY those feeling states reported in spontaneous verbal and non-verbal communication (<i>persistent, very severe depression, with extreme hopelessness or tearfulness</i>)

INTERVIEWER: IF SCORED 1-4 ABOVE, REVIEW DATE OF EUTHYMIC BASELINE:
How long have you been feeling this way (OWN EQUIVALENT FOR DEPRESSED MOOD)?
(When was the last time you were feeling well, that is, not depressed at all, for at least 2 months?)

<p>How have you been spending your time since yesterday at this time (when not at work)?</p> <p>Have you felt interested in doing (THOSE THINGS), or do you feel you have to push yourself to do them?</p> <p>How much less interested in these things have you been, since this time yesterday, compared to when you're not depressed? How hard to do you have to push yourself to do them?</p> <p>Have you stopped doing anything you used to do? (What about hobbies?) IF YES: Why?</p> <p>About how many hours a day have you spent doing things that interest you, since this time yesterday?</p> <p>Is there anything you look forward to?</p> <p>IF WORKING (IN OR OUT OF THE HOME): Since this time yesterday, have you been able to get as much (work) done as you usually do?</p> <p>How much less productive or efficient are you compared to before you were depressed?</p>	<p>2. WORK AND ACTIVITIES:</p> <table border="1"> <tr> <td>0</td> <td>No difficulty</td> </tr> <tr> <td>1</td> <td>Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies (<i>mild reduction in interest or pleasure; no clear impairment in functioning</i>)</td> </tr> <tr> <td>2</td> <td>Loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities) (<i>clear reduction in interest, pleasure or functioning</i>)</td> </tr> <tr> <td>3</td> <td>Decrease in actual time spent in activities or decrease in productivity. In hosp., pt. spends less than 3 hrs./day in activities (<i>hospital job or hobbies</i>) exclusive of ward chores (<i>profound reduction in interest, pleasure, or functioning</i>)</td> </tr> <tr> <td>4</td> <td>Stopped working because of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted (<i>unable to work or fulfill primary role because of illness, and total loss of interest</i>)</td> </tr> </table>	0	No difficulty	1	Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies (<i>mild reduction in interest or pleasure; no clear impairment in functioning</i>)	2	Loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities) (<i>clear reduction in interest, pleasure or functioning</i>)	3	Decrease in actual time spent in activities or decrease in productivity. In hosp., pt. spends less than 3 hrs./day in activities (<i>hospital job or hobbies</i>) exclusive of ward chores (<i>profound reduction in interest, pleasure, or functioning</i>)	4	Stopped working because of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted (<i>unable to work or fulfill primary role because of illness, and total loss of interest</i>)
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<p>Now let's talk about your sleep. What were your usual hours of going to sleep and waking up, before this began?</p> <p>When have you fallen asleep and awakened since this time yesterday?</p>							
<p>Have you had any trouble falling asleep at the beginning of your sleep time, over the past 24 hours? (Right after you went to bed, how long did it take you to fall asleep?)</p> <p>Did you change the time at which you tried to get to sleep, compared to before you became depressed?</p>	<p>3. INSOMNIA EARLY (INITIAL INSOMNIA):</p> <table border="1"> <tr> <td>0</td> <td>No difficulty falling asleep</td> </tr> <tr> <td>1</td> <td>Complains of occasional difficulty falling asleep (<i>i.e., 30 minutes or more, 2-3 nights</i>)</td> </tr> <tr> <td>2</td> <td>Complains of nightly difficulty falling asleep (<i>i.e., 30 minutes or more, 4 or more nights</i>)</td> </tr> </table>	0	No difficulty falling asleep	1	Complains of occasional difficulty falling asleep (<i>i.e., 30 minutes or more, 2-3 nights</i>)	2	Complains of nightly difficulty falling asleep (<i>i.e., 30 minutes or more, 4 or more nights</i>)
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<p>Since this time yesterday, did you wake up in the middle of your sleep time? IF YES: Did you get out of bed? What did you do? (Only go to the bathroom?)</p> <p>When you got back in bed, were you able to fall right back asleep? How long did it take you to fall back asleep?</p> <p>Did you wake up more than once during your sleep time in the past 24 hours? (IF YES: How long did it take for you to fall back to sleep each time?)</p> <p>Have you felt your sleeping has been restless or disturbed since this time yesterday?</p>	<p>4. INSOMNIA MIDDLE:</p> <table border="1"> <tr> <td>0</td> <td>No difficulty</td> </tr> <tr> <td>1</td> <td>Complains of being restless and disturbed during the night (or occasional difficulty, i.e., 2-3 nights, 30 minutes or more)</td> </tr> <tr> <td>2</td> <td>Waking during the night; any getting out of bed (except to void) (often, i.e., 4 or more nights of difficulty, 30 minutes or more)</td> </tr> </table>	0	No difficulty	1	Complains of being restless and disturbed during the night (or occasional difficulty, i.e., 2-3 nights, 30 minutes or more)	2	Waking during the night; any getting out of bed (except to void) (often, i.e., 4 or more nights of difficulty, 30 minutes or more)
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2	Waking during the night; any getting out of bed (except to void) (often, i.e., 4 or more nights of difficulty, 30 minutes or more)						
<p>What time did you wake up for the last time, since this time yesterday?</p> <p>IF EARLY: Is that with an alarm clock, or did you just wake up yourself? What time do you usually wake up (that is, when you feel well)?</p>	<p>5. INSOMNIA LATE (TERMINAL INSOMNIA):</p> <table border="1"> <tr> <td>0</td> <td>No difficulty</td> </tr> <tr> <td>1</td> <td>Waking in early hours of morning but goes back to sleep (occasional, i.e., 2-3 nights difficulty)</td> </tr> <tr> <td>2</td> <td>Unable to fall asleep again if gets out of bed (often, i.e., 4 or more nights difficulty)</td> </tr> </table>	0	No difficulty	1	Waking in early hours of morning but goes back to sleep (occasional, i.e., 2-3 nights difficulty)	2	Unable to fall asleep again if gets out of bed (often, i.e., 4 or more nights difficulty)
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2	Unable to fall asleep again if gets out of bed (often, i.e., 4 or more nights difficulty)						
<p>Sometimes, along with depression or anxiety, people might lose interest in sex. Since this time yesterday, how has your interest in sex been? (I'm not asking about actual sexual activity, but about your interest in sex.)</p> <p>Has there been any change in your interest in sex (from when you were feeling OK)?</p> <p>IF YES: How much less interest have you had in the past 24 hours, compared to when you're not depressed? (Is it a little less or a lot less?)</p>	<p>6. GENITAL SYMPTOMS (such as loss of libido, menstrual disturbances):</p> <table border="1"> <tr> <td>0</td> <td>Absent</td> </tr> <tr> <td>1</td> <td>Mild (somewhat less interest than usual)</td> </tr> <tr> <td>2</td> <td>Severe (a lot less interest than usual)</td> </tr> </table>	0	Absent	1	Mild (somewhat less interest than usual)	2	Severe (a lot less interest than usual)
0	Absent						
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<p>How has your appetite been since this time yesterday? (What about compared to your usual appetite?)</p> <p>IF LESS: How much less than usual?</p> <p>Have you had to force yourself to eat?</p> <p>Have other people had to urge you to eat? (Have you skipped meals?)</p>	<p>7. SOMATIC SYMPTOMS GASTROINTESTINAL:</p> <table border="1"> <tr> <td>0</td> <td>None</td> </tr> <tr> <td>1</td> <td>Loss of appetite but eating without encouragement (appetite somewhat less than usual)</td> </tr> <tr> <td>2</td> <td>Difficulty eating without urging (appetite significantly less than usual)</td> </tr> </table>	0	None	1	Loss of appetite but eating without encouragement (appetite somewhat less than usual)	2	Difficulty eating without urging (appetite significantly less than usual)
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<p>Have you lost any weight since this (DEPRESSION) began?</p> <p>IF YES: Do you think you lost any weight in the last 24 hours? (Was it because of feeling depressed or down?) How much do you think you lost?</p> <p>IF NOT SURE: Do you think your clothes are any looser on you?</p> <p>FOLLOW-UP: Have you gained back any of the weight you've lost since this (DEPRESSION) began? IF YES: How much?</p>	<p>8. LOSS OF WEIGHT</p> <p>Rate by history:</p> <table border="1"> <tr> <td>0</td> <td>No weight loss</td> </tr> <tr> <td>1</td> <td>Probable weight loss due to current depression</td> </tr> <tr> <td>2</td> <td>Definite (<i>according to patient</i>) weight loss due to depression</td> </tr> </table>	0	No weight loss	1	Probable weight loss due to current depression	2	Definite (<i>according to patient</i>) weight loss due to depression				
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<p>How has your energy been since this time yesterday?</p> <p>IF LOW ENERGY: Have you felt tired? (How much of the time? How bad has it been?)</p> <p>Since this time yesterday, have you had any aches or pains? (What about backaches or muscle aches?) (How much of the time? How bad has it been?)</p> <p>Have you felt any heaviness in your limbs, back, or head?</p>	<p>9. SOMATIC SYMPTOMS GENERAL:</p> <table border="1"> <tr> <td>0</td> <td>None</td> </tr> <tr> <td>1</td> <td>Heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatigability (<i>somewhat less energy than usual; mild, intermittent loss of energy or muscle aches/heaviness</i>)</td> </tr> <tr> <td>2</td> <td>Any clear-cut symptoms (<i>persistent, significant loss of energy or muscle aches/heaviness</i>)</td> </tr> </table>	0	None	1	Heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatigability (<i>somewhat less energy than usual; mild, intermittent loss of energy or muscle aches/heaviness</i>)	2	Any clear-cut symptoms (<i>persistent, significant loss of energy or muscle aches/heaviness</i>)				
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<p>Since this time yesterday, have you been putting yourself down, feeling you've done things wrong, or let others down?</p> <p>IF YES: What have your thoughts been?</p> <p>Have you been feeling guilty about anything that you've done or not done?</p> <p>IF YES: What have your thoughts been?</p> <p>What about things that happened a long time ago?</p> <p>Have you thought that you've brought (THIS DEPRESSION) on yourself in some way?</p> <p>(Have you been hearing voices or seeing visions since this time yesterday? IF YES: Tell me about that.)</p>	<p>10. FEELINGS OF GUILT:</p> <table border="1"> <tr> <td>0</td> <td>Absent</td> </tr> <tr> <td>1</td> <td>Self-reproach; feels he has let people down</td> </tr> <tr> <td>2</td> <td>Ideas of guilt or rumination over past errors or sinful deeds (<i>feelings of guilt, remorse or shame</i>)</td> </tr> <tr> <td>3</td> <td>Present illness is a punishment; delusions of guilt (<i>severe, pervasive feelings of guilt</i>)</td> </tr> <tr> <td>4</td> <td>Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations</td> </tr> </table>	0	Absent	1	Self-reproach; feels he has let people down	2	Ideas of guilt or rumination over past errors or sinful deeds (<i>feelings of guilt, remorse or shame</i>)	3	Present illness is a punishment; delusions of guilt (<i>severe, pervasive feelings of guilt</i>)	4	Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
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<p>Since this time yesterday, have you had thoughts that life is not worth living?</p> <p>What about thinking you'd be better off dead?</p> <p>Have you had thoughts of hurting or killing yourself? IF YES: What have you thought about? Have you actually done anything to hurt yourself?</p>	<p>11. SUICIDE:</p> <table border="1"> <tr> <td>0</td> <td>Absent</td> </tr> <tr> <td>1</td> <td>Feels life is not worth living</td> </tr> <tr> <td>2</td> <td>Wishes he were dead or any thoughts of possible death to self</td> </tr> <tr> <td>3</td> <td>Suicidal ideas or gesture</td> </tr> <tr> <td>4</td> <td>Attempts at suicide</td> </tr> </table>	0	Absent	1	Feels life is not worth living	2	Wishes he were dead or any thoughts of possible death to self	3	Suicidal ideas or gesture	4	Attempts at suicide
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<p>Have you been feeling anxious or tense since this time yesterday? IF YES: Is this more than is normal for you?</p> <p>Have you been feeling irritable since this time yesterday? (IF YES): Can you give me some examples? How bad has it been?</p> <p>Have you been worrying a lot about little things, things you don't ordinarily worry about? IF YES: Like what, for example?</p> <p>How about worrying about big problems more than you need to?</p> <p>How much of the time has that happened since this time yesterday?</p> <p>Has this caused you any problems or difficulties? IF YES: Like what, for example?</p>	<p>12. ANXIETY PSYCHIC:</p> <table border="1"> <tr> <td>0</td> <td>No difficulty</td> </tr> <tr> <td>1</td> <td>Subjective tension and irritability (<i>mild, occasional</i>)</td> </tr> <tr> <td>2</td> <td>Worrying about minor matters (<i>moderate, causes some distress</i>)</td> </tr> <tr> <td>3</td> <td>Apprehensive attitude apparent in face or speech (<i>severe; significant impairment in functioning due to anxiety</i>)</td> </tr> <tr> <td>4</td> <td>Fears expressed without questioning (<i>symptoms incapacitating</i>)</td> </tr> </table>	0	No difficulty	1	Subjective tension and irritability (<i>mild, occasional</i>)	2	Worrying about minor matters (<i>moderate, causes some distress</i>)	3	Apprehensive attitude apparent in face or speech (<i>severe; significant impairment in functioning due to anxiety</i>)	4	Fears expressed without questioning (<i>symptoms incapacitating</i>)
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<p>Tell me if you've had any of the following physical symptoms since this time yesterday. (READ LIST)</p> <p>FOR EACH SX ACKNOWLEDGED AS PRESENT: How much has (THE SX) been bothering you since this time yesterday? [How bad has it gotten? How much of the time, or how often, have you had it? Did (the symptom) interfere at all with your functioning or your usual activities?]</p> <p>NOTE: DO NOT RATE SXs THAT ARE CLEARLY RELATED TO A DOCUMENTED PHYSICAL CONDITION.</p>	<p>13. ANXIETY SOMATIC (physiologic concomitants of anxiety, such as GI - dry mouth, gas, indigestion, diarrhea, stomach cramps, belching CV - heart palpitations, headaches Resp - hyperventilating, sighing Urinary frequency Sweating):</p> <table border="1"> <tr><td>0</td><td>Not present</td></tr> <tr><td>1</td><td>Mild (<i>symptom(s) present only infrequently, no impairment, minimal distress</i>)</td></tr> <tr><td>2</td><td>Moderate (<i>symptom(s) more persistent, or some interference with usual activities, moderate distress</i>)</td></tr> <tr><td>3</td><td>Severe (<i>significant impairment in functioning</i>)</td></tr> <tr><td>4</td><td>Incapacitating</td></tr> </table>	0	Not present	1	Mild (<i>symptom(s) present only infrequently, no impairment, minimal distress</i>)	2	Moderate (<i>symptom(s) more persistent, or some interference with usual activities, moderate distress</i>)	3	Severe (<i>significant impairment in functioning</i>)	4	Incapacitating
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<p>Since this time yesterday, how much have your thoughts been focused on your physical health or how your body is working (compared to your normal thinking)? (Have you worried a lot about being or becoming physically ill? Have you really been preoccupied with this?)</p> <p>Have you worried a lot that you have a specific medical illness?</p> <p>Do you complain much about how you feel physically?</p> <p>Have you seen a doctor about these problems since this time yesterday? IF YES: What did the doctor say?</p>	<p>14. HYPOCHONDRIASIS:</p> <table border="1"> <tr><td>0</td><td>Not present</td></tr> <tr><td>1</td><td>Self-absorption (<i>bodily</i>) (<i>some inappropriate worry about his/her health OR slightly concerned despite reassurance</i>)</td></tr> <tr><td>2</td><td>Preoccupation with health (<i>often has excessive worries about his/her health OR definitely concerned has specific illness despite medical reassurance</i>)</td></tr> <tr><td>3</td><td>Frequent complaints, requests for help, etc. (<i>is certain there is a physical problem which the doctors cannot confirm; exaggerated or unrealistic concerns about body and physical health</i>)</td></tr> <tr><td>4</td><td>Hypochondriacal delusions</td></tr> </table>	0	Not present	1	Self-absorption (<i>bodily</i>) (<i>some inappropriate worry about his/her health OR slightly concerned despite reassurance</i>)	2	Preoccupation with health (<i>often has excessive worries about his/her health OR definitely concerned has specific illness despite medical reassurance</i>)	3	Frequent complaints, requests for help, etc. (<i>is certain there is a physical problem which the doctors cannot confirm; exaggerated or unrealistic concerns about body and physical health</i>)	4	Hypochondriacal delusions
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<p>RATING BASED ON OBSERVATION DURING INTERVIEW</p>	<p>15. INSIGHT:</p> <table border="1"> <tr><td>0</td><td>Acknowledges being depressed and ill OR not currently depressed</td></tr> <tr><td>1</td><td>Acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc.</td></tr> <tr><td>2</td><td>Denies being ill at all</td></tr> </table>	0	Acknowledges being depressed and ill OR not currently depressed	1	Acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc.	2	Denies being ill at all				
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<p>RATING BASED ON OBSERVATION DURING INTERVIEW</p> <p>IF INTERVIEWING BY PHONE:</p> <p>During this interview have you been fidgeting a lot or moving around a lot in your chair?</p> <p>Have you had trouble sitting still?</p> <p>Have you been shaking your legs or playing with your hair or your hands?</p>	<p>16. AGITATION:</p> <table border="1"> <tr> <td>0</td> <td>None</td> </tr> <tr> <td>1</td> <td>Fidgetiness (<i>slight agitation or mild restlessness</i>)</td> </tr> <tr> <td>2</td> <td>Playing with hands, hair, etc. (<i>moderate to marked restlessness or agitation</i>)</td> </tr> <tr> <td>3</td> <td>Moving about, can't sit still (<i>cannot remain seated</i>)</td> </tr> <tr> <td>4</td> <td>Hand-wringing, nail biting, hair-pulling, biting of lips (<i>interview cannot be conducted; severe agitation</i>)</td> </tr> </table>	0	None	1	Fidgetiness (<i>slight agitation or mild restlessness</i>)	2	Playing with hands, hair, etc. (<i>moderate to marked restlessness or agitation</i>)	3	Moving about, can't sit still (<i>cannot remain seated</i>)	4	Hand-wringing, nail biting, hair-pulling, biting of lips (<i>interview cannot be conducted; severe agitation</i>)
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3	Moving about, can't sit still (<i>cannot remain seated</i>)										
4	Hand-wringing, nail biting, hair-pulling, biting of lips (<i>interview cannot be conducted; severe agitation</i>)										
<p>RATING BASED ON OBSERVATION DURING INTERVIEW</p> <p>IF INTERVIEWING BY PHONE:</p> <p>During this interview have you been moving slowly, reacting slowly, or speaking more slowly than usual for you?</p>	<p>17. RETARDATION (slowness of thought and speech; impaired ability to concentrate; decreased motor activity):</p> <table border="1"> <tr> <td>0</td> <td>Normal speech and thought</td> </tr> <tr> <td>1</td> <td>Slight retardation at interview (<i>mild psychomotor retardation</i>)</td> </tr> <tr> <td>2</td> <td>Obvious retardation at interview (<i>moderate; some difficulty with interview, noticeable pauses and slowness of thought</i>)</td> </tr> <tr> <td>3</td> <td>Interview difficult (<i>severe psychomotor retardation; very long pauses</i>)</td> </tr> <tr> <td>4</td> <td>Complete stupor (<i>extreme retardation; interview barely possible</i>)</td> </tr> </table>	0	Normal speech and thought	1	Slight retardation at interview (<i>mild psychomotor retardation</i>)	2	Obvious retardation at interview (<i>moderate; some difficulty with interview, noticeable pauses and slowness of thought</i>)	3	Interview difficult (<i>severe psychomotor retardation; very long pauses</i>)	4	Complete stupor (<i>extreme retardation; interview barely possible</i>)
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TIME ENDED SIGH-D-17:	_____ AM / PM ET / CT / PT
TOTAL HAM-D-17 SCORE:	_____

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**STRUCTURED INTERVIEW GUIDE FOR THE
HAMILTON DEPRESSION RATING SCALE – 17 ITEM VERSION (SIGH-D-17)**

Janet B.W. Williams, PhD

INTERVIEWER

The first question for each item should be asked exactly as written. Often this question will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information. You should ask for examples for any symptoms acknowledged as present (e.g., "Can you give me an example of that?"). For some of the HAM-D items, you may find you have already asked about some of the symptoms (for a previous item). You do not need to repeat questions about these symptoms unless you need additional information to rate their severity.

Time period. The interview questions indicate that the ratings should be based on the subject's condition in the past week.

Administration method. This version includes interview questions to help the clinician rate psychomotor agitation and psychomotor retardation, when the interview is administered by telephone. Several research studies have demonstrated that depression scale scores are equivalent whether the scale is administered face-to-face, by telephone, or by video (Williams JBW and Kobak KA: Development and Reliability of a Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale. Br J Psychiatry 192: 52-58, 2008; Kobak KA: A comparison of face-to-face and remote administration of the Hamilton Depression Rating Scale via videoconferencing. J Telemed Telecare 10, 231-235, 2004).

Referent of "usual" or "normal" condition. In the HAM-D, most items are rated positive only if they represent a change from usual functioning. For this reason, several of the interview questions in the HAM-D refer to the subject's usual or normal functioning. The referent should be to the last time they felt okay (i.e., not depressed or high and normal interest in things) for at least two months. When no clear euthymic baseline can be established, one should rate symptomatic behavior as one sees it, even if it is not a change from the subject's usual dysphoric self.

This instrument provides an interview guide for the Hamilton Depression Scale (Hamilton, Max: A rating scale for depression. J Neurol Neurosurg Psychiatr 23:56-61, 1960). The anchor point descriptions for all items except Helplessness, Hopelessness, and Worthlessness, with very minor modifications, have been taken from the ECDEU Assessment Manual (Guy, William, ECDEU Assessment Manual for Psychopharmacology, Revised 1976, DHEW Publication No. (ADM) 76-338). The loss of weight item has been simplified to eliminate the section for ratings by ward staff. A reliability study of the SIGH-D (interview guide for the HAM-D alone) was published in the Archives of General Psychiatry (1988;45:742-747). Additional designators were added in parentheses to the anchor points by Kobak, Lipsitz and Williams to further standardize ratings.

For further information and permission to use or translate the SIGH-D, contact Dr. Williams at jbw@ny@gmail.com.

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STRUCTURED INTERVIEW GUIDE FOR THE
HAMILTON DEPRESSION RATING SCALE – 17 ITEM VERSION (SIGH-D-17)

SUBJECT'S INITIALS: _____ TIME BEGAN SIGH-D: _____

INTERVIEWER: _____ DATE: ____/____/____

OVERVIEW: I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUTPATIENT: Have you been working? IF NOT: Why not?

What's your mood been like this past week
(compared to when you feel okay)?

Have you been feeling down or depressed?

IF YES: Can you describe what this feeling has been like for you? How bad is the feeling?

Does the feeling lift at all if something good happens?

How are you feeling about the future?

IF UNKNOWN: Have you been feeling discouraged or pessimistic?

IF YES: What have your thoughts been?

In the last week, how often have you felt (OWN EQUIVALENT FOR DEPRESSED MOOD)? On how many days? For how long each day?

Have you been crying at all? How often?

IF SCORED 1-4 ABOVE, ASK: How long have you been feeling this way (OWN EQUIVALENT FOR DEPRESSED MOOD)?

1. DEPRESSED MOOD (sadness, hopeless, helpless, worthless):

0	Absent
1	Indicated only on questioning (<i>occasional, mild depression</i>)
2	Spontaneously reported verbally (<i>persistent, mild to moderate depression</i>)
3	Communicated non-verbally, i.e., facial expression, posture, voice, tendency to weep (<i>persistent, moderate to severe depression</i>)
4	VIRTUALLY ONLY those feeling states reported in spontaneous verbal and non-verbal communication (<i>persistent, very severe depression, with extreme hopelessness or tearfulness</i>)

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<p>How have you been spending your time this past week (when not at work)?</p> <p>Have you felt interested in doing (THOSE THINGS), or do you feel you have to push yourself to do them?</p> <p>How much less interested in these things have you been this past week compared to when you're not depressed? How hard to do you have to push yourself to do them?</p> <p>Have you stopped doing anything you used to do? (What about hobbies?) IF YES: Why?</p> <p>About how many hours a day do you spend doing things that interest you?</p> <p>Is there anything you look forward to?</p> <p>IF WORKING (IN OR OUT OF THE HOME): Have you been able to get as much (work) done as you usually do?</p> <p>How much less productive or efficient are you compared to before you were depressed?</p>	<p>2. WORK AND ACTIVITIES:</p> <table border="1"> <tr> <td>0</td> <td>No difficulty</td> </tr> <tr> <td>1</td> <td>Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies (<i>mild reduction in interest or pleasure; no clear impairment in functioning</i>)</td> </tr> <tr> <td>2</td> <td>Loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation (<i>feels he has to push self to work or activities</i>) (<i>clear reduction in interest, pleasure or functioning</i>)</td> </tr> <tr> <td>3</td> <td>Decrease in actual time spent in activities or decrease in productivity. In hosp., pt. spends less than 3 hrs./day in activities (<i>hospital job or hobbies</i>) exclusive of ward chores (<i>profound reduction in interest, pleasure, or functioning</i>)</td> </tr> <tr> <td>4</td> <td>Stopped working because of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted (<i>unable to work or fulfill primary role because of illness, and total loss of interest</i>)</td> </tr> </table>	0	No difficulty	1	Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies (<i>mild reduction in interest or pleasure; no clear impairment in functioning</i>)	2	Loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation (<i>feels he has to push self to work or activities</i>) (<i>clear reduction in interest, pleasure or functioning</i>)	3	Decrease in actual time spent in activities or decrease in productivity. In hosp., pt. spends less than 3 hrs./day in activities (<i>hospital job or hobbies</i>) exclusive of ward chores (<i>profound reduction in interest, pleasure, or functioning</i>)	4	Stopped working because of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted (<i>unable to work or fulfill primary role because of illness, and total loss of interest</i>)
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<p>Now let's talk about your sleep. What were your usual hours of going to sleep and waking up, before this began?</p> <p>When have you been falling asleep and waking up over the past week?</p>							
<p>Have you had any trouble falling asleep at the beginning of the night? (Right after you go to bed, how long has it been taking you to fall asleep?)</p> <p>How many nights this week have you had trouble falling asleep?</p> <p>Have you changed the time at which you try to get to sleep since you've been depressed?</p>	<p>3. INSOMNIA EARLY (INITIAL INSOMNIA):</p> <table border="1"> <tr> <td>0</td> <td>No difficulty falling asleep</td> </tr> <tr> <td>1</td> <td>Complains of occasional difficulty falling asleep (<i>i.e., 30 minutes or more, 2-3 nights</i>)</td> </tr> <tr> <td>2</td> <td>Complains of nightly difficulty falling asleep (<i>i.e., 30 minutes or more, 4 or more nights</i>)</td> </tr> </table>	0	No difficulty falling asleep	1	Complains of occasional difficulty falling asleep (<i>i.e., 30 minutes or more, 2-3 nights</i>)	2	Complains of nightly difficulty falling asleep (<i>i.e., 30 minutes or more, 4 or more nights</i>)
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<p>During the past week, have you been waking up in the middle of the night? IF YES: Do you get out of bed? What do you do? (Only go to the bathroom?)</p> <p>When you get back in bed, are you able to fall right back asleep? How long does it take you to fall back asleep?</p> <p>Do you wake up more than once during the night? (IF YES: How long does it take for you to fall back to sleep each time?)</p> <p>Have you felt your sleeping has been restless or disturbed some nights?</p> <p>How many nights this week have you had that kind of trouble?</p>	<p>4. INSOMNIA MIDDLE:</p> <table border="1"> <tr> <td>0</td> <td>No difficulty</td> </tr> <tr> <td>1</td> <td>Complains of being restless and disturbed during the night (or occasional difficulty, i.e., 2-3 nights, 30 minutes or more)</td> </tr> <tr> <td>2</td> <td>Waking during the night; any getting out of bed (except to void) (often, i.e., 4 or more nights of difficulty, 30 minutes or more)</td> </tr> </table>	0	No difficulty	1	Complains of being restless and disturbed during the night (or occasional difficulty, i.e., 2-3 nights, 30 minutes or more)	2	Waking during the night; any getting out of bed (except to void) (often, i.e., 4 or more nights of difficulty, 30 minutes or more)
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2	Waking during the night; any getting out of bed (except to void) (often, i.e., 4 or more nights of difficulty, 30 minutes or more)						
<p>What time have you been waking up in the morning for the last time, this past week?</p> <p>IF EARLY: Is that with an alarm clock, or do you just wake up yourself? What time do you usually wake up (that is, when you feel well)?</p> <p>How many mornings this past week have you awakened early?</p>	<p>5. INSOMNIA LATE (TERMINAL INSOMNIA):</p> <table border="1"> <tr> <td>0</td> <td>No difficulty</td> </tr> <tr> <td>1</td> <td>Waking in early hours of morning but goes back to sleep (occasional, i.e., 2-3 nights difficulty)</td> </tr> <tr> <td>2</td> <td>Unable to fall asleep again if gets out of bed (often, i.e., 4 or more nights difficulty)</td> </tr> </table>	0	No difficulty	1	Waking in early hours of morning but goes back to sleep (occasional, i.e., 2-3 nights difficulty)	2	Unable to fall asleep again if gets out of bed (often, i.e., 4 or more nights difficulty)
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1	Waking in early hours of morning but goes back to sleep (occasional, i.e., 2-3 nights difficulty)						
2	Unable to fall asleep again if gets out of bed (often, i.e., 4 or more nights difficulty)						
<p>Sometimes, along with depression or anxiety, people might lose interest in sex. This week, how has your interest in sex been? (I'm not asking about actual sexual activity, but about your interest in sex.)</p> <p>Has there been any change in your interest in sex (from when you were feeling OK)?</p> <p>IF YES: How much less interest do you have compared to when you're not depressed? (Is it a little less or a lot less?)</p>	<p>6. GENITAL SYMPTOMS (such as loss of libido, menstrual disturbances):</p> <table border="1"> <tr> <td>0</td> <td>Absent</td> </tr> <tr> <td>1</td> <td>Mild (somewhat less interest than usual)</td> </tr> <tr> <td>2</td> <td>Severe (a lot less interest than usual)</td> </tr> </table>	0	Absent	1	Mild (somewhat less interest than usual)	2	Severe (a lot less interest than usual)
0	Absent						
1	Mild (somewhat less interest than usual)						
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<p>How has your appetite been this past week? (What about compared to your usual appetite?)</p> <p>IF LESS: How much less than usual?</p> <p>Have you had to force yourself to eat?</p> <p>Have other people had to urge you to eat? (Have you skipped meals?)</p>	<p>7. SOMATIC SYMPTOMS GASTROINTESTINAL:</p> <table border="1"> <tr> <td>0</td> <td>None</td> </tr> <tr> <td>1</td> <td>Loss of appetite but eating without encouragement (appetite somewhat less than usual)</td> </tr> <tr> <td>2</td> <td>Difficulty eating without urging (appetite significantly less than usual)</td> </tr> </table>	0	None	1	Loss of appetite but eating without encouragement (appetite somewhat less than usual)	2	Difficulty eating without urging (appetite significantly less than usual)
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2	Difficulty eating without urging (appetite significantly less than usual)						

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<p>Have you lost any weight since this (DEPRESSION) began?</p> <p>IF YES: Did you lose any weight this last week? (Was it because of feeling depressed or down?) How much did you lose?</p> <p>IF NOT SURE: Do you think your clothes are any looser on you?</p> <p>FOLLOW-UP: Have you gained any of the weight back? IF YES: How much?</p>	<p>8. LOSS OF WEIGHT</p> <p>Rate by history:</p> <table border="1"> <tr> <td>0</td><td>No weight loss</td></tr> <tr> <td>1</td><td>Probable weight loss due to current depression</td></tr> <tr> <td>2</td><td>Definite (according to patient) weight loss due to depression</td></tr> </table>	0	No weight loss	1	Probable weight loss due to current depression	2	Definite (according to patient) weight loss due to depression				
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<p>How has your energy been this past week?</p> <p>IF LOW ENERGY: Have you felt tired? (How much of the time? How bad has it been?)</p> <p>This week, have you had any aches or pains? (What about backaches or muscle aches?) (How much of the time? How bad has it been?)</p> <p>Have you felt any heaviness in your limbs, back, or head?</p>	<p>9. SOMATIC SYMPTOMS GENERAL:</p> <table border="1"> <tr> <td>0</td><td>None</td></tr> <tr> <td>1</td><td>Heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatigability (somewhat less energy than usual; mild, intermittent loss of energy or muscle aches/heaviness)</td></tr> <tr> <td>2</td><td>Any clear-cut symptoms (persistent, significant loss of energy or muscle aches/heaviness)</td></tr> </table>	0	None	1	Heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatigability (somewhat less energy than usual; mild, intermittent loss of energy or muscle aches/heaviness)	2	Any clear-cut symptoms (persistent, significant loss of energy or muscle aches/heaviness)				
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<p>Have you been putting yourself down this past week, feeling you've done things wrong, or let others down?</p> <p>IF YES: What have your thoughts been?</p> <p>Have you been feeling guilty about anything that you've done or not done?</p> <p>IF YES: What have your thoughts been?</p> <p>What about things that happened a long time ago?</p> <p>Have you thought that you've brought (THIS DEPRESSION) on yourself in some way?</p> <p>(Have you been hearing voices or seeing visions in the last week? IF YES: Tell me about them.)</p>	<p>10. FEELINGS OF GUILT:</p> <table border="1"> <tr> <td>0</td><td>Absent</td></tr> <tr> <td>1</td><td>Self-reproach; feels he has let people down</td></tr> <tr> <td>2</td><td>Ideas of guilt or rumination over past errors or sinful deeds (feelings of guilt, remorse or shame)</td></tr> <tr> <td>3</td><td>Present illness is a punishment; delusions of guilt (severe, pervasive feelings of guilt)</td></tr> <tr> <td>4</td><td>Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations</td></tr> </table>	0	Absent	1	Self-reproach; feels he has let people down	2	Ideas of guilt or rumination over past errors or sinful deeds (feelings of guilt, remorse or shame)	3	Present illness is a punishment; delusions of guilt (severe, pervasive feelings of guilt)	4	Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
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<p>This past week, have you had thoughts that life is not worth living?</p> <p>What about thinking you'd be better off dead?</p> <p>Have you had thoughts of hurting or killing yourself? IF YES: What have you thought about? Have you actually done anything to hurt yourself?</p>	<p>11. SUICIDE:</p> <table border="1"> <tr> <td>0</td> <td>Absent</td> </tr> <tr> <td>1</td> <td>Feels life is not worth living</td> </tr> <tr> <td>2</td> <td>Wishes he were dead or any thoughts of possible death to self</td> </tr> <tr> <td>3</td> <td>Suicidal ideas or gesture</td> </tr> <tr> <td>4</td> <td>Attempts at suicide</td> </tr> </table>	0	Absent	1	Feels life is not worth living	2	Wishes he were dead or any thoughts of possible death to self	3	Suicidal ideas or gesture	4	Attempts at suicide
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3	Suicidal ideas or gesture										
4	Attempts at suicide										
<p>Have you been feeling anxious or tense this past week? IF YES: Is this more than is normal for you?</p> <p>Have you been feeling irritable this past week? (IF YES): Can you give me some example? How bad has it been?</p> <p>Have you been worrying a lot about little things, things you don't ordinarily worry about? IF YES: Like what, for example?</p> <p>How about worrying about big problems more than you need to?</p> <p>How much of the time has that happened this week?</p> <p>Has this caused you any problems or difficulties? IF YES: Like what, for example?</p>	<p>12. ANXIETY PSYCHIC:</p> <table border="1"> <tr> <td>0</td> <td>No difficulty</td> </tr> <tr> <td>1</td> <td>Subjective tension and irritability (<i>mild, occasional</i>)</td> </tr> <tr> <td>2</td> <td>Worrying about minor matters (<i>moderate, causes some distress</i>)</td> </tr> <tr> <td>3</td> <td>Apprehensive attitude apparent in face or speech (<i>severe; significant impairment in functioning due to anxiety</i>)</td> </tr> <tr> <td>4</td> <td>Fears expressed without questioning (<i>symptoms incapacitating</i>)</td> </tr> </table>	0	No difficulty	1	Subjective tension and irritability (<i>mild, occasional</i>)	2	Worrying about minor matters (<i>moderate, causes some distress</i>)	3	Apprehensive attitude apparent in face or speech (<i>severe; significant impairment in functioning due to anxiety</i>)	4	Fears expressed without questioning (<i>symptoms incapacitating</i>)
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<p>Tell me if you've had any of the following physical symptoms in the past week. (READ LIST)</p> <p>FOR EACH SX ACKNOWLEDGED AS PRESENT: How much has (THE SX) been bothering you this past week? [How bad has it gotten? How much of the time, or how often, have you had it? Did (the symptom) interfere at all with your functioning or your usual activities?]</p> <p>NOTE: DO NOT RATE SXs THAT ARE CLEARLY RELATED TO A DOCUMENTED PHYSICAL CONDITION.</p>	<p>13. ANXIETY SOMATIC (physiologic concomitants of anxiety, such as GI - dry mouth, gas, indigestion, diarrhea, stomach cramps, belching CV - heart palpitations, headaches Resp - hyperventilating, sighing Urinary frequency Sweating):</p> <table border="1"> <tr> <td>0</td> <td>Not present</td> </tr> <tr> <td>1</td> <td>Mild (<i>symptom(s) present only infrequently, no impairment, minimal distress</i>)</td> </tr> <tr> <td>2</td> <td>Moderate (<i>symptom(s) more persistent, or some interference with usual activities, moderate distress</i>)</td> </tr> <tr> <td>3</td> <td>Severe (<i>significant impairment in functioning</i>)</td> </tr> <tr> <td>4</td> <td>Incapacitating</td> </tr> </table>	0	Not present	1	Mild (<i>symptom(s) present only infrequently, no impairment, minimal distress</i>)	2	Moderate (<i>symptom(s) more persistent, or some interference with usual activities, moderate distress</i>)	3	Severe (<i>significant impairment in functioning</i>)	4	Incapacitating
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3	Severe (<i>significant impairment in functioning</i>)										
4	Incapacitating										
<p>In the last week, how much have your thoughts been focused on your physical health or how your body is working (compared to your normal thinking)? (Have you worried a lot about being or becoming physically ill? Have you really been preoccupied with this?)</p> <p>Have you worried a lot that you have a specific medical illness?</p> <p>Do you complain much about how you feel physically?</p> <p>Have you seen a doctor about these problems? IF YES: What did the doctor say?</p>	<p>14. HYPOCHONDRIASIS:</p> <table border="1"> <tr> <td>0</td> <td>Not present</td> </tr> <tr> <td>1</td> <td>Self-absorption (<i>bodily</i>) (<i>some inappropriate worry about his/her health OR slightly concerned despite reassurance</i>)</td> </tr> <tr> <td>2</td> <td>Preoccupation with health (<i>often has excessive worries about his/her health OR definitely concerned has specific illness despite medical reassurance</i>)</td> </tr> <tr> <td>3</td> <td>Frequent complaints, requests for help, etc. (<i>is certain there is a physical problem which the doctors cannot confirm; exaggerated or unrealistic concerns about body and physical health</i>)</td> </tr> <tr> <td>4</td> <td>Hypochondriacal delusions</td> </tr> </table>	0	Not present	1	Self-absorption (<i>bodily</i>) (<i>some inappropriate worry about his/her health OR slightly concerned despite reassurance</i>)	2	Preoccupation with health (<i>often has excessive worries about his/her health OR definitely concerned has specific illness despite medical reassurance</i>)	3	Frequent complaints, requests for help, etc. (<i>is certain there is a physical problem which the doctors cannot confirm; exaggerated or unrealistic concerns about body and physical health</i>)	4	Hypochondriacal delusions
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4	Hypochondriacal delusions										
<p>RATING BASED ON OBSERVATION DURING INTERVIEW</p>	<p>15. INSIGHT:</p> <table border="1"> <tr> <td>0</td> <td>Acknowledges being depressed and ill OR not currently depressed</td> </tr> <tr> <td>1</td> <td>Acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc.</td> </tr> <tr> <td>2</td> <td>Denies being ill at all</td> </tr> </table>	0	Acknowledges being depressed and ill OR not currently depressed	1	Acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc.	2	Denies being ill at all				
0	Acknowledges being depressed and ill OR not currently depressed										
1	Acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc.										
2	Denies being ill at all										

| SIGH-D-17 Feb. 2013

<p>RATING BASED ON OBSERVATION DURING INTERVIEW</p> <p>IF INTERVIEWING BY PHONE:</p> <p>During this interview have you been fidgeting a lot or moving around a lot in your chair?</p> <p>Have you had trouble sitting still?</p> <p>Have you been shaking your legs or playing with your hair or your hands?</p>	<p>16. AGITATION:</p> <table border="1"> <tr> <td>0</td> <td>None</td> </tr> <tr> <td>1</td> <td>Fidgetiness (<i>slight agitation or mild restlessness</i>)</td> </tr> <tr> <td>2</td> <td>Playing with hands, hair, etc. (<i>moderate to marked restlessness or agitation</i>)</td> </tr> <tr> <td>3</td> <td>Moving about, can't sit still (<i>cannot remain seated</i>)</td> </tr> <tr> <td>4</td> <td>Hand-wringing, nail biting, hair-pulling, biting of lips (<i>interview cannot be conducted; severe agitation</i>)</td> </tr> </table>	0	None	1	Fidgetiness (<i>slight agitation or mild restlessness</i>)	2	Playing with hands, hair, etc. (<i>moderate to marked restlessness or agitation</i>)	3	Moving about, can't sit still (<i>cannot remain seated</i>)	4	Hand-wringing, nail biting, hair-pulling, biting of lips (<i>interview cannot be conducted; severe agitation</i>)
0	None										
1	Fidgetiness (<i>slight agitation or mild restlessness</i>)										
2	Playing with hands, hair, etc. (<i>moderate to marked restlessness or agitation</i>)										
3	Moving about, can't sit still (<i>cannot remain seated</i>)										
4	Hand-wringing, nail biting, hair-pulling, biting of lips (<i>interview cannot be conducted; severe agitation</i>)										
<p>RATING BASED ON OBSERVATION DURING INTERVIEW</p> <p>IF INTERVIEWING BY PHONE:</p> <p>During this interview have you been moving slowly, reacting slowly, or speaking more slowly than usual for you?</p>	<p>17. RETARDATION (slowness of thought and speech; impaired ability to concentrate; decreased motor activity):</p> <table border="1"> <tr> <td>0</td> <td>Normal speech and thought</td> </tr> <tr> <td>1</td> <td>Slight retardation at interview (<i>mild psychomotor retardation</i>)</td> </tr> <tr> <td>2</td> <td>Obvious retardation at interview (<i>moderate; some difficulty with interview, noticeable pauses and slowness of thought</i>)</td> </tr> <tr> <td>3</td> <td>Interview difficult (<i>severe psychomotor retardation; very long pauses</i>)</td> </tr> <tr> <td>4</td> <td>Complete stupor (<i>extreme retardation; interview barely possible</i>)</td> </tr> </table>	0	Normal speech and thought	1	Slight retardation at interview (<i>mild psychomotor retardation</i>)	2	Obvious retardation at interview (<i>moderate; some difficulty with interview, noticeable pauses and slowness of thought</i>)	3	Interview difficult (<i>severe psychomotor retardation; very long pauses</i>)	4	Complete stupor (<i>extreme retardation; interview barely possible</i>)
0	Normal speech and thought										
1	Slight retardation at interview (<i>mild psychomotor retardation</i>)										
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3	Interview difficult (<i>severe psychomotor retardation; very long pauses</i>)										
4	Complete stupor (<i>extreme retardation; interview barely possible</i>)										

TIME ENDED SIGH-D-17:	_____ AM / PM ET / CT / PT
TOTAL HAM-D-17 SCORE:	_____

Appendix 2. MONTGOMERY-ÅSBERG DEPRESSION RATING SCALE (MADRS)

SIGMA 2011, v. 1.2 – 24 hr. version

STRUCTURED INTERVIEW GUIDE FOR THE MONTGOMERY AND ASBERG DEPRESSION RATING SCALE (SIGMA) – 24 HR TWENTY-FOUR HOUR ASSESSMENT VERSION

Janet B.W. Williams, Ph.D. and Kenneth A. Kobak, Ph.D.

INTERVIEWING GUIDELINES: The questions in bold for each item should be asked exactly as written unless the information has been previously obtained, in which case it is appropriate to restate the information for confirmation. Follow-up questions are provided for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information. Note that questions in parentheses are optional, for use, for example, if information is unknown. Statements in ALL CAPITALS are interviewer instructions and should not be read to the subject.

RATING GUIDELINES: Ratings should be based on the subject's condition as observed over the past 24 hours. As specified in the item descriptions, three of the items, Reduced Sleep, Reduced Appetite, and Inability to Feel, are rated as present only when they reflect a change from before the depression began (EUTHYMIC BASELINE). In most cases, this version will be used after the original Past Week version of the scale, during which a euthymic baseline (the most recent 2-month period of non-depressed functioning) was established. The interviewer for this 24-hour version should use this euthymic baseline as a reference point for the Reduced Sleep, Reduced Appetite, and Inability to Feel items. When a clear euthymic baseline has not been established because of chronic depressive symptoms, these three items should be rated as observed over the past 24 hours instead of as compared to a previous time point.

This interview guide is based on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery SA, Asberg M: A new depression scale designed to be sensitive to change. *Br J Psychiatry*; 1979 **134**: 382-9). The scale itself has been retained in its original form, except for reversing the order of the first two items. This guide adds interview questions to aid in the assessment and application of the MADRS. Previous versions of this guide appeared in 1988, 1992, 1996, 2005 and 2008. This version of the SIGMA has been designed for assessments that capture a 24-hour time frame. A 4-hour version and a Since Last Evaluation version have also been designed for studies needing to capture assessments over those time periods.

©2008, 2011 The Royal College of Psychiatrists. The SIGMA may be copied by individual researchers or clinicians for their own use without seeking permission from the publishers. The scale must be copied in full and all copies must acknowledge the following source: Williams JBW, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Asberg Depression Rating Scale (SIGMA). *Br J Psychiatry* 2008;192:52-58. Brianne Brown, PsyD, contributed to this revision. Written permission must be obtained from the Royal College of Psychiatrists for copying, distribution to others, for replication (in print, online or by any other medium), and translations. Scientific correspondence should be addressed to Dr. Janet Williams at jbwwny@gmail.com. To inform an ongoing survey, researchers and clinicians are asked to notify Dr. Williams of their intention to use the SIGMA.

SIGMA 2011, v. 1.2 – 24 hr. version

**STRUCTURED INTERVIEW GUIDE FOR THE
MONTGOMERY AND ASBERG DEPRESSION RATING SCALE (SIGMA) – 24 HR
TWENTY-FOUR HOUR ASSESSMENT VERSION**

PT'S INITIALS: _____ PT'S ID: _____ TIME BEGAN SIGMA: _____ AM / PM

INTERVIEWER: _____ DATE: _____

OVERVIEW:

I'd like to ask you some questions about the past 24 hours. How have you been feeling since this time yesterday?

IF OUTPATIENT: Have you been working? (What kind of work do you do? Have you been able to work your normal hours?)

IF NOT WORKING OR WORKING LESS, CLARIFY WHY.

Since this time yesterday, have you been feeling sad or unhappy? (Depressed at all?) IF YES: Can you describe what this has been like for you? (IF UNKNOWN: How bad has that been?)

IF DEPRESSED: Does the feeling lift at all if something good happens? How much does your mood lift? Does the feeling ever go away completely? (How often have you had lifts in your mood since this time yesterday? What things have made you feel better?)

How often did you feel (depressed/OWN EQUIVALENT) since this time yesterday? (IF UNKNOWN: How much of the time have you felt that way since this time yesterday?)

Since this time yesterday, how have you been feeling about the future? (Have you been discouraged or pessimistic?) What have your thoughts been? How (discouraged or pessimistic) have you been? How often have you felt that way since this time yesterday? Do you think things will ever get better for you?

INTERVIEWER: REVIEW DATE OF EUTHYMIC BASELINE (When was the last time you were well, not depressed at all, for at least 2 months?)

1. REPORTED SADNESS. Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

0 - Occasional sadness in keeping with the circumstances.

1 -

2 - Sad or low but brightens up without difficulty.

3 -

4 - Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.

5 -

6 - Continuous or unvarying sadness, misery, or despondency.

SIGMA 2011, v. 1.2 – 24 hr. version

<p>RATING BASED ON OBSERVATION DURING INTERVIEW AND THE FOLLOWING QUESTIONS.</p> <p>Since this time yesterday, do you think you have looked sad or depressed to other people? Did anyone say you looked sad or down?</p> <p>How about when you've looked in the mirror - did you look gloomy or depressed?</p> <p>IF YES: How sad or depressed do you think you have looked? How much of the time since this time yesterday do you think you have looked depressed or down?</p> <p>Has it been hard for you to laugh or smile since this time yesterday?</p>	<p>2. APPARENT SADNESS. Representing despondency, gloom and despair. (More than just ordinary transient low spirits) reflected in speech, facial expressions, and posture. Rate by depth and inability to brighten up.</p> <p>0 – No sadness 1 – 2 – Looks dispirited but does brighten up without difficulty. 3 – 4 – Appears sad and unhappy most of the time. 5 – 6 – Looks miserable all the time. Extremely despondent.</p>
<p>Have you felt tense or edgy over the past 24 hours, since yesterday at this time? Have you felt anxious or nervous?</p> <p>IF YES: Can you describe what that has been like for you? How bad has it been?</p> <p>What about feeling fearful that something bad is about to happen?</p> <p>How much of the time have you felt (anxious/tense/OWN EQUIVALENT) since this time yesterday?</p> <p>Have you felt panicky since this time yesterday? IF YES: Can you describe this feeling? How often have you felt this way since yesterday at this time?</p> <p>IF YES TO ANY TENSION SYMPTOM: How hard has it been to control these feelings? (What has it taken to help you feel calmer? Has anything worked to calm you down?)</p>	<p>3. INNER TENSION. Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.</p> <p>0 – Placid. Only fleeting inner tension. 1 – 2 – Occasional feelings of edginess and ill-defined discomfort. 3 – 4 – Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty. 5 – 6 – Unrelenting dread or anguish. Overwhelming panic.</p>
<p>How has your sleeping been in the past 24 hours? (How many hours did you sleep, compared to usual?)</p> <p>Did you have trouble falling asleep since this time yesterday? (How long did it take you to fall asleep in the past 24 hours? How does that compare to your usual pattern?)</p> <p>In the past 24 hours were you able to stay asleep through the night? (Did you wake up at all in the middle of the night? How long did it take you to fall back to sleep? How does that compare to EUTHYMIC BASELINE?)</p> <p>In the past 24 hours did you awaken earlier than (EUTHYMIC BASELINE)?</p> <p>IF UNKNOWN: Has your sleeping been restless or disturbed since this time yesterday?</p>	<p>4. REDUCED SLEEP. Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.</p> <p>0 – Sleeps as usual. 1 – 2 – Slight difficulty dropping off to sleep or slightly reduced, light, or fitful sleep. 3 – 4 – Sleep reduced or broken by at least 2 hours. 5 – 6 – Less than 2 or 3 hours sleep.</p>

SIGMA 2011, v. 1.2 – 24 hr. version

<p>How has your appetite been since this time yesterday? (What about compared to your usual appetite?)</p> <p>IF NOT REDUCED: Have you been less interested in food compared to (EUTHYMIC BASELINE)? (How much less?)</p> <p>Does food taste as good as usual (compared to EUTHYMIC BASELINE)? IF LESS: How much less? Does it have any taste at all?</p> <p>(Have you had to push yourself to eat or have other people had to urge you to eat over the past 24 hours?)</p>	<p>5. REDUCED APPETITE. Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.</p> <p>0 - Normal or increased appetite. 1 - 2 - Slightly reduced appetite. 3 - 4 - No appetite. Food is tasteless. 5 - 6 - Needs persuasion to eat at all.</p>
<p>Have you had trouble concentrating or collecting your thoughts since this time yesterday? (How about at home or at work?) IF YES: Can you give me some examples? (Have you been able to concentrate on reading a book or on the computer? Do you need to read things over and over again? Are you able to follow movies or television?)</p> <p>How often has that happened since this time yesterday? Has this caused any problems for you?</p> <p>Have you had any trouble following a conversation? (IF YES: How bad has that been? How often has that happened since this time yesterday?)</p> <p>NOTE: ALSO CONSIDER BEHAVIOR DURING INTERVIEW.</p>	<p>6. CONCENTRATION DIFFICULTIES. Representing difficulties in collecting one's thoughts amounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.</p> <p>0 - No difficulties in concentration. 1 - 2 - Occasional difficulties in collecting one's thoughts. 3 - 4 - Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation. 5 - 6 - Unable to read or converse without great difficulty.</p>
<p>Have you had any trouble getting started at things since this time yesterday? IF YES: What things? How bad has that been?</p> <p>Have you had difficulty getting started at simple routine everyday things (like getting dressed, brushing your teeth, showering)?</p> <p>Since this time yesterday, have you been OK once you get started at things or has it still been more of an effort to get something done?</p> <p>Has there been anything that you needed to do in the past 24 hours that you were unable to do? Have you needed help to do things? IF YES: What things? How often?</p> <p>Have you done everyday things more slowly than usual since this time yesterday? IF YES: Like what, for example? How bad has that been?</p>	<p>7. LASSITUDE. Representing a difficulty getting started, or slowness initiating and performing everyday activities.</p> <p>0 - Hardly any difficulty in getting started. No sluggishness. 1 - 2 - Difficulties in starting activities. 3 - 4 - Difficulties in simple routine activities, which are carried out with effort. 5 - 6 - Complete lassitude. Unable to do anything without help.</p>

SIGMA 2011, v. 1.2 – 24 hr. version

<p>Over the last 24 hours, have you been less interested in things around you, or in activities you used to enjoy, compared to (EUTHYMIC BASELINE)? IF YES: What things? How much less interested are you in (those things), compared to (EUTHYMIC BASELINE)?</p> <p>What things have you enjoyed over the past 24 hours? How much did you enjoy them?</p> <p>Has there been any change in your ability to feel emotions since (EUTHYMIC BASELINE)? (Do you feel things less intensely than you used to, things like anger, grief, pleasure?) IF YES: Can you tell me more about that? (IF UNKNOWN: Are you able to feel any emotions at all?)</p> <p>Have your feelings towards family and friends changed at all since (EUTHYMIC BASELINE)? IF YES: Do you feel less towards them than you used to (AT EUTHYMIC BASELINE)?</p>	<p>8. INABILITY TO FEEL. Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.</p> <p>0 - Normal interest in the surroundings and in other people. 1 - 2 - Reduced ability to enjoy usual interests. 3 - 4 - Loss of interest in the surroundings. Loss of feelings for friends and acquaintances. 5 - 6 - The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure, and a complete or even painful failure to feel for close relatives and friends.</p>
<p>Have you been putting yourself down, or feeling that you're a failure in some way, since this time yesterday? (Have you been blaming yourself for things that you've done, or not done?) IF YES: What have your thoughts been? How often have you felt that way?</p> <p>Since this time yesterday have you been feeling guilty about anything? What about feeling as if you have done something bad or sinful? IF YES: What have your thoughts been? How often have you felt that way over the past 24 hours?</p> <p>ALSO CONSIDER RESPONSES TO QUESTIONS ABOUT PESSIMISM FROM ITEM 1.</p>	<p>9. PESSIMISTIC THOUGHTS. Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin.</p> <p>0 - No pessimistic thoughts. 1 - 2 - Fluctuating ideas of failure, self-reproach, or self-depreciation. 3 - 4 - Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future. 5 - 6 - Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakeable.</p>

SIGMA 2011, v. 1.2 – 24 hr. version

<p>Since this time yesterday, have you felt like life isn't worth living? (IF NO: What about feeling as if you're tired of living?) IF YES: Tell me about that. How often have you felt that way since this time yesterday?</p> <p>Since this time yesterday, have you thought that you would be better off dead? IF YES: Tell me about that. How often have you felt that way since this time yesterday?</p> <p>Have you had thoughts of hurting or even killing yourself since this time yesterday? IF YES: What have you thought about? How often have you had these thoughts since this time yesterday? How long have they lasted? Have you actually made plans? IF YES: What are these plans? Have you made any preparations to carry out these plans? (Have you told anyone about it?)</p>	<p>10. SUICIDAL THOUGHTS. Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparation for suicide. Suicidal attempts should not in themselves influence this rating.</p> <p>0 - Enjoys life or takes it as it comes. 1 - 2 - Weary of life. Only fleeting suicidal thoughts. 3 - 4 - Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention. 5 - 6 - Explicit plans for suicide when there is an opportunity. Active preparations for suicide.</p>
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TIME ENDED SIGMA:	____ AM / PM
TOTAL MADRS SCALE SCORE:	____

SIGMA 2011, v. 1.2

**STRUCTURED INTERVIEW GUIDE FOR THE
MONTGOMERY AND ASBERG DEPRESSION RATING SCALE (SIGMA)**

Janet B.W. Williams, Ph.D. and Kenneth A. Kobak, Ph.D.

INTERVIEWING GUIDELINES: The questions in bold for each item should be asked exactly as written unless the information has been previously obtained, in which case it is appropriate to restate the information for confirmation. Follow-up questions are provided for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information. Note that questions in parentheses are optional, for use, for example, if information is unknown. Statements in ALL CAPITALS are interviewer instructions and should not be read to the subject.

RATING GUIDELINES: Ratings should be based on the subject's condition as observed in the past week (past 7 days). As specified in the item descriptions, three of the items, Reduced Sleep, Reduced Appetite, and Inability to Feel, are rated as present only when they reflect a change from before the depression began (EUTHYMIC BASELINE). The interviewer should attempt to identify the most recent 2-month period of non-depressed functioning and use this as a reference point. In some cases, such as when the subject has dysthymia, the referent should be to the last time the subject felt alright (i.e., not depressed or high) for at least a few weeks. When a clear euthymic baseline cannot be established because of chronic depressive symptoms, these items should be rated as observed over the past 7 days instead of comparing to a previous time point.

This interview guide is based on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery SA, Asberg M: A new depression scale designed to be sensitive to change. *Br J Psychiatry*; 1979 **134**: 382-9). The scale itself has been retained in its original form, except for reversing the order of the first two items. This guide adds interview questions to aid in the assessment and application of the MADRS. Previous versions of this guide appeared in 1988, 1992, 1996, 2005 and 2008.

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SIGMA 2011, v. 1.2

**STRUCTURED INTERVIEW GUIDE FOR THE
MONTGOMERY AND ASBERG DEPRESSION RATING SCALE (SIGMA)**

PT'S INITIALS: _____ PT'S ID: _____

TIME BEGAN SIGMA: _____ AM / PM

INTERVIEWER: _____

DATE: _____

OVERVIEW:

I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)?

IF OUTPATIENT: Have you been working? (What kind of work do you do? Have you been able to work your normal hours?) IF NOT WORKING OR WORKING LESS, CLARIFY WHY.

In the past week, have you been feeling sad or unhappy? (Depressed at all?) IF YES: Can you describe what this has been like for you? (IF UNKNOWN: How bad has that been?)

IF DEPRESSED: Does the feeling lift at all if something good happens? How much does your mood lift? Does the feeling ever go away completely? (How often have you had lifts in your mood this week? What things have made you feel better?)

How often did you feel (depressed/OWN EQUIVALENT) this past week? (IF UNKNOWN: How many days this week did you feel that way? How much of each day?)

In the past week, how have you been feeling about the future? (Have you been discouraged or pessimistic?) What have your thoughts been? How (discouraged or pessimistic) have you been? How often have you felt that way? Do you think things will ever get better for you?

ESTABLISH EUTHYMIC BASELINE: When was the last time you were well, not depressed at all, for at least 2 months?

1. REPORTED SADNESS. Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

0 - Occasional sadness in keeping with the circumstances.

1 -

2 - Sad or low but brightens up without difficulty.

3 -

4 - Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.

5 -

6 - Continuous or unvarying sadness, misery, or despondency.

<p style="text-align: right;">SIGMA 2011, v. 1.2</p> <p>RATING BASED ON OBSERVATION DURING INTERVIEW AND THE FOLLOWING QUESTIONS.</p> <p>In the past week, do you think you have looked sad or depressed to other people? Did anyone say you looked sad or down?</p> <p>How about when you've looked in the mirror; did you look gloomy or depressed?</p> <p>IF YES: How sad or depressed do you think you have looked? How much of the time over the past week do you think you have looked depressed or down?</p> <p>Has it been hard for you to laugh or smile in the past week?</p>	<p>2. APPARENT SADNESS. Representing despondency, gloom and despair. (More than just ordinary transient low spirits) reflected in speech, facial expressions, and posture. Rate by depth and inability to brighten up.</p> <p>0 – No sadness 1 – 2 – Looks dispirited but does brighten up without difficulty. 3 – 4 – Appears sad and unhappy most of the time. 5 – 6 – Looks miserable all the time. Extremely despondent.</p>
<p>Have you felt tense or edgy in the last week? Have you felt anxious or nervous?</p> <p>IF YES: Can you describe what that has been like for you? How bad has it been?</p> <p>What about feeling fearful that something bad is about to happen?</p> <p>How much of the time have you felt (anxious/tense/OWN EQUIVALENT) over the past week?</p> <p>Have you felt panicky in the past week? IF YES: Can you describe this feeling? How often have you felt this way? IF YES TO ANY TENSION SYMPTOM: How hard has it been to control these feelings? (What has it taken to help you feel calmer? Has anything worked to calm you down?)</p>	<p>3. INNER TENSION. Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.</p> <p>0 – Placid. Only fleeting inner tension. 1 – 2 – Occasional feelings of edginess and ill-defined discomfort. 3 – 4 – Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty. 5 – 6 – Unrelenting dread or anguish. Overwhelming panic.</p>
<p>How has your sleeping been in the last week? (How many hours have you been sleeping, compared to usual?)</p> <p>Have you had trouble falling asleep? (How long has it been taking you to fall asleep this past week? How many nights?)</p> <p>Have you been able to stay asleep through the night? (Have you been waking up at all in the middle of the night? How long does it take you to fall back to sleep? How many nights?)</p> <p>Have there been any mornings this past week when you have awakened earlier than (EUTHYMIC BASELINE)?</p> <p>IF UNKNOWN: Has your sleeping been restless or disturbed?</p>	<p>4. REDUCED SLEEP. Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.</p> <p>0 – Sleeps as usual. 1 – 2 – Slight difficulty dropping off to sleep or slightly reduced, light, or fitful sleep. 3 – 4 – Sleep reduced or broken by at least 2 hours. 5 – 6 – Less than 2 or 3 hours sleep.</p>

<p>How has your appetite been this past week? (What about compared to your usual appetite?)</p> <p>IF NOT REDUCED: Have you been less interested in food? (How much less?)</p> <p>Does food taste as good as usual? IF LESS: How much less? Does it have any taste at all?</p> <p>(Have you had to push yourself to eat or have other people had to urge you to eat?)</p>	<p style="text-align: right;">SIGMA 2011, v. 1.2</p> <p>5. REDUCED APPETITE. Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.</p> <p>0 - Normal or increased appetite. 1 - 2 - Slightly reduced appetite. 3 - 4 - No appetite. Food is tasteless. 5 - 6 - Needs persuasion to eat at all.</p>
<p>Have you had trouble concentrating or collecting your thoughts in the past week? (How about at home or at work?) IF YES: Can you give me some examples? (Have you been able to concentrate on reading a book or on the computer? Do you need to read things over and over again? Are you able to follow movies or television?)</p> <p>How often has that happened in the past week? Has this caused any problems for you?</p> <p>Have you had any trouble following a conversation? (IF YES: How bad has that been? How often has that happened this past week?)</p> <p>NOTE: ALSO CONSIDER BEHAVIOR DURING INTERVIEW.</p>	<p>6. CONCENTRATION DIFFICULTIES. Representing difficulties in collecting one's thoughts amounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.</p> <p>0 - No difficulties in concentration. 1 - 2 - Occasional difficulties in collecting one's thoughts. 3 - 4 - Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation. 5 - 6 - Unable to read or converse without great difficulty.</p>
<p>Have you had any trouble getting started at things in the past week? IF YES: What things? How bad has that been? Have you had difficulty getting started at simple routine everyday things (like getting dressed, brushing your teeth, showering)?</p> <p>Are you OK once you get started at things or is it still more of an effort to get something done?</p> <p>Has there been anything that you needed to do that you were unable to do? Have you needed help to do things? IF YES: What things? How often?</p> <p>Have you done everyday things more slowly than usual? IF YES: Like what, for example? How bad has that been?</p>	<p>7. LASSITUDE. Representing a difficulty getting started, or slowness initiating and performing everyday activities.</p> <p>0 - Hardly any difficulty in getting started. No sluggishness. 1 - 2 - Difficulties in starting activities. 3 - 4 - Difficulties in simple routine activities, which are carried out with effort. 5 - 6 - Complete lassitude. Unable to do anything without help.</p>

SIGMA 2011, v. 1.2	
<p>Have you been less interested in things around you, or in activities you used to enjoy? IF YES: What things? How much less interested in (those things) are you now compared to (EUTHYMIC BASELINE)?</p> <p>What things have you enjoyed this week? How much did you enjoy them?</p> <p>Has there been any change in your ability to feel emotions? (Do you feel things less intensely than you used to, things like anger, grief, pleasure?) IF YES: Can you tell me more about that? (IF UNKNOWN: Are you able to feel any emotions at all?)</p> <p>Have your feelings towards family and friends changed at all? IF YES: Do you feel less towards them than you used to?</p>	<p>8. INABILITY TO FEEL. Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.</p> <p>0 - Normal interest in the surroundings and in other people. 1 - 2 - Reduced ability to enjoy usual interests. 3 - 4 - Loss of interest in the surroundings. Loss of feelings for friends and acquaintances. 5 - 6 - The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure, and a complete or even painful failure to feel for close relatives and friends.</p>
<p>Have you been putting yourself down, or feeling that you're a failure in some way, over the past week? (Have you been blaming yourself for things that you've done, or not done?) IF YES: What have your thoughts been? How often have you felt that way?</p> <p>In the past week have you been feeling guilty about anything? What about feeling as if you have done something bad or sinful? IF YES: What have your thoughts been? How often have you felt that way?</p> <p>ALSO CONSIDER RESPONSES TO QUESTIONS ABOUT PESSIMISM FROM ITEM 1.</p>	<p>9. PESSIMISTIC THOUGHTS. Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin.</p> <p>0 - No pessimistic thoughts. 1 - 2 - Fluctuating ideas of failure, self-reproach, or self-depreciation. 3 - 4 - Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future. 5 - 6 - Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakeable.</p>
<p>This past week, have you felt like life isn't worth living? (IF NO: What about feeling as if you're tired of living?) IF YES: Tell me about that. How often have you felt that way?</p> <p>This week, have you thought that you would be better off dead? IF YES: Tell me about that. How often have you felt that way?</p> <p>Have you had thoughts of hurting or even killing yourself this past week? IF YES: What have you thought about? How often have you had these thoughts? How long have they lasted? Have you actually made plans? IF YES: What are these plans? Have you made any preparations to carry out these plans? (Have you told anyone about it?)</p>	<p>10. SUICIDAL THOUGHTS. Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparation for suicide. Suicidal attempts should not in themselves influence this rating.</p> <p>0 - Enjoys life or takes it as it comes. 1 - 2 - Weary of life. Only fleeting suicidal thoughts. 3 - 4 - Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention. 5 - 6 - Explicit plans for suicide when there is an opportunity. Active preparations for suicide.</p>
TIME ENDED SIGMA:	_____ AM / PM
TOTAL MADRS SCALE SCORE:	_____

APPENDIX 3. HAMILTON ANXIETY RATING SCALE (HAM-A)

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON ANXIETY SCALE (SIGH-A) – 24 HR TWENTY-FOUR HOUR ASSESSMENT VERSION

Janet B.W. Williams, PhD

INTERVIEWER: The first question for each item, in bold type, should be asked exactly as written. For each symptom endorsed, use the additional probes at the top of each page to determine the frequency and severity of the symptom, including how bad it's been, how much distress it has caused, and if the symptom has caused any impairment. Follow-up questions are provided for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information. You should ask for examples for any symptoms acknowledged as present (e.g., "Can you give me an example of that?"). For some of the HAM-A items, you may find you have already asked about some of the symptoms (for a previous item). You do not need to repeat questions about these symptoms unless you need additional information to rate their severity.

All of the items have the same anchor points. The following may be useful as a guide to rating item severity:

ABSENT	Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety
MILD	Score 1 if symptom is infrequent, with no impairment and no more than mild distress
MODERATE	Score 2 if symptom is more frequent, with moderate distress or limited interference with usual activities
SEVERE	Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning
VERY SEVERE	Score 4 if symptom is incapacitating

For each symptom, ask:

- Tell me what that was like. Can you give me some **examples**?
- How **bad** has this been over the past week?
- How much has it **bothered** you? Has it caused you any **problems**?
- How much of the **time** or how **often** have you had this over the past week?

NOTES:

Time period. For this 24 hour version, the ratings should be based on the patient's condition over the past 24 hours. Unlike the HAMD, change from usual self is not required for most items to be rated positively on the HAMA. However, symptoms should not be rated positively if they are clearly due to a cause unrelated to anxiety, e.g., respiratory symptoms due to pneumonia.

Panic attacks. If the patient has panic attacks, this could affect the ratings of many of the symptoms. It is recommended that you consider the total amount of time during the past 24 hours that the panic attack symptoms occurred, as well as their severity. For example, a patient who has several severe but short-lived panic attacks during the past 24 hours, even if they otherwise do not have many anxiety symptoms, would probably have a high total HAM-A score.

This instrument provides an interview guide for the Hamilton Anxiety Scale (Hamilton M: The assessment of anxiety states by rating. *Brit J Med Psychol* 32:50-55, 1959; Hamilton M: The diagnosis and rating of anxiety. In *Studies of Anxiety*. MH Lader, Ed., Headley Bros., Kent, 1969). The anchor point descriptions for the scale have been taken from the ECDEU Assessment Manual (Guy, William, *ECDEU Assessment Manual for Psychopharmacology*, Revised 1976, DHEW Publication No. (ADM) 76-338), except that "sighing" and "dyspnea," which appear twice in that version, have been taken out of the item "cardiovascular symptoms," and remain under "respiratory symptoms." Kenneth A. Kobak, PhD and Joshua D. Lipsitz, PhD contributed to revisions of this interview guide.

For further information and permission to use or translate the SIGH-A, contact Dr. Williams at jbwwny@gmail.com.

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**STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON ANXIETY SCALE
(SIGH-A) – 24 HR
TWENTY-FOUR HOUR ASSESSMENT VERSION**

PT'S INITIALS: _____ PT'S ID: _____

TIME BEGAN SIGH-A: _____ AM / PM
ET / CT / PT

INTERVIEWER: _____

DATE: ____ / ____ / ____

OVERVIEW: I'd like to ask you some questions about the past 24 hours. How have you been feeling since this time yesterday? IF OUTPATIENT: Have you been working? IF NOT: Why not?

Suggested follow-up questions:

- Tell me what that was like. Can you give me some **examples**?
- How **bad** has this been since this time yesterday?
- How much has it **bothered** you? Has it caused you any **problems**?
- How much of the **time** or how **often** have you had this since this time yesterday?

ABSENT	Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety
MILD	Symptom is infrequent, with no impairment and no more than mild distress
MODERATE	Symptom is more frequent, with moderate distress or limited interference with usual activities
SEVERE	Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning
VERY SEVERE	Symptom is incapacitating

Since this time yesterday, how much have you been worrying? (What have you been worried about? How hard has it been to stop worrying?)

(IF UNKNOWN): How much have you been afraid that the worst is going to happen?

Have you been feeling nervous or anxious since this time yesterday?

Have you been feeling irritable since this time yesterday?

1. ANXIOUS MOOD
(worries, anticipation of the worst, fearful anticipation, irritability):

- 0 - not present
- 1 - mild
- 2 - moderate
- 3 - severe
- 4 - very severe

IF SCORED 1-4 ABOVE, FOR CONTEXT, ASK: How long have you been feeling this way?

<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been since this time yesterday? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this since this time yesterday? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
	<p>MILD Symptom is infrequent, with no impairment and no more than mild distress</p>
	<p>MODERATE Symptom is more frequent, with moderate distress or limited interference with usual activities</p>
	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>Since this time yesterday, how much have you felt tense, keyed up, or on edge?</p> <p>Have you gotten tired easily?</p> <p>How much have you been bothered by any of these things:</p> <ul style="list-style-type: none"> • being startled easily? • crying easily? • trembling? • feeling restless? • not being able to relax? 	<p>2. TENSION (feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>Since this time yesterday, have you been afraid of . . .</p> <ul style="list-style-type: none"> • the dark? • of strangers? • of being left alone? • of animals? • of traffic? • of crowds? <p>Have you had any other specific fears since this time yesterday?</p> <p>NOTE: INCLUDE ANY IRRATIONAL ANXIETY ABOUT</p>	<p>3. FEARS (of dark, of strangers, of being left alone, of animals, of traffic, of crowds):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been since this time yesterday? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this since this time yesterday? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
	<p>MILD Symptom is infrequent, with no impairment and no more than mild distress</p>
	<p>MODERATE Symptom is more frequent, with moderate distress or limited interference with usual activities</p>
	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

OBJECTS OR SITUATIONS.	
<p>Now let's talk about your sleep.</p>	
<p>Since this time yesterday, have you had trouble falling asleep?</p> <p>How long has it taken you to fall asleep? IF MORE THAN 30 MINUTES: How many times since this time yesterday did this happen?</p> <p>Since this time yesterday, did you wake up in the middle of your sleep time? IF YES: How long were you awake? How often did this happen?</p> <p>IF UNKNOWN: Since this time yesterday, has your sleep been restless or disturbed? IF YES: For how much of your sleep time has this been the case?</p> <p>Did you feel tired when you woke up because you felt you didn't have a good sleep?</p> <p>How about having bad dreams or nightmares?</p>	<p>4. INSOMNIA (difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>

<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been since this time yesterday? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this since this time yesterday? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
	<p>MILD Symptom is infrequent, with no impairment and no more than mild distress</p>
	<p>MODERATE Symptom is more frequent, with moderate distress or limited interference with usual activities</p>
	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>Since this time yesterday have you had trouble concentrating?</p> <p>IF YES: Can you give me some examples?</p> <p>How about trouble reading – like a book or a newspaper? Do you need to read things over and over again?</p> <p>Have you had any trouble following a conversation?</p> <p>Have you had trouble remembering things since this time yesterday?</p> <p>IF UNKNOWN: What about remembering appointments or errands you have to do?</p>	<p>5. INTELLECTUAL (difficulty in concentrating, poor memory):</p> <p>0 - not present</p> <p>1 - mild</p> <p>2 - moderate</p> <p>3 - severe</p> <p>4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been since this time yesterday? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this since this time yesterday? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
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	<p>VERY SEVERE Symptom is incapacitating</p>

<p>Since this time yesterday, have you felt sad, depressed, or down?</p> <p>Can you describe the feeling? How bad has it been?</p> <p>IF YES: Does the feeling lift if something good happens?</p> <p>How have you been feeling about the future, since this time yesterday?</p> <p>Have you been feeling discouraged or pessimistic?</p> <p>What have your thoughts been?</p> <p>Have you been crying since this time yesterday?</p> <p>Have you been less interested in things, or not enjoying things you usually enjoy doing?</p> <p>Have you awakened earlier than usual, when you have slept since this time yesterday? (Is that with an alarm clock, or did you just wake up yourself?)</p> <p>Since this time yesterday, have you been feeling better or worse at any particular time of day - morning or evening? IF VARIATION: How much worse?</p>	<p>6. DEPRESSED MOOD (loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing):</p> <p>0 - not present</p> <p>1 - mild</p> <p>2 - moderate</p> <p>3 - severe</p> <p>4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been since this time yesterday? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this since this time yesterday? 	<table> <tr> <td>ABSENT</td><td>Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</td></tr> <tr> <td>MILD</td><td>Symptom is infrequent, with no impairment and no more than mild distress</td></tr> <tr> <td>MODERATE</td><td>Symptom is more frequent, with moderate distress or limited interference with usual activities</td></tr> <tr> <td>SEVERE</td><td>Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</td></tr> <tr> <td>VERY SEVERE</td><td>Symptom is incapacitating</td></tr> </table>	ABSENT	Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety	MILD	Symptom is infrequent, with no impairment and no more than mild distress	MODERATE	Symptom is more frequent, with moderate distress or limited interference with usual activities	SEVERE	Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning	VERY SEVERE	Symptom is incapacitating
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SEVERE	Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning										
VERY SEVERE	Symptom is incapacitating										

<p>Since this time yesterday, have you had any . . .</p> <ul style="list-style-type: none"> • muscle aches or pains? • muscle twitching? • tight or stiff muscles? • sudden muscle jerks? • grinding of your teeth? • an unsteady voice? 	<p>7. SOMATIC (MUSCULAR) (pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>Since this time yesterday, have you had . . .</p> <ul style="list-style-type: none"> • ringing in your ears? • blurred vision? • hot or cold flashes? • feelings of physical weakness (not just feeling tired)? • How about pricking sensations? 	<p>8. SOMATIC (SENSORY) (tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been since this time yesterday? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this since this time yesterday? 	<table border="1"> <tr> <td>ABSENT</td> <td>Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</td> </tr> <tr> <td>MILD</td> <td>Symptom is infrequent, with no impairment and no more than mild distress</td> </tr> <tr> <td>MODERATE</td> <td>Symptom is more frequent, with moderate distress or limited interference with usual activities</td> </tr> <tr> <td>SEVERE</td> <td>Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</td> </tr> <tr> <td>VERY SEVERE</td> <td>Symptom is incapacitating</td> </tr> </table>	ABSENT	Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety	MILD	Symptom is infrequent, with no impairment and no more than mild distress	MODERATE	Symptom is more frequent, with moderate distress or limited interference with usual activities	SEVERE	Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning	VERY SEVERE	Symptom is incapacitating
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<p>Since this time yesterday, has . . .</p> <ul style="list-style-type: none"> • your heart raced, skipped or pounded? • Have you had pain in your chest? • Had any throbbing blood vessels? • Any fainting feelings? 	<p>9. CARDIOVASCULAR SYMPTOMS (tachycardia, palpitations, pain in chest, throbbing vessels, fainting feelings):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>										
<p>Since this time yesterday, have you had . . .</p> <ul style="list-style-type: none"> • pressure or tightness in your chest? • choking feelings? • What about sighing? • Have you had shortness of breath? 	<p>10. RESPIRATORY SYMPTOMS (pressure or constriction in chest, choking feelings, sighing, dyspnea):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>										

<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been since this time yesterday? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this since this time yesterday? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
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	<p>VERY SEVERE Symptom is incapacitating</p>

<p>Since this time yesterday, have you had ...</p> <ul style="list-style-type: none"> • trouble swallowing? • stomach pain or fullness? • gas? • nausea? • vomiting? • burning or rumbling in your stomach? • loose bowels? • constipation? • Have you lost weight since this time yesterday? IF YES: How much? (Have you been trying to lose weight?) DO NOT RATE LOSS OF WEIGHT DUE TO DIETING. 	<p>11. GASTROINTESTINAL SYMPTOMS (difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been since this time yesterday? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this since this time yesterday? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
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	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>Since this time yesterday, have you had to urinate frequently? IF NO: Have you had the urge to?</p> <p>How has your interest in sex been since this time yesterday? I'm not asking about performance, but about your interest in sex.</p> <p>Is this a change for you? IF YES: How much of a change?</p> <p>FOR WOMEN: When some women feel nervous or anxious, they have trouble having an orgasm, although they have had them in the past. Have you had difficulty with orgasm since this time yesterday? IF YES: How much trouble have you had?</p> <p>Have you had your period in the last month or so? IF YES: Has it been especially heavy? IF NOT: Do you know why not?</p> <p>FOR MEN: Sometimes when men feel nervous or anxious, they have trouble with premature ejaculation, or they have trouble keeping an erection. Has that happened to you since this time yesterday? IF YES: How much trouble have you had?</p>	<p>12. GENITOURINARY SYMPTOMS (frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been since this time yesterday? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this since this time yesterday? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
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	<p>VERY SEVERE Symptom is incapacitating</p>

<p>Since this time yesterday, has your mouth been dry?</p> <p>Have you had any flushing in your face?</p> <p>Have you been pale?</p> <p>Have you felt lightheaded?</p> <p>Have you had headaches?</p> <p>How about feeling the hair rise on your arms, the back of your neck, or your head?</p> <p>Have you tended to sweat a lot since this time yesterday?</p>	<p>13. AUTONOMIC SYMPTOMS (dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair):</p> <p>0 - not present</p> <p>1 - mild</p> <p>2 - moderate</p> <p>3 - severe</p> <p>4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> Tell me what that was like. Can you give me some examples? How bad has this been since this time yesterday? How much has it bothered you? Has it caused you any problems? How much of the time or how often have you had this since this time yesterday? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
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	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>RATING BASED ON OBSERVATION DURING INTERVIEW (CIRCLE SYMPTOMS PRESENT).</p> <p>FOR TELEPHONE ASSESSMENT: During this interview, have you been fidgiting at all, or having trouble sitting still? Have you been doing anything like playing with your hands or hair, or tapping your foot?</p> <p>IF YES: How bad has that been?</p> <p>Have your hands been shaky?</p> <p>What about swallowing or feeling the need to swallow?</p> <p>If you looked in a mirror right now, would your face look relaxed? IF NO: Would it look strained or tight?</p> <p>Do you think you look pale?</p>	<p>14. BEHAVIOR AT INTERVIEW (fidgiting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos, etc.):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
--	--

TIME ENDED SIGH-A:	_____	AM / PM	ET / CT / PT
TOTAL HAM-A SCORE:	___		

**STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON ANXIETY SCALE
(SIGH-A)**

Janet B.W. Williams, PhD

INTERVIEWER: The questions for each item that appear in bold type should be asked exactly as written. Follow-up questions are provided for further exploration of symptoms. For each symptom endorsed, use the additional probes at the top of each page to determine the frequency and severity of the symptom, including how bad it's been, how much distress it has caused, and if the symptom has caused any impairment. These questions should be asked until you have enough information to rate the item confidently. You may also have to add your own follow-up questions to obtain necessary information. For some of the HAM-A items, you may find you have already asked about some of the symptoms (for a previous item). You do not need to repeat questions about these symptoms unless you need additional information to rate their severity.

All of the items have the same anchor points. The following may be useful as a guide to rating item severity:

ABSENT	Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety
MILD	Score 1 if symptom is infrequent, with no impairment and no more than mild distress
MODERATE	Score 2 if symptom is more frequent, with moderate distress or limited interference with usual activities
SEVERE	Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning
VERY SEVERE	Score 4 if symptom is incapacitating

For each symptom, ask:

- Tell me what that was like. Can you give me some **examples**?
- How **bad** has this been over the past week?
- How much has it **bothered** you? Has it caused you any **problems**?
- How much of the **time** or how **often** have you had this over the past week?

NOTES:

Time period. The ratings should be based on the patient's condition during the past week. Unlike the HAMD, change from usual self is not required for most items to be rated positively on the HAM-A. However, symptoms should not be rated positively if they are clearly due to a cause unrelated to anxiety, e.g., respiratory symptoms due to pneumonia.

Panic attacks. If the patient has panic attacks, this could affect the ratings of many of the symptoms. It is recommended that you consider the total amount of time during the past week that the panic attack symptoms occurred, as well as their severity. For example, a patient who has a few severe but short-lived panic attacks during the week, but who otherwise does not have many anxiety symptoms, would probably not have a very high total HAM-A score.

This instrument provides an interview guide for the Hamilton Anxiety Scale (Hamilton M: The assessment of anxiety states by rating. *Brit J Med Psychol* 32:50-55, 1959; Hamilton M: The diagnosis and rating of anxiety. In *Studies of Anxiety*, MH Lader, Ed., Headley Bros., Kent, 1969). The anchor point descriptions for the scale have been taken from the ECDEU Assessment Manual (Guy, William, *ECDEU Assessment Manual for Psychopharmacology*, Revised 1976, DHEW Publication No. (ADM) 76-338), except that "sighing" and "dyspnea," which appear twice in that version, have been taken out of the item "cardiovascular symptoms," and left under "respiratory symptoms." Kenneth A. Kobak, PhD and Joshua D. Lipsitz, PhD contributed to revisions of this interview guide. Dr. Williams' degree was changed to PhD; no other changes have been made to the interview guide since the date of this revision.

For further information and permission to use or translate the SIGH-A, contact Dr. Williams at jbwmy@gmail.com.

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Revision 15Jan08

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SIGH-A

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON ANXIETY SCALE (SIGH-A)*

PT'S INITIALS: _____ PT'S ID: _____

TIME BEGAN SIGH-A: _____ AM / PM
ET / CT / PT

INTERVIEWER: _____

DATE: ____ / ____ / ____

OVERVIEW: I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUTPATIENT: Have you been working? IF NOT: Why not?

Suggested follow-up questions:

- Tell me what that was like. Can you give me some **examples**?
- How **bad** has this been over the past week?
- How much has it **bothered** you? Has it caused you any **problems**?
- How much of the **time** or how **often** have you had this the past week?

ABSENT	Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety
MILD	Symptom is infrequent, with no impairment and no more than mild distress
MODERATE	Symptom is more frequent, with moderate distress or limited interference with usual activities
SEVERE	Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning
VERY SEVERE	Symptom is incapacitating

In the last week, how much have you been worrying?
(What have you been worried about? How hard has it been to stop worrying?)

(IF UNKNOWN): How much have you been afraid that the worst is going to happen?

Have you been feeling nervous or anxious this past week?

Have you been feeling irritable this past week?

1. ANXIOUS MOOD
(worries, anticipation of the worst, fearful anticipation, irritability):

- 0 - not present
- 1 - mild
- 2 - moderate
- 3 - severe
- 4 - very severe

IF SCORED 1-4 ABOVE, FOR CONTEXT, ASK: How long have you been feeling this way?

<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> Tell me what that was like. Can you give me some examples? How bad has this been over the past week? How much has it bothered you? Has it caused you any problems? How much of the time or how often have you had this over the past week? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
	<p>MILD Symptom is infrequent, with no impairment and no more than mild distress</p>
	<p>MODERATE Symptom is more frequent, with moderate distress or limited interference with usual activities</p>
	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>In the past week, how much have you felt tense, keyed up, or on edge?</p> <p>Have you gotten tired easily?</p> <p>How much have you been bothered by any of these things:</p> <ul style="list-style-type: none"> being startled easily? crying easily? trembling? feeling restless? not being able to relax? 	<p>2. TENSION (feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>This past week, have you been afraid of . . .</p> <ul style="list-style-type: none"> the dark? of strangers? of being left alone? of animals? of traffic? of crowds? <p>Have you had any other specific fears this past week?</p> <p>NOTE: INCLUDE ANY IRRATIONAL ANXIETY ABOUT OBJECTS OR SITUATIONS.</p>	<p>3. FEARS (of dark, of strangers, of being left alone, of animals, of traffic, of crowds):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been over the past week? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this over the past week? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
	<p>MILD Symptom is infrequent, with no impairment and no more than mild distress</p>
	<p>MODERATE Symptom is more frequent, with moderate distress or limited interference with usual activities</p>
	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>Now let's talk about your sleep.</p>	
<p>In the last week, have you had trouble falling asleep?</p> <p>How long has it been taking you to fall asleep? IF MORE THAN 30 MINUTES: How many nights this past week did this happen?</p> <p>In the past week have you been waking up in the middle of the night? IF YES: How long are you awake? How many nights this past week did this happen?</p> <p>IF UNKNOWN: In the past week, has your sleep been restless or disturbed? IF YES: How many nights this past week?</p> <p>Have you felt tired when you woke up because you felt you didn't get a good night's sleep? IF YES: How many times?</p> <p>How about having bad dreams or nightmares?</p>	<p>4. INSOMNIA (difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>

<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been over the past week? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this over the past week? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
	<p>MILD Symptom is infrequent, with no impairment and no more than mild distress</p>
	<p>MODERATE Symptom is more frequent, with moderate distress or limited interference with usual activities</p>
	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>In the last week, have you had trouble concentrating?</p> <p>IF YES: Can you give me some examples?</p> <p>How about trouble reading – like a book or a newspaper? Do you need to read things over and over again?</p> <p>Have you had any trouble following a conversation?</p> <p>Have you had trouble remembering things this past week?</p> <p>IF UNKNOWN: What about remembering appointments or errands you have to do?</p>	<p>5. INTELLECTUAL (difficulty in concentrating, poor memory):</p> <p>0 - not present</p> <p>1 - mild</p> <p>2 - moderate</p> <p>3 - severe</p> <p>4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been over the past week? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this over the past week? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
	<p>MILD Symptom is infrequent, with no impairment and no more than mild distress</p>
	<p>MODERATE Symptom is more frequent, with moderate distress or limited interference with usual activities</p>
	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>In the past week, have you felt sad, depressed, or down?</p> <p>Can you describe the feeling? How bad has it been?</p> <p>IF YES: Does the feeling lift if something good happens?</p> <p>How have you been feeling about the future?</p> <p>Have you been feeling discouraged or pessimistic? .</p> <p>What have your thoughts been?</p> <p>Have you been crying this past week?</p> <p>Have you been less interested in things, or not enjoying things you usually enjoy doing?</p> <p>Have there been times this past week when you have awakened earlier than usual? (Is that with an alarm clock, or did you just wake up yourself?)</p> <p>IF EARLY WAKING: How many times?</p> <p>This past week, have you been feeling better or worse at any particular time of day - morning or evening? IF VARIATION: How much worse? How many days has this been the pattern?</p>	<p>6. DEPRESSED MOOD (loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing):</p> <p>0 - not present</p> <p>1 - mild</p> <p>2 - moderate</p> <p>3 - severe</p> <p>4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> Tell me what that was like. Can you give me some examples? How bad has this been over the past week? How much has it bothered you? Has it caused you any problems? How much of the time or how often have you had this over the past week? 	ABSENT	Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety
	MILD	Symptom is infrequent, with no impairment and no more than mild distress
	MODERATE	Symptom is more frequent, with moderate distress or limited interference with usual activities
	SEVERE	Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning
	VERY SEVERE	Symptom is incapacitating

<p>In the last week, have you had any . . .</p> <ul style="list-style-type: none"> muscle aches or pains? muscle twitching? tight or stiff muscles? sudden muscle jerks? grinding of your teeth? Having an unsteady voice? 	<p>7. SOMATIC (MUSCULAR) (pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>In the past week, have you had . . .</p> <ul style="list-style-type: none"> ringing in your ears? blurred vision? hot or cold flashes? feelings of physical weakness (not just feeling tired)? How about pricking sensations? 	<p>8. SOMATIC (SENSORY) (tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> Tell me what that was like. Can you give me some examples? How bad has this been over the past week? How much has it bothered you? Has it caused you any problems? How much of the time or how often have you had this over the past week? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
	<p>MILD Symptom is infrequent, with no impairment and no more than mild distress</p>
	<p>MODERATE Symptom is more frequent, with moderate distress or limited interference with usual activities</p>
	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>In the past week, has . . .</p> <ul style="list-style-type: none"> your heart raced, skipped or pounded? Have you had pain in your chest? Had any throbbing blood vessels? Any fainting feelings? 	<p>9. CARDIOVASCULAR SYMPTOMS (tachycardia, palpitations, pain in chest, throbbing vessels, fainting feelings):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>In the last week, have you had . . .</p> <ul style="list-style-type: none"> pressure or tightness in your chest? choking feelings? What about sighing? Have you had shortness of breath? 	<p>10. RESPIRATORY SYMPTOMS (pressure or constriction in chest, choking feelings, sighing, dyspnea):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> Tell me what that was like. Can you give me some examples? How bad has this been over the past week? How much has it bothered you? Has it caused you any problems? How much of the time or how often have you had this over the past week? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
	<p>MILD Symptom is infrequent, with no impairment and no more than mild distress</p>
	<p>MODERATE Symptom is more frequent, with moderate distress or limited interference with usual activities</p>
	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>In the last week, have you had ...</p> <ul style="list-style-type: none"> trouble swallowing? stomach pain or fullness? gas? nausea? vomiting? burning or rumbling in your stomach? loose bowels? constipation? Have you lost weight in the past week? IF YES: How much? (Have you been trying to lose weight?) DO NOT RATE LOSS OF WEIGHT DUE TO DIETING. 	<p>11. GASTROINTESTINAL SYMPTOMS (difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> • Tell me what that was like. Can you give me some examples? • How bad has this been over the past week? • How much has it bothered you? Has it caused you any problems? • How much of the time or how often have you had this over the past week? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
	<p>MILD Symptom is infrequent, with no impairment and no more than mild distress</p>
	<p>MODERATE Symptom is more frequent, with moderate distress or limited interference with usual activities</p>
	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>In the past week, have you had to urinate frequently? IF NO: Have you had the urge to?</p> <p>How has your interest in sex been this past week? I'm not asking about performance, but about your interest in sex.</p> <p>Is this a change for you? IF YES: How much of a change?</p> <p>FOR WOMEN: When some women feel nervous or anxious, they have trouble having an orgasm, although they have had them in the past. Have you had difficulty with orgasm in the past week? IF YES: How much trouble have you had?</p> <p>Have you had your period in the last month or so? IF YES: Has it been especially heavy? IF NOT: Do you know why not?</p> <p>FOR MEN: Sometimes when men feel nervous or anxious, they have trouble with premature ejaculation, or they have trouble keeping an erection. Has that happened to you in the past week? IF YES: How much trouble have you had?</p>	<p>12. GENITOURINARY SYMPTOMS (frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> Tell me what that was like. Can you give me some examples? How bad has this been over the past week? How much has it bothered you? Has it caused you any problems? How much of the time or how often have you had this over the past week? 	<p>ABSENT Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</p>
	<p>MILD Symptom is infrequent, with no impairment and no more than mild distress</p>
	<p>MODERATE Symptom is more frequent, with moderate distress or limited interference with usual activities</p>
	<p>SEVERE Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</p>
	<p>VERY SEVERE Symptom is incapacitating</p>

<p>In the past week, has your mouth been dry?</p> <p>Have you had any flushing in your face?</p> <p>Have you been pale?</p> <p>Have you felt lightheaded?</p> <p>Have you had headaches?</p> <p>How about feeling the hair rise on your arms, the back of your neck, or your head?</p> <p>Have you tended to sweat a lot in the past week?</p>	<p>13. AUTONOMIC SYMPTOMS (dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair):</p> <p>0 - not present</p> <p>1 - mild</p> <p>2 - moderate</p> <p>3 - severe</p> <p>4 - very severe</p>
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<p>Suggested follow up questions:</p> <ul style="list-style-type: none"> Tell me what that was like. Can you give me some examples? How bad has this been over the past week? How much has it bothered you? Has it caused you any problems? How much of the time or how often have you had this over the past week? 	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="text-align: center; width: 15%;">ABSENT</td> <td>Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety</td> </tr> <tr> <td style="text-align: center;">MILD</td> <td>Symptom is infrequent, with no impairment and no more than mild distress</td> </tr> <tr> <td style="text-align: center;">MODERATE</td> <td>Symptom is more frequent, with moderate distress or limited interference with usual activities</td> </tr> <tr> <td style="text-align: center;">SEVERE</td> <td>Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning</td> </tr> <tr> <td style="text-align: center;">VERY SEVERE</td> <td>Symptom is incapacitating</td> </tr> </table>	ABSENT	Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety	MILD	Symptom is infrequent, with no impairment and no more than mild distress	MODERATE	Symptom is more frequent, with moderate distress or limited interference with usual activities	SEVERE	Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning	VERY SEVERE	Symptom is incapacitating
ABSENT	Score 0 if symptoms are absent, insignificant, or clearly due to causes other than anxiety										
MILD	Symptom is infrequent, with no impairment and no more than mild distress										
MODERATE	Symptom is more frequent, with moderate distress or limited interference with usual activities										
SEVERE	Score 3 if symptom is severe and persistent or results in severe distress or marked impairment in functioning										
VERY SEVERE	Symptom is incapacitating										

<p>RATING BASED ON OBSERVATION DURING INTERVIEW (CIRCLE SYMPTOMS PRESENT):</p> <p>FOR TELEPHONE ASSESSMENT: During this interview, have you been fidgeting at all, or having trouble sitting still? Have you been doing anything like playing with your hands or hair, or tapping your foot?</p> <p>IF YES: How bad has that been?</p> <p>Have your hands been shaky?</p> <p>What about swallowing or feeling the need to swallow?</p> <p>If you looked in a mirror right now, would your face look relaxed? IF NO: Would it look strained or tight?</p> <p>Do you think you look pale?</p>	<p>14. BEHAVIOR AT INTERVIEW (fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos, etc.):</p> <p>0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe</p>
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TIME ENDED SIGH-A:	_____	AM / PM	ET / CT / PT
TOTAL HAM-A SCORE:	— —		

APPENDIX 4. CLINICAL GLOBAL IMPRESSION–IMPROVEMENT SCALE (CGI-I) AND SEVERITY SCALE (CGI-S)

Clinical Global Impression – Improvement (CGI-I) Scale

Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to his/her condition at baseline, how much has patient changed? (Note that subject's illness is the disease under study; in this case, Major Depressive Disorder – NOT other conditions/co-morbidities.)

1	Very much improved	Nearly all better; good level of functioning; minimal symptoms; represents a very substantial change
2	Much improved	Notably better with significant reduction of symptoms; increase in the level of functioning but some symptoms remain
3	Minimally improved	Slightly better with little or no clinically meaningful reduction of symptoms. Represents very little change in basic clinical status, level of care, or functional capacity
4	No change	Symptoms remain essentially unchanged
5	Minimally worse	Slightly worse but may not be clinically meaningful, may represent very little change in basic clinical status or functional capacity
6	Much worse	Clinically significant increase in symptoms and diminished functioning
7	Very much worse	Severe exacerbation of symptoms and loss of functioning

Rater Signature: _____ Date (DD/MM/YYYY): _____

Busner, J., Targum, S. (2007), as adapted from Spearing, et al. *Psychiatry Research*, 1997. 73:159-171.

Modified from Guy W. Clinical Global Impressions: In ECDEU Assessment Manual for Psychopharmacology. 1976; 218-222. Revised DHEW Pub. (ADM) Rockville, MD: National Institute for Mental Health

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Clinical Global Impression – Severity of Illness (CGI-S) Scale

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time? (Note that subject's illness is the disease under study; in this case, Major Depressive Disorder – NOT other conditions/co-morbidities.)

1	Normal, not at all ill	Symptoms of disorder not present during the timeframe
2	Borderline ill	Subtle or suspected pathology
3	Mildly ill	Clearly established symptoms with minimal, if any, distress or difficulty in social and occupational function
4	Moderately ill	Overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication
5	Markedly ill	Intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress
6	Severely ill	Disruptive pathology; behavior and function are frequently influenced by symptoms; may require assistance from others
7	Among the most extremely ill patients	Pathology drastically interferes in many life functions; may be hospitalized

Rater Signature: _____ Date (DD/MMM/YYYY): _____

Busner, J., Targum, S. (2007), as adapted from Kay, Stanley R., Positive and Negative Symptoms in Schizophrenia: Assessment and Research. Clinical and Experimental Psychiatry, Monograph No. 5. Brunner/Mazel, 1991.

Modified from Guy W. Clinical Global Impressions: In ECDEU Assessment Manual for Psychopharmacology. 1976; 218-222. Revised DHEW Pub. (ADM) Rockville, MD: National Institute for Mental Health






APPENDIX 5. SHORT-FORM 36 (SF-36)

Your Health and Well-Being






This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
				
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
				
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

SF-36v2® Health Survey © 1992, 1996, 2000 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.

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(SF-36v2® Health Survey Acute, United States (English))

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot ▼	Yes, limited a little ▼	No, not limited at all ▼
a <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
c Lifting or carrying groceries	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
d Climbing <u>several</u> flights of stairs	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
e Climbing <u>one</u> flight of stairs	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
f Bending, kneeling, or stooping	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
g Walking <u>more than a mile</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
h Walking <u>several hundred yards</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
i Walking <u>one hundred yards</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
j Bathing or dressing yourself	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

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4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c Were limited in the <u>kind of</u> work or other activities	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c Did work or other activities <u>less carefully than usual</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

7. How much bodily pain have you had during the past week?

None	Very mild	Mild	Moderate	Severe	Very severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b Have you been very nervous?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d Have you felt calm and peaceful?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
e Did you have a lot of energy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
f Have you felt downhearted and depressed?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
g Did you feel worn out?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
h Have you been happy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
i Did you feel tired?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	▼	▼	▼	▼	▼
a I seem to get sick a little easier than other people	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b I am as healthy as anybody I know	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c I expect my health to get worse.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d My health is excellent.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Thank you for completing these questions!

APPENDIX 6. THE FATIGUE ASSOCIATED WITH DEPRESSION (FAS-D) PATIENT-REPORTED OUTCOME (PRO)

Please mark an "X" in the box that best describes your experience during the past week.

In the PAST WEEK, how often have you felt...	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Always (5)
1. Fatigued	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Tired	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Exhausted	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Like you had no energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Physically weak	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Like everything requires too much effort	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The following items ask about the impact of fatigue on various aspects of your life.

In the PAST WEEK, how much has your fatigue...	Not at all (1)	A little (2)	Somewhat (3)	Quite a bit (4)	Very much (5)
7. Limited your ability to complete daily household chores	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Interfered with family activities or relationships	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Interfered with doing things you enjoy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Interfered with social activities, like spending time with friends	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Interfered with taking care of yourself (e.g., bathing, dressing, brushing your teeth)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Do you have a spouse or significant other?

- ☐ Yes (Please answer item 12.)
- ☐ No (Leave item 12 blank.)

In the PAST WEEK, how much has your fatigue...	Not at all (1)	A little (2)	Somewhat (3)	Quite a bit (4)	Very much (5)
12. Interfered with your intimate relationship (i.e., with a spouse or significant other)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Do you have a job or go to school?

- ☐ Yes (Please answer item 13.)
- ☐ No (Leave item 13 blank.)

In the PAST WEEK, how much has your fatigue...	Not at all (1)	A little (2)	Somewhat (3)	Quite a bit (4)	Very much (5)
13. Limited your productivity at work or school	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

APPENDIX 7. COLUMBIA - SUICIDE SEVERITY RATING SCALE (C-SSRS)

COLUMBIA-SUICIDE SEVERITY
RATING SCALE
(C-SSRS)

Baseline/Screening Version

Version 1/14/09

**Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;
Burke, A.; Oquendo, M.; Mann, J.**

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AUS_1_eng-US01.doc

SUICIDAL IDEATION			
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.		Lifetime: Time He/She Felt Most Suicidal	Past 24 Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
If yes, describe:			
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
If yes, describe:			
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it." <i>Have you been thinking about how you might do this?</i>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
If yes, describe:			
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
If yes, describe:			
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
If yes, describe:			
INTENSITY OF IDEATION			
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.			
Lifetime -	Most Severe Ideation: Type # (1-5) Description of Ideation	Most Severe	Most Severe
Past 24 Months -	Most Severe Ideation: Type # (1-5) Description of Ideation		
Frequency <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		—	—
Duration <i>When you have the thoughts how long do they last?</i> (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous		—	—
Controllability <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (6) Does not attempt to control thoughts		—	—
Deterrents <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (6) Does not apply		—	—
Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (6) Does not apply		—	—

SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)		Lifetime		Past 24 Months	
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <i>any</i> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <i>There does not have to be any injury or harm</i> , just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? What did you do? Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to end your life when you _____? Or did you think it was possible you could have died from _____? Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:		Yes <input type="checkbox"/>	No <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Total # of Attempts _____		Total # of Attempts _____			
Has subject engaged in Non-Suicidal Self-Injurious Behavior?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:		Yes <input type="checkbox"/>	No <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Total # of interrupted _____		Total # of interrupted _____			
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:		Yes <input type="checkbox"/>	No <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Total # of aborted _____		Total # of aborted _____			
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:		Yes <input type="checkbox"/>	No <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Suicidal Behavior: Suicidal behavior was present during the assessment period?		Yes <input type="checkbox"/>	No <input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Answer for Actual Attempts Only		Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:	
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death		Enter Code _____	Enter Code _____	Enter Code _____	
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care		Enter Code _____	Enter Code _____	Enter Code _____	

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;
Burke, A.; Oquendo, M.; Mann, J.*

Disclaimer:

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For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION		Since Last Visit
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.		
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it....and I would never go through with it". <i>Have you been thinking about how you might do this?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some</u> intent to act on such thoughts, as opposed to "I have the thoughts but I definitely will not do anything about them". <i>Have you had these thoughts and had some intention of acting on them?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).		Most Severe
Most Severe Ideation: _____		
Type # (1-5) _____ Description of Ideation _____		
Frequency <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		—
Duration <i>When you have the thoughts how long do they last?</i> (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous		—
Controllability <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (6) Does not attempt to control thoughts		—
Deterrents <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (6) Does not apply		—
Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (6) Does not apply		—

SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)		Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm , just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? What did you do? Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to end your life when you _____? Or Did you think it was possible you could have died from _____? Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of Attempts _____ Yes No <input type="checkbox"/> <input type="checkbox"/>
Has subject engaged in Non-Suicidal Self-Injurious Behavior? Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of interrupted _____ Yes No <input type="checkbox"/> <input type="checkbox"/>
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of aborted _____ Yes No <input type="checkbox"/> <input type="checkbox"/>
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>
Suicidal Behavior: Suicidal behavior was present during the assessment period?		Yes No <input type="checkbox"/> <input type="checkbox"/>
Suicide:		Yes No <input type="checkbox"/> <input type="checkbox"/>
Answer for Actual Attempts Only		Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death		Enter Code _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care		Enter Code _____

APPENDIX 8. STANFORD SLEEPINESS SCALE (SSS)

Stanford Sleepiness Scale

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	Scale Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

APPENDIX 9. REMISSION OF DEPRESSION QUESTIONNAIRE (RDQ)

Patient Name: _____

Date: _____

Instructions. The purpose of this questionnaire is to determine how well individuals with depression have responded to treatment. The items on the scale ask about different aspects of depression such as symptoms, coping with stress, ability to function, sense of well-being, and enjoyment in life. Use the following scale to indicate how well it describes you **for the past week**.

0=not at all or rarely true 1=sometimes true 2=often or almost always true

Symptoms of Depression

1. I felt sad or depressed..... 0 1 2
2. I was not interested in the things I usually enjoy... 0 1 2
3. My appetite was poor. 0 1 2
4. My appetite was much greater than usual..... 0 1 2
5. I had difficulty sleeping. 0 1 2
6. I was sleeping too much. 0 1 2
7. My energy level was low. 0 1 2
8. I felt guilty. 0 1 2
9. I thought I was a failure. 0 1 2
10. I had problems concentrating. 0 1 2
11. I had difficulty making decisions. 0 1 2
12. I wished I was dead. 0 1 2
13. I had thoughts about killing myself..... 0 1 2

Other Symptoms Often Present in Depressed Patients

14. I felt anxious. 0 1 2
15. I worried excessively. 0 1 2
16. I got irritated easily. 0 1 2
17. I felt "on edge". 0 1 2
18. I had a sense of dread or impending doom..... 0 1 2

Coping Ability

19. I coped well with the normal stresses and
hassles of life..... 0 1 2
20. I am able to bounce back from stressful situations. 0 1 2
21. I could keep myself from feeling depressed..... 0 1 2

Positive Mental Health

22. I felt at ease. 0 1 2
23. I cared about things in my life. 0 1 2
24. I was able to have fun. 0 1 2
25. I saw myself as a person of value. 0 1 2
26. I had a positive outlook on life. 0 1 2
27. I could focus and concentrate well. 0 1 2
28. I could make decisions without a lot of self-doubt... 0 1 2
29. I felt confident. 0 1 2
30. I woke up feeling fresh and rested..... 0 1 2
31. When I woke up I looked forward to the day. 0 1 2
32. I had the desire to do things. 0 1 2

Functioning

33. I was functioning well in my work (at a paid job,
at home, or at school). 0 1 2
34. I was participating in social activities. 0 1 2
35. I was able to fulfill my usual responsibilities. 0 1 2

Life Satisfaction

36. I was satisfied with life. 0 1 2
37. My life was fulfilling. 0 1 2
38. I was engaging in life rather than hiding from it.... 0 1 2

General Sense of Well-Being

39. I felt mentally healthy. 0 1 2
40. I felt in control of my emotions. 0 1 2
41. I had a general sense of well-being..... 0 1 2

APPENDIX 10. HEALTH-RELATED PRODUCTIVITY QUESTIONNAIRE

Health Related Productivity Questionnaire

These questions deal with how [X] or its treatment(s) have affected your ability to remain in the workforce and perform work and daily activities in your home. Your responses and those of other patients will help us to understand the impact of [X] on these aspects of your life.

1. What is your **current** employment status?

- ☐ Currently employed full-time → Please go to Question 2
☐ Currently employed part-time → Please go to Question 2
☐ Not currently employed → Please go to Question 5

2. How many hours were you scheduled to work at your job during the last **week**?

(If none or you are not employed, put a "0" here and go to Question 5.)

_____ Hours

3. Did [X] or its treatment(s) keep you from working any of your scheduled hours during the last **week**?

- ☐ Yes → I missed _____ hours of work because of [X] or its treatment(s).
☐ No, [X] or its treatment(s) did not keep me from working my scheduled hours.

4. For the hours that you **did** work during the past week, how did [X] or its treatment(s) impact your **work output**?

Write a number
on the line
below, based on
this scale.

0%.....100%
[X] or its treatment(s) [X] or its treatment(s)
had no impact kept me from
on how much I accomplished accomplishing anything

_____ % impact on work output

5. How many hours of household chores (cooking, cleaning, gardening, repairs, etc.) did you plan to do during the last **week**?

(If none, put a "0" here and go to Question 8.)

_____ Hours

6. Did [X] or its treatment(s) keep you from doing any of your planned hours of household chores last **week**?

- ☐ Yes → I worked _____ hours less because of [X] or its treatment(s).
☐ No, [X] or its treatment(s) did not keep me from working my planned hours.

7. For the hours of household chores you **did** during the past week, how did [X] or its treatment(s) impact your **work output**?

Write a number
on the line
below, based on
this scale.

0%.....100%
[X] or its treatment(s) [X] or its treatment(s)
had no impact kept me from
on how much I accomplished accomplishing anything

_____ % impact on work output

[This block of items dealing with education are relevant for only certain age categories and should be considered to be optional]

- Q. How many hours of homework or classes did you plan to do during the last **week**?
(If none, put a "0" here and go to Question 8.)

_____ Hours

- Q. Did [X] or its treatment(s) keep you from doing any of your planned hours of homework or classes last **week**?

- ☐ Yes → I completed _____ hours less because of [X] or its treatment(s).
☐ No, [X] or its treatment(s) did not keep me from completing my planned hours.

- Q. For the hours of homework or classes you **did** during the past week, how did [X] or its treatment(s) impact your **work output**?

Write a number
on the line
below, based on
this scale.

0%.....100%
|
[X] or its treatment(s) [X] or its treatment(s)
had no impact kept me from
on how much I accomplished accomplishing anything

_____ % impact on work output

[This block of items deals with workforce participation and should be collected at study start]

8. How long has it been since [X] developed?

_____ Months _____ Years

9. Which of the following statements are true of your life **since** [X] **developed** (mark all that apply):

- ☐ [X] or its treatment(s) forced me to work part-time when I wanted to work **full-time**.
For how long was this true? _____ Months _____ Years
☐ [X] or its treatment(s) kept me from having a job when I wanted to work **full-time**.
For how long was this true? _____ Months _____ Years
☐ [X] or its treatment(s) kept me from having a job when I wanted to work **part-time**.
For how long was this true? _____ Months _____ Years
☐ None of the above

Summary of Changes Page
Protocol 217-MDD-201
Date 13 Jan 2017

The following changes, and the rationale for the changes, were made to the attached protocol in this amendment.

Section number and title in Original Protocol (24 Oct 2016)	Section number and title in Amendment 1 (13 Jan 2017)	Original text:	Changed to:
Protocol Signature Page	Protocol Signature Page	Date of Original Protocol: 24 October 2016	Date of Original Protocol: 24 October 2016 Date of Amendment 1: 13 January 2017
Document header	Document header	Version 1.0 24 October 2016	Version 1.0 1.0 24 October 24-13 October January 2016
Title Page	Title Page	Date of Original Protocol: 24 October 2016 Handan Gunduz-Bruce, M.D., M.B.A. Medical Director Phone: 203-500-9240 Handan.Gunduz- Bruce@sagerx.com	Date of Original Protocol: 24 October 13 January 2016 Handan Gunduz-Bruce, M.D., M.B.A. Medical Director Phone: 203-500-9240 Handan.Gunduz- Bruce@sagerx.com Inder Kaul, M.D., M.P.H. Study Physician Phone: 617-538-0292 inder.kaul@sagerx.com
Table 1: Emergency Contact Information	Table 1: Emergency Contact Information	Cincinnati Children's Hospital Medical Center Medical Vigilance Solutions Drug and Poison Information Center 3333 Burnet Avenue, MLC 9004 Cincinnati, OH 45229-3039 1-877-462-0134	INC Research 3201 Beechleaf Ct., Suite 600 Raleigh, NC 27604 USA Cincinnati Children's Hospital Medical Center Medical Vigilance Solutions Drug and Poison Information

Section number and title in Original Protocol (24 Oct 2016)	Section number and title in Amendment 1 (13 Jan 2017)	Original text:	Changed to:
			Center 3333 Burnet Avenue, MLC 9004 Cincinnati, OH 45229-3039 1-877-462-0134
Synopsis	Synopsis	The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit, which can occur on any one calendar day of the 7-day window (from Day -7 through Day -1).	The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit, which can occur on any two consecutive calendar days of the 7-day window (from Day -7 through Day -1).
Synopsis (pg. 6, 7, and 10), Section 7.1 and Section 9.3	Synopsis (pg. 6, 7, and 10), Section 7.1 and Section 9.3	Part B may be initiated after termination or completion of Part A if there is a clear signal of activity based on the 17 item Hamilton Rating Scale for Depression (HAM-D) scores and/or other scales being assessed. Part A may be terminated and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed.	Part B may be initiated after termination or completion and enrollment into of Part A stopped if there is a clear signal of activity based on the 17 item Hamilton Rating Scale for Depression (HAM-D) scores and/or other scales being assessed. Enrollment into Part A may be terminated stopped and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed.
Synopsis	Synopsis	For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of blinded study drug administration.	For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last measurement prior to the start of blinded study drug administration.

Section number and title in Original Protocol (24 Oct 2016)	Section number and title in Amendment 1 (13 Jan 2017)	Original text:	Changed to:
Section 13.1.6	Section 13.1.6	All samples will be analyzed at the central laboratory. Subjects may be considered eligible for the study based on local laboratory results; however, screening samples must also be sent to the central laboratory.	All required samples in Part A will be analyzed at the central local laboratory ies . All samples in Part B will be analyzed at the central laboratory. Subjects may be considered eligible for the study based on local laboratory results; however, screening samples in Part B must also be sent to the central laboratory.
Section 13.1.6.2	Section 13.1.6.2	Serum chemistry tests will include serum electrolytes; renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide; liver function tests, including total bilirubin, aspartate aminotransferase, and alanine aminotransferase; total protein; and albumin.	Serum chemistry tests will include serum electrolytes; renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide; liver function tests, including alkaline phosphatase , total bilirubin, aspartate aminotransferase, and alanine aminotransferase; total protein; and albumin; and thyroid stimulating hormone .
Synopsis and Section 8.2	Synopsis and Section 8.2	--	15. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
Table 2, Table 3, Section 13.1.6, and Section 17.3	Table 2, Table 3, Section 13.1.6, and Section 17.3	Where consent is given, an optional blood sample for hormone and exploratory biochemistry testing and optional genetic sample for biomarker testing will be	Where consent is given, an optional blood sample for hormone and exploratory biochemistry testing will be collected at the Screening visit, Day 8 and Day 15 and

Section number and title in Original Protocol (24 Oct 2016)	Section number and title in Amendment 1 (13 Jan 2017)	Original text:	Changed to:
		collected at the Screening visit.	an optional genetic sample for biomarker testing will be collected at the Screening visit.
Table 2, Table 3, and Section 12.1	Table 2, Table 3, and Section 12.1	Plasma samples for PK analysis in Part A and Part B will be collected predose and 0.25,...	Plasma samples for PK analysis in Part A and Part B will be collected predose on Days 2, 3, 4, 5, and 6 , predose and 0.25,...
Table 2 and Table 3	Table 2 and Table 3	k. To be completed at 8:00 AM (±30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.	k. To be completed at 8:00 AM (±30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28. The assessment timeframe for HAM-D and HAM-A scales will refer to the past 7 days (1 week) on Screening, Day 1, Day 15/ET, Day 21, and Day 28 visits, and the past 24 hours on visits occurring on Days 2 through 8.
Section 17.3	Section 17.3	As additional assessments, the ICF will contain provisions for optional consent for the collection of blood samples for hormone and biomarker testing during screening and the collection of breast milk for biobanking and PK analysis purposes.	As additional assessments, the ICF will contain provisions for optional consent for the collection of blood samples for hormone biochemistry during screening, Day 8, and Day 15 and biomarker testing during screening and the collection of breast milk for biobanking and PK analysis purposes.

Section number and title in Original Protocol (24 Oct 2016)	Section number and title in Amendment 1 (13 Jan 2017)	Original text:	Changed to:
Section 20	Section 20	<p>Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32:50-5.</p> <p>Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62.</p> <p>McDowell, I. Measuring Health: A guide to rating scales and questionnaires. 2006: 3rd Ed. New York: Oxford University Press.</p> <p>Müller-Thomsen T, Arlt S, Mann U, Mass R, Ganzer S. Detecting depression in Alzheimer's disease: evaluation of four different scales. Arch Clin Neuropsychol. 2005;20:271-6.</p>	<p>Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32:50-5.</p> <p>Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62.</p> <p>McDowell, I. Measuring Health: A guide to rating scales and questionnaires. 2006: 3rd Ed. New York: Oxford University Press.</p> <p>Müller-Thomsen T, Arlt S, Mann U, Mass R, Ganzer S. Detecting depression in Alzheimer's disease: evaluation of four different scales. Arch Clin Neuropsychol. 2005;20:271-6.</p>
		<p>Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.</p>	<p>Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.</p>

Section number and title in Original Protocol (24 Oct 2016)	Section number and title in Amendment 1 (13 Jan 2017)	Original text:	Changed to:
			<p>Busner J, Targum S. CGI-S. (2007a), as adapted from Kay, Stanley R, Positive and Negative Symptoms in Schizophrenia: Assessment and Research. Clinical and Experimental Psychiatry, Monograph No. 5. Brunner/Mazel, 1991. Modified from Guy W. Clinical Global Impressions: In ECDEU Assessment Manual for Psychopharmacology. 1976; 218-22. Revised DHEW Pub. (ADM) Rockville, MD: National Institute for Mental Health.</p> <p>Busner J, Targum S. CGI-I. (2007b), as adapted from Spearing, et al. Psychiatry Research, 1997;73:159 71. Modified from Guy W. Clinical Global Impressions: In ECDEU Assessment Manual for Psychopharmacology. 1976; 218-22. Revised DHEW Pub. (ADM) Rockville, MD: National Institute for Mental Health.</p>

Section number and title in Original Protocol (24 Oct 2016)	Section number and title in Amendment 1 (13 Jan 2017)	Original text:	Changed to:
			<p>Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. <i>Psychophysiology</i>. 1973 Jul;10(4):431-6.</p> <p>Matza LS, Murray LT, Phillips GA, et al. Qualitative Research on Fatigue Associated with Depression: Content Validity of the Fatigue Associated with Depression Questionnaire (FAsD-V2). <i>Patient</i>. 2015 Oct;8(5):433-43.</p> <p>Posner K, Brent D, Lucas C, et al. C-SSRS BL/Scr: 2008a Research Foundation for Mental Hygiene, Inc.C-SSRS—Baseline/Screening (Version 1/14/09).</p> <p>Posner K, Brent D, Lucas C, et al. C-SSRS SLV: 2008b Research Foundation for Mental Hygiene, Inc.C-SSRS—Since Last Visit (Version 1/14/09).</p> <p>Williams JBW, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Asberg Depression Rating Scale (SIGMA). <i>Br J Psychiatry</i>. 2008;192:52-8.</p>

Section number and title in Original Protocol (24 Oct 2016)	Section number and title in Amendment 1 (13 Jan 2017)	Original text:	Changed to:
			<p>Williams JBW. SIGH-D 24hr: V1.3 – 24 HR Version. 2013a.</p> <p>Williams JBW. SIGH-D Past week: Past Week Version. 2013b.</p> <p>Williams JBW. SIGH-A 24hr: V1.3 – 24 HR Version. 2013c.</p> <p>Williams JBW. SIGH-A Past week: Past Week Version. 2013d.</p>

**Summary of Changes to
Protocol 217-MDD-201 v3.0, Amendment #2
Date of Amendment: 09 March 2017**

The following changes were made in Protocol 217-MDD-201 v3.0, Amendment #2. In addition, minor revisions to formatting, punctuation, spelling, and wording (eg, capitalization, abbreviation, word order) that are not listed below were made throughout the protocol.

Section Number and Title	Original Text:	Changed To:
Title Page	<div>Investigational Product SAGE-217</div> <div>Clinical Phase 2a</div> <div>Sponsor Sage Therapeutics, Inc.</div> <div>Sponsor Contact George Nomikos, M.D., Ph.D. Senior Medical Director Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: 617-949-2881 George.Nomikos@sagerx.com</div> <div>Sponsor Medical Monitor Inder Kaul, M.D., M.P.H. Study Physician Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: 617-538-0292</div> <div>Date of Original Protocol Version 1.0, 24 October 2016 Version 2.0, 13 January 2017</div> <div>Date of Amendment One</div>	<div>Investigational Product SAGE-217</div> <div>Clinical Phase 2a</div> <div>Sponsor Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142</div> <div>Sponsor Contact George Nomikos, M.D., Ph.D. Senior Medical Director Phone: 617-949-2881 George.Nomikos@sagerx.com</div> <div>Sponsor Medical Monitor Handan Gunduz-Bruce, M.D., M.B.A. Medical Director Phone: 203-500-9240 Handan.Gunduz-Bruce@sagerx.com</div> <div>Date of Original Protocol Version 1.0, 24 October 2016 Version 2.0, 13 January 2017 Version 3.0, 09 March 2017</div> <div>Date of Amendment One Date of Amendment Two</div>

Section Number and Title	Original Text:	Changed To:
Protocol Signature Page	<p>Protocol Number:217-MDD-201</p> <p>Product: SAGE-217 Oral Solution</p> <p>IND No.: 132,131</p> <p>Study Phase: 2a</p> <p>Sponsor: Sage Therapeutics</p> <p>Date of Amendment One: Version 2.0 13 January 2017</p> <p>...</p> <p>Abdul J. Sankoh, Ph.D.</p> <p>Vice President of Data Science</p> <p>Sage Therapeutics</p>	<p>Protocol Number:217-MDD-201</p> <p>Product: SAGE-217 Oral Solution (Part A) SAGE-217 Capsules (Part B)</p> <p>IND No.: 132,131</p> <p>Study Phase: 2a</p> <p>Sponsor:Sage Therapeutics</p> <p>Date of Amendment Two: Version 3.0 09 March 2017</p> <p>...</p> <p>Abdul J. Sankoh, Ph.D.</p> <p>Vice President of Data Science</p> <p>Sage Therapeutics</p>
Synopsis, Name of the Investigational Product	SAGE-217	SAGE-217 Oral Solution (Part A) SAGE-217 Capsules (Part B)
Synopsis, Methodology Section 7.1, Overall Study Design	<p>This study will assess the safety, tolerability, pharmacokinetics (PK), and efficacy of SAGE-217 Oral Solution in adult subjects diagnosed with moderate to severe major depressive disorder (MDD). There are two parts to the study:</p> <ul style="list-style-type: none"> •Part A: Open-label dosing with SAGE-217 Oral Solution (14 days). All subjects will receive a 30 mg SAGE-217 Oral Solution dose administered at 8:00 PM (±15 minutes) with food on Day 1 to Day 14 as tolerated. •Part B: Randomized, double-blind, parallel-group, placebo-controlled (14 days). Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥30 days) 	<p>This study will assess the safety, tolerability, pharmacokinetics (PK), and efficacy of SAGE-217 Oral Solution (Part A) and SAGE-217 Capsules (Part B) in adult subjects diagnosed with moderate to severe major depressive disorder (MDD).</p> <p>There are two parts to the study:</p> <ul style="list-style-type: none"> •Part A: Open-label dosing with SAGE-217 Oral Solution (14 days). All subjects will receive a 30-mg dose of SAGE-217 Oral Solution administered at 8:00 PM (±15 minutes) with food on Day 1 to Day 14, as tolerated. Part A will consist of an up to 7 day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 2-week Follow-up Period. •Part B: Randomized, double-blind, parallel-group,

Section Number and Title	Original Text:	Changed To:
	<p>and randomized within each stratum in a 1:1 fashion to receive SAGE-217 Oral Solution 30 mg or matching placebo for 14 days beginning on Day 1 as tolerated. All doses of study drug will be administered at 8:00 PM (±15 minutes) with food.</p> <p>...</p> <p>Both parts of the study will consist of an up to 7 day Screening Period (Days -7 to -1), a 14 day Treatment Period, and a 2-week Follow-up Period. During the study Treatment Period, subjects must remain inpatient for the first 7 days at minimum and per Investigator's judgement thereafter.</p>	<p>placebo-controlled (14 days). Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥30 days) and randomized within each stratum in a 1:1 ratio to receive SAGE-217 Capsules (30 mg) or matching placebo for 14 days beginning on Day 1, as tolerated. All doses of study drug will be administered at 8:00 PM (±15 minutes) with food. Part B will consist of an up to 7 day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 4-week Follow-up Period.</p> <p>...</p> <p>During the study Treatment Period, subjects must remain inpatient for the first 7 days at minimum and per Investigator's judgement thereafter.</p>
Synopsis, Methodology, Screening Period	<p>Most eligibility criteria are the same for both parts of the study.</p>	<p><i>NA</i></p>
Synopsis, Methodology, Treatment Period	<p>Subjects who cannot tolerate 20 mg will be terminated from the study.</p> <p>...</p> <p>Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B.</p> <p>Part B - Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥30 days) and randomized within each stratum to one of two treatment groups</p>	<p>Subjects who cannot tolerate 20 mg may terminated from the study at the discretion of the Investigator.</p> <p>...</p> <p>Part B - Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥30 days) and randomized within each stratum to one of two treatment groups (SAGE-217 Capsules [30 mg dose] or matching placebo) in a 1:1 ratio. Subjects will be administered study drug at 8:00 PM (±15 minutes) with food for 14 days.</p>

Section Number and Title	Original Text:	Changed To:
	<p>(SAGE-217 Oral Solution 30 mg or matching placebo) in a 1:1 ratio. Subjects will be administered study drug at 8:00 PM (±15 minutes) with food for 14 days. Subjects who cannot tolerate 30 mg will receive 20 mg for the rest of the Treatment Period. Subjects who cannot tolerate 20 mg will be terminated from the study.</p> <p>...</p> <p>The outpatient phase treatment may be provided at the clinical site or, if suitable arrangements can be made, via home administration. Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.</p> <p>With the exception of subjects permitted to use current stable antidepressant treatment, initiation of psychotropic medications and other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of the Day 15 assessments (Parts A and B). Psychotropic medications, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the Day 15 assessments (Parts A and B).</p> <p>Efficacy and safety assessments will be performed periodically during the study, and blood samples will be collected for analysis of SAGE-217 as outlined in the Schedule of Events (Table 2 and</p>	<p>Subjects who cannot tolerate 30 mg will receive 20 mg for the rest of the Treatment Period. Subjects who experience intolerable AEs at the 20 mg dose level may be terminated from the study at the discretion of the Investigator.</p> <p>...</p> <p>The outpatient treatment may be provided at the clinical site or, if suitable arrangements can be made, via home administration. All dosing will be observed, either in the clinical unit or by a healthcare professional at home. Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.</p> <p>With the exception of subjects permitted to use current stable antidepressant treatment, initiation of psychotropic medications and other medications that may potentially have an impact on efficacy or safety endpoints will not be allowed between screening and completion of the Day 15 assessments (Parts A and B). Psychotropic medications, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the Day 15 assessments (Part A). Psychotropic medications that are used with the intent to treat depressive symptoms such as antidepressants, atypical antipsychotics, etc., must have been initiated at least 30 days prior to screening and must remain at a stable dose until completion of the Day 15</p>

Section Number and Title	Original Text:	Changed To:
	Table 3).	assessments (Part B).
Synopsis, Methodology, Follow-up Period	Follow-up Period: Follow-up visits will be conducted on an outpatient basis. Follow-up visits for Parts A and B will be conducted at 1 week (21±1 day) and 2 weeks (28±3 days) after the last dose of study drug.	Follow-up Period: Follow-up visits will be conducted on an outpatient basis. Follow-up visits will be conducted weekly for 2 weeks after completion of the Treatment Period in Part A (Day 28 ±1 day) and weekly for 4 weeks after completion of the Treatment Period in Part B (Day 42 ±1 day). Efficacy, safety, and PK assessments will be performed periodically during the study, as outlined in the Schedule of Events (Table 2 and Table 3).
Synopsis, Objectives Section 6.1, Part A	Part A: Primary: The primary objective of the study is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg. Secondary: The secondary objective of Part A is to determine if treatment with SAGE-217 Oral Solution 30 mg for 14 days reduces depressive symptoms.	Part A: Primary: The primary objective of Part A is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg. Secondary: The secondary objective of Part A is to determine if treatment with SAGE-217 Oral Solution 30 mg for 14 days reduces depressive symptoms. Pharmacokinetic: The PK objective of Part A is to assess the PK profile of SAGE-217 Oral Solution in plasma samples.
Synopsis, Objectives Section 6.2, Part B	Part B: Primary: The primary objective of the study is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg.	Part B: Primary: The primary objective of Part B is to evaluate the safety and tolerability of SAGE-217 Capsules (30 mg).

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	<p>Secondary:</p> <p>The secondary efficacy objective for Part B of the study is to determine if treatment with SAGE-217 Oral Solution 30 mg reduces depressive symptoms in subjects with moderate to severe MDD compared to matching placebo.</p>	<p>Secondary:</p> <p>The secondary efficacy objective for Part B of the study is to determine if treatment with SAGE-217 Capsules (30 mg) reduces depressive symptoms in subjects with moderate to severe MDD compared to matching placebo.</p> <p>Exploratory:</p> <p>The exploratory objective for Part B of the study is to assess the patient-reported outcome (PRO) measures as they relate to quality of life, work function, productivity, and depressive symptoms.</p> <p>Pharmacokinetic:</p> <p>The PK objective of Part B is to assess the PK profile of SAGE-217 Capsules in plasma samples.</p>

Section Number and Title	Original Text:	Changed To:
Synopsis, Endpoints Section 6.3, Endpoints	<p>Part A:</p> <p>Primary:</p> <p>The primary endpoint is the safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); Stanford Sleepiness Scale (SSS) score; physical examination; and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).</p> <p>Secondary:</p> <p>Reduction in depressive symptoms as assessed by the following:</p> <ul style="list-style-type: none"> • Change from baseline in HAM-D total score at all time points; • HAM-D response; • HAM-D remission; • Change from baseline in the MADRS total score at all time points; • Change from baseline in HAM-D subscale and individual item scores at all time points; and <p>CGI-I response.</p> <p>Part B:</p> <p>Primary:</p> <p>The primary endpoint is the safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS.</p> <p>Secondary:</p> <p>Reduction in depressive symptoms as assessed by the following:</p> <ul style="list-style-type: none"> • Change from baseline in HAM-D total score all time points; • HAM-D response; 	<p>Part A:</p> <p>Primary:</p> <p>The primary endpoint for Part A is the safety and tolerability of SAGE-217 Oral Solution as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); Stanford Sleepiness Scale (SSS) score; physical examination; and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).</p> <p>Secondary:</p> <p>Reduction in depressive symptoms as assessed by the following:</p> <ul style="list-style-type: none"> • Change from baseline in HAM-D total score at Day 15 (ET) and all other time points; • HAM-D response; • HAM-D remission; • Change from baseline in the MADRS total score at Day 15 (ET) and all other time points; • Change from baseline in HAM-D subscale and individual item scores at Day 15 (ET) and all other time points; • Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at all time points; and • CGI-I response (defined as a CGI-I score of “very much improved” or “much improved”). <p>Pharmacokinetic:</p> <ul style="list-style-type: none"> • Maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (t_{max}), plasma elimination half-life (t_{1/2}), area under the curve extrapolated to infinity (AUC_∞), and steady state concentration (C_{ss}). <p>Part B:</p> <p>Primary:</p> <p>The primary endpoint for Part B is the safety and tolerability of SAGE-217 Capsules as assessed by the</p>

Section Number and Title	Original Text:	Changed To:
Synopsis, Pharmacokinetic Section 6.3, Pharmacokinetic Objective	Pharmacokinetic: The PK objective of Part A and Part B is: To assess the PK profile of SAGE 217 Oral Solution in plasma samples.	<i>NA</i>
Synopsis, Number of subjects (planned) Section 9.1, Number of Subjects	Up to 52 subjects may be randomized in Part B to ensure at least 46 evaluable subjects for Part B. Evaluable subjects are defined as those subjects receiving study drug with at least one post-baseline HAM-D assessment.	Up to 66 subjects may be randomized in Part B to ensure at least 58 evaluable subjects for Part B. Evaluable subjects are defined as those subjects receiving study drug with at least one post-baseline HAM-D assessment. Additional subjects may be enrolled if the drop-out rate is higher than 10%.
Synopsis, Inclusion Criteria Section 8.1, Subject Inclusion Criteria	7. Subject has a HAM-A total score of ≥ 20 at screening and Day 1 (prior to dosing) (Part B only).	7. Removed per Amendment #2.
Synopsis, Exclusion Criteria Section 8.2, Subject Exclusion Criteria	13. Subject has had administration of psychotropics that have been initiated within 14 days prior to screening and/or are not being taken at a stable dose.	13. Subject has had administration of psychotropics that have been initiated within 14 days prior to screening and/or are not being taken at a stable dose in Part A. Subject has had administration of psychotropic medications that are used with the intent to treat depressive symptoms such as antidepressants, atypical antipsychotics, etc., which have been initiated within 30 days prior to screening and/or are not being taken at a stable dose in Part B.
Synopsis, Reference Therapy, dosage, and mode of administration	Reference therapy is taste-matched placebo.	Part A: None Part B: Placebo for Part B is hard gelatin capsules for oral administration containing only the excipients listed above for the active capsule treatment. Subjects will receive two placebo

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		capsules per dose.
Synopsis, Randomization, Section 9.2.2, Part B	Subjects in Part B will be randomized within each antidepressant treatment stratum to receive SAGE-217 Oral Solution or matching placebo oral solution in a 1:1 ratio. Subjects, clinicians, and the study team will be blinded to treatment allocation . The pharmacist and/or designated pharmacy staff, who will prepare the oral solutions according to the randomization schedule, will be unblinded.	Subjects in Part B will be randomized within each antidepressant treatment stratum to receive SAGE-217 Capsules or matching placebo capsules in a 1:1 ratio. Subjects, clinicians, and the study team will be blinded to treatment assignment. The pharmacist and/or designated pharmacy staff, who will prepare the study drug according to the randomization schedule, will be unblinded.
Synopsis, Dose Adjustment for Safety/Tolerability Reasons	During the Treatment Period, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who experience moderate or severe adverse events that according to the clinical judgement of the Investigator are related to study drug while receiving the 30 mg dose of study drug will receive 20 mg for the remaining of the Treatment Period. Subjects who experience moderate or severe related adverse events while receiving the 20 mg dose of study drug may not be able to continue receiving study drug based on the evaluation and clinical judgment of the Investigator, and may be terminated from the study. Dosing may also be modified based on tolerability as assessed with SSS scores. Enrollment into Part A may be stopped and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed. The study may be terminated if there is clear lack of activity based on HAM-D scores during Part A. A Data Review Team will assess the	During the Treatment Period, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects who cannot tolerate 30 mg will receive 20 mg for the remaining of the Treatment Period. Subjects who experience intolerable AEs at the 20-mg dose level may be terminated from the study at the discretion of the Investigator. Dosing may also be modified based on tolerability as assessed with SSS scores.

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	HAM-D and other data on an ongoing basis during Part A.	
Synopsis, Criteria for Evaluation	<p>Reduction of depressive symptoms will be assessed by the change from baseline at various time points in HAM-D total score; HAM-D response; HAM-D remission; change from baseline in the MADRS total score; CGI-I response; change from baseline in HAM-D subscale and individual item scores; change from baseline in HAM-A total score; change from baseline in SF-36; and change from baseline in FAs-D.</p> <p>...</p> <p>The safety and tolerability of SAGE-217 Oral Solution will be evaluated by frequency, type, and severity of adverse events; mean changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C SSRS during both Part A and Part B.</p>	<p>Reduction of depressive symptoms will be assessed by the change from baseline at various post baseline time points in HAM-D total score; HAM-D response; HAM-D remission; change from baseline in the MADRS total score; CGI-I response; change from baseline in HAM-D subscale and individual item scores; and change from baseline in HAM-A total score.</p> <p>...</p> <p>The safety and tolerability of SAGE-217 Oral Solution or SAGE-217 Capsules will be evaluated by frequency, type, and severity of adverse events; mean changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C SSRS during both Part A and Part B.</p>
Synopsis, Statistical Methods, Analysis Populations Sets and Methods	<p>The Safety Population (for both Part A and Part B), defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data. Adverse events will be classified by type, incidence, severity, and causality. The overall incidence of adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Data for vital signs, clinical laboratory measurements, ECG, physical examinations, and concomitant medication usage will also be</p>	<p>The Safety Set (for both Part A and Part B), defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data. Adverse events will be classified by type, incidence, severity, and causality. The overall incidence of adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Data for vital signs, clinical laboratory measurements, ECG, and concomitant medication usage will also be summarized.</p>

Section Number and Title	Original Text:	Changed To:
	<p>summarized.</p> <p>...</p> <p>The Efficacy Population (for both Part A and Part B), defined as all subjects in the Safety Population who complete at least 1 day of dosing of study drug and have at least one post-baseline efficacy evaluation, will be used to analyze efficacy data.</p> <p>....</p> <p>For Part B, the change from baseline in HAM-D total score will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, antidepressant use strata, assessment time point, and time point-by-treatment as explanatory variables. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 Oral Solution and matching placebo at the 15 day time point. Model-based point estimates (ie, least squares [LS] means), 95% confidence intervals, and p values will be reported. An unstructured covariance structure will be used to model the within-subject errors. Continuous variables will be analyzed using similar methods. Binary efficacy endpoints, including responder and remission endpoints, will be analyzed using logistic regression model.</p> <p>The PK Population will consist of all subjects in the Safety Population with sufficient plasma concentrations for PK evaluations, and will be used to summarize PK data.</p>	<p>...</p> <p>The Efficacy Set (for both Part A and Part B), defined as all subjects in the Safety Set who complete at least 1 day of dosing of study drug and have at least one post-baseline efficacy evaluation, will be used to analyze efficacy data.</p> <p>...</p> <p>For Part B, the change from baseline in HAM-D total score will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include center, treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. Center will be treated as random and all other explanatory variables as fixed effects. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 Capsules and matching placebo at the 15 day time point. Model-based point estimates (ie, least squares [LS] means), 95% confidence intervals, and p values will be reported. An unstructured covariance structure will be used to model the within-subject errors. Other continuous endpoints will be analyzed using similar methods. Binary efficacy endpoints, including responder and remission endpoints, will be analyzed using generalized estimating equation (GEE) models. The PK Set will consist of all subjects in the Safety Set with sufficient plasma concentrations for PK evaluations, and will be used to summarize PK data.</p>

Section Number and Title	Original Text:	Changed To:
Synopsis, Statistical Methods, Analysis Populations and Methods, Sample Size Calculation Section 14.8, Determination of Sample Size	For Part B, assuming a two-sided t-test at an alpha level of 0.10 , a sample size of 23 subjects per group would provide 80% power to detect an effect size of 0.75 between the SAGE-217 Oral Solution and matching placebo groups with regard to the secondary efficacy outcome variable of change from baseline in HAM-D total score. An effect size of 0.75 corresponds to a matching placebo-adjusted difference of 7.5 points in the change from baseline in HAM-D total score at 15 days with an assumed SD of 10 points. By including two treatment groups and using a 1:1 randomization, a total of 46 subjects are required. Assuming a non evaluability rate of 10%, up to 52 subjects will be randomized.	For Part B, assuming a two-sided t-test at an alpha level of 0.05 , a sample size of 29 subjects per group would provide 80% power to detect an effect size of 0.75 between the SAGE-217 Capsules and matching placebo groups with regard to the efficacy outcome variable of change from baseline in HAM-D total score. An effect size of 0.75 corresponds to a matching placebo-adjusted difference of 7.5 points in the change from baseline in HAM-D total score at 15 days with an assumed SD of 10 points. By including two treatment groups and using a 1:1 randomization, a total of 58 subjects are required. Assuming a non evaluability rate of 10%, up to 66 subjects will be randomized. Additional subjects may be enrolled if the drop-out rate is higher than 10%.
Table 3, Schedule of Events, Part B		<i>Day 35 and Day 42 follow-up visits added and footnotes were adjusted accordingly. Addition of Remission in Depression Questionnaire (RDQ) and Health-Related Productivity Questionnaire; adjust frequency of SF-36 and FAs-D. Edits to other footnotes as needed. (see Table for details)</i>
Section 7.1, Overall Study Design	This study is a two-part, multicenter, Phase 2a study to evaluate the safety, tolerability, PK, and efficacy of SAGE-217 Oral Solution in approximately 62 adult subjects with MDD. Part A of the study is an open-label design with SAGE-217 Oral Solution dosing for 14 days. Part B of the study is a randomized, double-blind, parallel-group, placebo-controlled design with SAGE-217 Oral Solution or	This study is a two-part, multicenter, Phase 2a study to evaluate the safety, tolerability, PK, and efficacy of SAGE-217 Oral Solution (Part A) and SAGE-217 Capsules (Part B) in approximately 76 adult subjects with MDD. Part A of the study is an open-label design with SAGE-217 Oral Solution dosing for 14 days. Part A will consist of an up to 7-day Screening Period (Days -7 to -1), a 14-day

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	<p>matching placebo dosing for 14 days. Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B.</p> <p>Parts A and B of the study will consist of an up to 7 day Screening Period (Days -7 to -1), a 14 day Treatment Period, and a 2-week Follow-up Period (through Day 28).</p> <p>...</p> <p>In Part A and Part B, study drug (SAGE-217 Oral Solution or matching placebo) will be administered at the study center for at least the first 7 days of the Treatment Period, which includes Day 1 of study drug administration through completion of study drug administration on Day 14. ... For the outpatient phase, dosing will be done at the clinical site or, if suitable arrangements can be made, via home administration where local regulations allow.</p> <p>...</p> <p>Subjects will be monitored for safety during the Treatment and Follow-up Periods including monitoring for adverse events/serious adverse events, routine clinical laboratory assessments, physical examination, vital signs, and ECG.</p> <p>...</p> <p>Subjects who experience moderate or severe related adverse events while receiving the 20 mg dose of study drug may not be able to continue receiving study drug based on the evaluation and clinical judgment of the Investigator, and may be terminated</p>	<p>Treatment Period, and a 2-week Follow-up Period.</p> <p>Part B of the study is a randomized, double-blind, parallel-group, placebo-controlled design with SAGE-217 Capsule or matching placebo dosing for 14 days.</p> <p>Part B will consist of an up to 7-day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 4-week Follow-up Period. Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B.</p> <p>...</p> <p>In Part A and Part B, study drug (SAGE-217 Oral Solution in Part A; SAGE-217 Capsule or matching placebo in Part B) will be administered at the study center for at least the first 7 days of the Treatment Period, which includes Day 1 of study drug administration through completion of study drug administration on Day 14. ... For the outpatient phase, dosing will be done at the clinical site or, if suitable arrangements can be made, via home administration where local regulations allow. All dosing will be observed, either in the clinical unit or by a healthcare professional at home.</p> <p>...</p> <p>Subjects will be monitored for safety during the Treatment and Follow-up Periods including monitoring for adverse events/serious adverse events, routine clinical laboratory assessments, physical examination, vital signs, and ECG (only Day 15 during Follow-up).</p>

Section Number and Title	Original Text:	Changed To:
	<p>from the study.</p>	<p>...</p> <p>Subjects who experience intolerable AEs at the 20-mg dose level may be terminated from the study at the discretion of the Investigator.</p> <p>...</p> <p>Follow-up visits will be conducted on an outpatient basis. Follow-up visits will be conducted weekly for 2 weeks after completion of the Treatment Period in Part A (Day 28 ±1 day) and weekly for 4 weeks after completion of the Treatment Period in Part B (Day 42 ±1 day).</p>
Section 7.2, Blinding and Randomization	<p>Subjects who meet the entrance criteria will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥30 days) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 Oral Solution or taste- matched placebo according to a computer-generated randomization schedule.</p> <p>...</p> <p>The randomization schedule will be generated using SAS V9.2 or later. Only the clinic pharmacist or designated pharmacy staff, who is responsible for preparing the solutions, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual solution contents to the Investigator, who should also alert Sage of the emergency (see Section 13.6 for more details related to unblinding).</p>	<p>Subjects who meet the entrance criteria will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥30 days) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 Capsules or matched placebo according to a computer-generated randomization schedule.</p> <p>...</p> <p>The randomization schedule will be generated using SAS V9.2 or later. Only the clinic pharmacist or designated pharmacy staff, who is responsible for preparing the study drug, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual study drug contents to the Investigator, who should also alert Sage of the emergency (see Section 13.6 for more details related to unblinding).</p>
Section 8.3.1, Study Drug Withdrawal	Subjects who withdraw or are withdrawn from the study will be replaced only if they withdraw prior to	Subjects who withdraw or are withdrawn from the study will be replaced only if they withdraw prior to

Section Number and Title	Original Text:	Changed To:
	dosing. Subjects who are withdrawn from the study, fail to return or are no longer qualified will not be replaced.	dosing. Subjects who are withdrawn from the study, fail to return or are no longer qualified will not be replaced. Additional subjects may be enrolled if the drop-out rate is higher than 10%.
Section 9.2.1, Part A	Subjects participating in Part A of the study will take study drug (SAGE-217) in an open-label manner.	Subjects participating in Part A of the study will take study drug (SAGE-217 Oral Solution) in an open-label manner.
Section 9.2.2, Part B	Subjects, clinicians, and study team will be blinded to treatment allocation. The pharmacist, who will prepare the oral solutions according to the randomization schedule, and an unblinded Monitor, who will perform drug accountability during the study, will be unblinded.	Subjects, clinicians, and study team will be blinded to treatment allocation. The pharmacist, who will prepare the study drug according to the randomization schedule, and a Monitor, who will perform drug accountability during the study, will be unblinded.
Section 9.3, Dose Adjustment Criteria	In both Part A and Part B, subjects who experience moderate or severe adverse events that according to the clinical judgement of the Investigator are related to study drug while receiving the 30 mg dose of study drug will receive 20 mg for the remaining of the Treatment Period. ... Enrollment into Part A may be stopped and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed. The study may be terminated if there is clear lack of activity based on HAM-D scores during Part A. A Data Review Team will assess the HAM-D and other data on an ongoing basis during Part A.	In Part A, subjects who experience moderate or severe adverse events that according to the clinical judgement of the Investigator are related to study drug while receiving the 30 mg dose of study drug will receive 20 mg for the remaining of the Treatment Period. ... In Part B, subjects who cannot tolerate 30 mg will receive 20 mg for the rest of the Treatment Period. Subjects who experience intolerable AEs at the 20 mg dose level may be terminated from the study at the discretion of the Investigator.
Section 9.4.1, Prior/Concomitant	Subjects will receive standard of care for adult patients diagnosed with moderate to severe MDD.	Subjects will receive standard of care for adult patients diagnosed with moderate to severe MDD.

Section Number and Title	Original Text:	Changed To:
Medications	<p>Psychotropic medications, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the Day 15 assessments (Parts A and B).</p> <p>Eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 Oral Solution or taste-matched placebo.</p> <p>In this study, psychotropic medications refer to central nervous system active medications taken to help depressive symptoms, and include antidepressants, benzodiazepines, and hypnotic agents. Subjects presenting to the study on antidepressants may be eligible to participate if they have been on a stable dose for at least 14 days. Those subjects on benzodiazepines and hypnotic agents may be considered for eligibility based on specific discussions between the Investigator and the Sponsor to ensure safety. Subjects on other psychotropic medications, including stimulants, antipsychotics, and mood stabilizers, are not eligible to participate in this study.</p> <p>...</p> <p>In both Part A and Part B, all medications should be documented throughout the study from 30 days prior to signing the ICF through Day 28 (± 3 days) and recorded on the eCRF.</p>	<p>Psychotropic medications, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the Day 15 assessments (Part A).</p> <p>Eligible subjects in Part B will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 Capsules or matched placebo.</p> <p>In this study, psychotropic medications refer to central nervous system active medications taken to help depressive symptoms, and include antidepressants, benzodiazepines, and hypnotic agents. Subjects presenting to the study on psychotropic medications may be eligible to participate if they have been on a stable dose for at least 14 days (Part A) or if the medications have been initiated at least 30 days prior to screening (Part B); the subject must remain at a stable dose until completion of the Day 15 assessments (Part B). Those subjects on benzodiazepines and hypnotic agents may be considered for eligibility based on specific discussions between the Investigator and the Sponsor to ensure safety. Subjects on other psychotropic medications, including stimulants, and mood stabilizers, are not eligible to participate in this study. Subjects who have been receiving atypical antipsychotics with the intent of treatment of depressive symptoms, but not psychotic symptoms, may be eligible.</p>

Section Number and Title	Original Text:	Changed To:
		<p>...</p> <p>In both Part A and Part B, all medications should be documented throughout the study from 30 days prior to signing the ICF through Day 28/42 (± 3 days) and recorded on the eCRF.</p>
Section 9.4.2, Restricted Medications	<ul style="list-style-type: none"> •Initiation of new antidepressant therapy is prohibited upon admission to the study center for those eligible subjects who desire study participation. Those subjects already taking an antidepressant at the time of study entry (and meeting all study inclusion criteria) will be permitted to remain on the pre-existing antidepressant at their current dose if they were on this medication for at least 14 days prior to study enrollment. •Benzodiazepines are to be avoided as much as possible. Eligible subjects taking a stable dose of benzodiazepine for at least 14 days prior to the study will be discussed on a case-by-case basis with the Sponsor to determine eligibility. Subjects may be permitted to continue to take their current dose of the benzodiazepine (to prevent acute withdrawal), but no new benzodiazepine use will be permitted during the course of the study. ... •Anticonvulsants and atypical antipsychotics are prohibited. 	<ul style="list-style-type: none"> •Initiation of new antidepressant therapy is prohibited upon admission to the study center for those eligible subjects who desire study participation. Those subjects already taking an antidepressant at the time of study entry (and meeting all study inclusion criteria) will be permitted to remain on the pre-existing antidepressant at their current dose if they were on this medication for at least 30 days prior to study enrollment (Part B). •Benzodiazepines are to be avoided as much as possible. Eligible subjects taking a stable dose of benzodiazepine for at least 30 days prior to enrollment in Part B will be discussed on a case-by-case basis with the Sponsor to determine eligibility. Subjects may be permitted to continue to take their current dose of the benzodiazepine (to prevent acute withdrawal), but no new benzodiazepine use will be permitted during the course of the study. ... •Anticonvulsants are prohibited. Atypical antipsychotics are allowed only if the indication has been for the treatment of the depressive episode and not for treatment of psychotic symptoms.
Section 11.1, Hamilton	The HAM-D assessments are to be completed at	The HAM-D assessments are to be completed at 8:00

Section Number and Title	Original Text:	Changed To:
Rating Scale for Depression (HAM-D)	<p>8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.</p> <p>...</p> <p>The HAM-D total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (ie, "Not assessed").</p>	<p>AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15, Day 21, and Day 28 for Part A and Day 15, Day 21, Day 28, Day 35, and Day 42 in Part B).</p> <p>...</p> <p>The HAM-D total score will be calculated as the sum of the 17 individual item scores.</p>
Section 11.2, Montgomery-Åsberg Depression Rating Scale (MADRS)	<p>The MADRS assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.</p>	<p>The MADRS assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15, Day 21, and Day 28 for Part A and Day 15, Day 21, Day 28, Day 35, and Day 42 in Part B).</p>
Section 11.3, Hamilton Anxiety Rating Scale (HAM-A)	<p>The HAM-A assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.</p>	<p>The HAM-A assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15, Day 21, and Day 28 for Part A and Day 15, Day 21, Day 28, Day 35, and Day 42 in Part B).</p>
Section 11.4, Clinical Global Impression (CGI)	<p>The CGI-S assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.</p> <p>...</p> <p>The CGI-I assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the</p>	<p>The CGI-S assessments are to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15, Day 21, and Day 28 for Part A and Day 15, Day 21, Day 28, Day 35, and Day 42 in Part B).</p> <p>...</p> <p>The CGI-I assessments are to be completed at</p>

Section Number and Title	Original Text:	Changed To:
	morning on Day 15, Day 21, and Day 28.	8:00 AM (\pm 30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15, Day 21, and Day 28 for Part A and Day 15, Day 21, Day 28, Day 35, and Day 42 in Part B).

Section Number and Title	Original Text:	Changed To:
Section 11.5, Short Form-36 (SF-36)	<p>The SF-36® Health Survey is a subject-reported 36-item instrument for measuring functional health and well-being in eight dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) (Ware 2007). Scores are provided for each of the eight dimensions and are totaled into a Physical Component Summary and a Mental Component Summary. Higher SF-36 scores indicate a better state of health. The SF-36 requires approximately 10 minutes to complete, and can be self-administered or completed by interview in person or by telephone. In Part B, the SF-36 assessments are to be completed at 8:00 AM (±30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.</p>	<p>The Medical Outcomes Study Short Form-36 (SF-36v2) is a 36-item measure of health status that has undergone validation in many different disease states (Ware 2007). The SF-36 covers eight health dimensions including four physical health status domains (physical functioning, role participation with physical health problems [role-physical], bodily pain, and general health) and four mental health status domains (vitality, social functioning, role participation with emotional health problems [role-emotional], and mental health). In addition, two summary scores, physical component summary (PCS) and mental component summary (MCS), are produced by taking a weighted linear combination of the eight individual domains. The SF-36v2 is available with two recall periods: the standard recall period is 4 weeks and the acute recall period is 1 week. This study will use the acute version, which asks patients to respond to questions as they pertain to the past week. Higher SF-36 scores indicate a better state of health. The SF-36 requires approximately 10 minutes to complete, and can be self-administered or completed by interview in person or by telephone. In Part B, the SF-36 assessments are to be completed at 8:00 AM (±30 minutes) at each scheduled time point during the Treatment Period, and in the morning during the Follow-up Period (Day 15 and Day 42).</p>
Section 11.6, The Fatigue Associated	In Part B, the FAs-D assessments are to be completed at 8:00 AM (±30 minutes) at each	In Part B, the FAs-D assessments are to be completed at 8:00 AM (±30 minutes) at each scheduled time

Section Number and Title	Original Text:	Changed To:
with Depression (FAs D) Patient-Reported Outcome (PRO)	scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28.	point during the Treatment Period, and in the morning during the Follow-up Period (Day 15 and Day 42).
Section 11.7, Remission in Depression Questionnaire (RDQ)	<i>NA – new section</i>	Recent research suggests that the symptom-based definitions of remission used in efficacy studies do not adequately reflect the perspective of depressed patients receiving treatment in routine clinical settings. The Remission from Depression Questionnaire (RDQ) was developed to capture the broader array of domains considered by patients to be relevant to the construct of remission symptoms of depression, non-depressive symptoms, features of positive mental health, coping ability, functioning, life satisfaction, and a general sense of well-being. The RDQ is a reliable and valid measure that evaluates the multiple domains that depressed patients consider important in determining remission. The RDQ demonstrated excellent internal consistency, with a Cronbach’s alpha of 0.97 for the total scale and above 0.80 for each of the seven subscales. The test-retest reliability of the total scale was 0.85 and above 0.60 for each subscale (Zimmerman 2013; Zimmerman 2014). In Part B, the RDQ is to be completed at 8:00 AM (±30 minutes) at each scheduled time point on Day 1, and in the morning during the Follow-up Period (Day 15 and Day 42). A copy of the RDQ is located in Appendix 9.
Section 11.8, Health-Related Productivity	<i>NA – new section</i>	The Health-Related Productivity Questionnaire (HRPQ) is a generic measure developed to

Section Number and Title	Original Text:	Changed To:
Questionnaire (HRPQ)		measure health-related work productivity in patients with a particular disease and/or being treated for the disease. The instrument collects productivity data in terms of absenteeism, presenteeism, and combined lost productivity for three work venues: work outside home, housework, and classes/homework (Kumar 2003). In Part B, the HRPQ is to be completed at 8:00 AM (±30 minutes) at each scheduled time point on Day 1, and in the morning during the Follow-up Period (Day 15 and Day 42). A copy of the HRPQ is located in Appendix 10.
Section 13.1.3, Weight and Height	Body weight and height will be measured at the Screening visit; weight will also be measured on in the morning on Day 15, and during the follow-up visits on Days 21 and 28.	Body weight and height will be measured at the Screening visit; weight will also be measured on in the morning on Day 15, and during the follow-up visits on Days 21 and 28 for Part A and Days 21, 28, 35, and 42 in Part B.
Section 13.1.4, Physical Examination	A physical examination of all major body systems will be undertaken and recorded at the Screening visit, Day 8, Day 15, and Day 21, with a brief physical examination on Day 28.	A physical examination of all major body systems will be undertaken and recorded at the Screening visit, Day 8, Day 15, and Day 21, with a brief physical examination on Day 28 in Part A; in Part B, a physical examination will be undertaken and recorded at the Screening visit, Day 8, and Day 15, with a brief physical examination on Day 42.
Section 13.1.6, Laboratory Assessments	Blood and urine samples will be collected for hematology, serum chemistry, coagulation, select hormone parameters, and urinalysis at the Screening visit, and in the morning on Days 8 and 15 and during the follow-up visits on Days 21 and 28.	Blood and urine samples will be collected for hematology, serum chemistry, coagulation, select hormone parameters, and urinalysis at the Screening visit, and in the morning on Days 8 and 15 and during the follow-up visits (Days 21 and 28 for Part A and

Section Number and Title	Original Text:	Changed To:
		Days 21, 28, 35, and 42 for Part B).
Section 13.1.6.3, Urinalysis	Urinalysis will include assessment of protein, blood, glucose, ketones, bile , urobilinogen, hemoglobin, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity.	Urinalysis will include assessment of protein, blood, glucose, ketones, bilirubin , urobilinogen, hemoglobin, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity.
Section 13.1.6.6, Pregnancy Test	Females of childbearing potential will be tested for pregnancy by serum pregnancy test at the Screening visit and by urine pregnancy test on Day 1 (predose) and at the follow-up visit on Day 28. In addition, female subjects who prematurely discontinue before Day 28 will have a pregnancy test performed at the early termination visit.	Females of childbearing potential will be tested for pregnancy by serum pregnancy test at the Screening visit and by urine pregnancy test on Day 1 (predose) and at the follow-up visit on Day 28 for Part A or Day 42 for Part B . In addition, female subjects who prematurely discontinue before Day 28/ 42 will have a pregnancy test performed at the early termination visit.
Section 13.1.6.8, Drugs of Abuse and Alcohol	A urine sample for assessment of selected drugs of abuse (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene) and a serum or breath sample for alcohol screen will be collected at screening and predose on Day 1. Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics that have been initiated at least 14 days prior to admission to the study center at a stable dose following discussion with the Sponsor (see Section 9.3).	Part A: A urine sample for assessment of selected drugs of abuse (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene) and a serum or breath sample for alcohol screen will be collected at screening and predose on Day 1. Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics that have been initiated at least 14 days prior to admission to the study center at a stable dose following discussion with the Sponsor (see Section 9.3). Part B: A urine and/or serum sample (as per the lab manual) for assessment of selected drugs of abuse (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene) will be collected

Section Number and Title	Original Text:	Changed To:
		at screening; a urine sample will be collected for assessment of drugs of abuse predose on Day 1. A serum or breath sample for alcohol screen (as per the standard procedures at each site) will be collected at screening and predose on Day 1. Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics that have been initiated at least 30 days prior to admission to the study center at a stable dose following discussion with the Sponsor (see Section 9.3).
Section 13.4, Recording Adverse Events	All adverse events will be followed until they are resolved or have reached a clinical plateau with no expectation of future change.	All adverse events, regardless of Investigator-determined causality, should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant.
Section 13.5, Reporting Adverse Events	All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day 28 follow-up visit.	All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day 28 follow-up visit (Part A) or the Day 42 follow-up visit (Part B).
Section 13.6, Emergency Identification of Study Drug	The pharmacist responsible for preparing the solutions will be unblinded and will retain an official paper copy of the randomization schedule.	The pharmacist and/or designated pharmacy staff responsible for preparing the study drug will be unblinded and will retain an official paper copy of the randomization schedule.
Section 13.7, Pregnancy	<i>NA – new section</i>	In the event either the subject or their partner becomes pregnant, the pregnancy will be followed. By enrolling in this study, all subjects are consenting to pregnancies being followed to conclusion either by the site if the study is still active or through Sage standard pharmacovigilance services if the study is no

Section Number and Title	Original Text:	Changed To:
		longer active.
Section 14.1, Data Analysis Sets and Methods	<p>14.1.1. Analysis Populations and Methods</p> <p>The Safety Population (for both Part A and Part B), defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data.</p> <p>The Efficacy Population (for both Part A and Part B), defined as all subjects in the Safety Population who complete at least 1 day of dosing of study drug and have at least one post-baseline efficacy evaluation, will be used to analyze efficacy data.</p> <p>The PK Population will consist of all subjects in the Safety Population with sufficient plasma concentrations for PK evaluations, and will be used to summarize PK data.</p>	<p>14.1.1. Data Analysis Sets</p> <p>The Safety Set (for both Part A and Part B), defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data.</p> <p>The Efficacy Set (for both Part A and Part B), defined as all subjects in the Safety Set who complete at least 1 day of dosing of study drug and have at least one post-baseline efficacy evaluation, will be used to analyze efficacy data.</p> <p>The PK Set will consist of all subjects in the Safety Set with sufficient plasma concentrations for PK evaluations, and will be used to summarize PK data.</p>
Section 14.5, Efficacy Analyses	<p>The main comparison will be between SAGE-217 Oral Solution and matching placebo at the 15-day time point.</p> <p>...</p> <p>Logistic regression methods will be used for the analysis of the following binary variables: HAM-D response (defined as $\geq 50\%$ reduction from baseline in HAM-D total score), HAM-D remission (defined as HAM-D total score of ≤ 7.0), and CGI-I response. Logistic regression models will include terms for center, treatment, antidepressant use strata, and baseline score. The comparison of interest will be the difference between SAGE-217 Oral Solution and matching placebo at the 15-day time point in Part B. Model based point estimates (ie, odds</p>	<p>The main comparison will be between SAGE-217 Capsules and matching placebo at the 15-day time point.</p> <p>Generalized estimating equation (GEE) methods will be used for the analysis of the following binary variables: HAM-D response (defined as $\geq 50\%$ reduction from baseline in HAM-D total score), HAM-D remission (defined as HAM-D total score of ≤ 7.0), and CGI-I response. GEE models will include terms for center, treatment, baseline score, antidepressant use strata, assessment time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 Capsule and matching placebo at the 15-day time point in Part B. Model based point</p>

Section Number and Title	Original Text:	Changed To:
	<p>ratios), 95% confidence intervals, and p-values will be reported. For the CGI-I response analysis, baseline CGI-S score will be included in the model.</p> <p>...</p> <p>Similar to the main comparison of HAM-D total score in Part B, descriptive summary statistics will be provided and an MMRM model will be used to analyze the change from baseline in SF 36 and FAs-D.</p>	<p>estimates (ie, odds ratios), 95% confidence intervals, and p-values will be reported. For the CGI-I response analysis, baseline CGI-S score will be included in the model.</p> <p>...</p> <p>Descriptive summary statistics will be for SF 36, FAs-D, RDQ, and HRPQ.</p>
Section 14.6.1, Adverse Events	<p>Incidences will be presented in order of decreasing frequency for the SAGE-217 Oral Solution treatment group. In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 13.3).</p> <p>...</p> <p>All adverse events and serious adverse events (including those with onset or worsening before the start of study drug) through the Day 28 follow-up visit will be listed.</p>	<p>Incidences will be presented in order of decreasing frequency for the SAGE-217 treatment group (Oral Solution for Part A and Capsules for Part B). In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 13.3).</p> <p>...</p> <p>All adverse events and serious adverse events (including those with onset or worsening before the start of study drug) through the Day 28 follow-up visit (Part A) or Day 42 follow-up visit (Part B) will be listed.</p>
Section 14.6.3, Physical Examinations	<p>Physical examinations in Parts A and B will be summarized at the Screening visit, Day 8, Day 15, Day 21, and Day 28 visits. Any clinically significant change in physical examination compared to those observed at screening should be noted as an adverse event.</p>	<p>Any clinically significant change in physical examination compared to those observed at screening should be noted as an adverse event.</p>
Section 14.6.6, Prior and Concomitant Medications	<p>Prior medications are defined as those taken during the 30 days prior to informed consent.</p>	<p>Prior medications are defined as those taken prior to the first dose of study drug.</p>

Section Number and Title	Original Text:	Changed To:
Section 14.7, Pharmacokinetic Analyses	Pharmacokinetic parameters will be summarized using appropriate descriptive statistics.	Pharmacokinetic parameters will be summarized using appropriate descriptive statistics. The PK parameters to be summarized where possible will include AUC_{∞}, C_{max}, t_{max}, $t_{1/2}$, and C_{ss}.

**Summary of Changes to
Protocol 217-MDD-201, Amendment #3
Date of Amendment: 06 June 2017**

The following changes were made in Protocol 217-MDD-201 v4.0, Amendment #3. In addition, minor editorial revisions (eg, formatting, punctuation) that are not listed below may have been made throughout the protocol.

Section Number and Title	Original Text:	Changed To:
Document Header	Version 3.0	Amendment 3 Version 3 4.0 CONFIDENTIAL
Title Page		Date of Amendment Three Version 4.0, 06 June 2017
Protocol Signature Page	Date of Amendment Two: Version 3.0 09 March 2017	Date of Amendment Two Three: Version 3 4.0 09 March 06 June 2017
2. Synopsis, Methodology	<ul style="list-style-type: none"> Part B: Randomized, double-blind, parallel-group, placebo-controlled (14 days). Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomized within each stratum in a 1:1 ratio to receive SAGE 217 Capsules (30 mg) or matching placebo for 14 days beginning on Day 1, as tolerated. All doses of study drug will be administered at 8:00 PM (± 15 minutes) with food. Part B will consist of an up to 7-day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 4-week Follow-up Period. 	<ul style="list-style-type: none"> Part B: Randomized, double-blind, parallel-group, placebo-controlled (14 days). Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomized within each stratum in a 1:1 ratio to receive SAGE 217 Capsules (30 mg) or matching placebo for 14 days beginning on Day 1, as tolerated. All doses of study drug will be administered at 8:00 PM (± 15 minutes) with food. Part B will consist of an up to 714-day Screening Period (Days -714 to -1), a 14-day Treatment Period, and a 4-week Follow-up Period.
2. Synopsis,	<u>Screening Period</u> : The Screening Period begins with	<u>Screening Period</u> : The Screening Period begins with

Section Number and Title	Original Text:	Changed To:
Methodology (Screening Period)	the signing of the informed consent form (ICF) at the Screening Visit, which can occur on any two consecutive calendar days of the 7-day window (from Day -7 through Day -1). The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Axis I Disorders (SCID I) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the HAM-D, Hamilton Anxiety Rating Scale (HAM-A), Clinical Global Impression - Severity (CGI S), and Montgomery-Åsberg Depression Rating Scale (MADRS). The Screening Period assessments will be conducted on an outpatient basis.	the signing of the informed consent form (ICF) at the Screening Visit, which can occur on any two consecutive calendar days of the 7-day (Part A) or 14-day (Part B) window (from Day -7 or -14, respectively , through Day -1). The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Axis I Disorders (SCID I) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the HAM-D, Hamilton Anxiety Rating Scale (HAM-A), Clinical Global Impression - Severity (CGI S), and Montgomery-Åsberg Depression Rating Scale (MADRS). The Screening Period assessments will be conducted on an outpatient basis.
2. Synopsis, Methodology (Follow-up Period); 7.1. Overall Study Design	Follow-up visits will be conducted on an outpatient basis. Follow-up visits will be conducted weekly for 2 weeks after completion of the Treatment Period in Part A (Day 28 ±1 day) and weekly for 4 weeks after completion of the Treatment Period in Part B (Day 42 ±1 day).	Follow-up visits will be conducted on an outpatient basis. Follow-up visits will be conducted weekly for 2 weeks after completion of the Treatment Period in Part A (Day 28 ±1 day) and weekly for 4 weeks after completion of the Treatment Period in Part B (Day 42 ±1 day 3 days).
2. Synopsis, Objectives; 6.2.1 Primary Objective	The primary objective of Part B is to evaluate the safety and tolerability of SAGE-217 Capsule (30 mg).	The primary objective of Part B is to evaluate the safety and tolerability of SAGE-217 Capsule (30 mg). The primary efficacy objective for Part B of the study is to determine if treatment with SAGE-217 Capsules (30 mg) reduces depressive symptoms in

Section Number and Title	Original Text:	Changed To:
		subjects with moderate to severe MDD compared to matching placebo.
2. Synopsis, Objectives; 6.2.2. Secondary Objective	The secondary efficacy objective for Part B of the study is to determine if treatment with SAGE-217 Capsules (30 mg) reduces depressive symptoms in subjects with moderate to severe MDD compared to matching placebo.	The secondary efficacy objective for Part B of the study is to determine if treatment with SAGE-217 Capsules (30 mg) reduces depressive symptoms in subjects with moderate to severe MDD compared to matching placebo. The secondary objective of Part B is to evaluate the safety and tolerability of SAGE-217 Capsule (30 mg).
2. Synopsis, Endpoints; 6.3.2.1. Primary	The primary endpoint for Part B is the safety and tolerability of SAGE-217 Capsules as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS.	The primary endpoint for Part B is the safety and tolerability of SAGE-217 Capsules as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS. reduction in depressive symptoms, compared to placebo, as assessed by the change in the 17-item HAM-D total score from baseline to Day 15.
2. Synopsis, Endpoints; 6.3.2.2. Secondary	Reduction in depressive symptoms, compared to placebo, as assessed by the following: <ul style="list-style-type: none"> • Change from baseline in the 17-item HAM-D total score at all time points; • HAM-D response; • HAM-D remission; • Change from baseline in the MADRS total score at Day 15 (ET) and all other time points; • Change from baseline in HAM-D subscale 	<ul style="list-style-type: none"> • Reduction in depressive symptoms, compared to placebo, as assessed by the following: <ul style="list-style-type: none"> • Change from baseline in the 17-item HAM-D total score from baseline at all time points; • HAM-D response; • HAM-D remission; • Change from baseline in the MADRS total score at Day 15 (ET) and all other time points; • Change from baseline in HAM-D subscale

Section Number and Title	Original Text:	Changed To:
	<p>and individual item scores at all time points;</p> <ul style="list-style-type: none"> • Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at Day 15 (ET) and all other time points; and • CGI I response. 	<p>and individual item scores at all time points;</p> <ul style="list-style-type: none"> • Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at Day 15 (ET) and all other time points; and • CGI I response. • The safety and tolerability of SAGE-217 Capsules as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS.
2. Synopsis, Inclusion Criteria, Section 8.1 Subject Inclusion Criteria	<p>9. Subject agrees to practice an acceptable method of highly effective birth control at screening and throughout study participation. Highly effective methods of birth control include sexual abstinence (for males and females); vasectomy; or a condom with spermicide in combination with a highly effective female partner's method (for males); and hormonal methods of contraception (ie, established use of oral, implantable, injectable, or transdermal hormones); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream, or suppository]) (for females).</p>	<p>12. Part A: Subject agrees to practice an acceptable method of highly effective birth control at screening and throughout study participation. Highly effective methods of birth control include sexual abstinence (for males and females); vasectomy; or a condom with spermicide in combination with a highly effective female partner's method (for males); and hormonal methods of contraception (ie, established use of oral, implantable, injectable, or transdermal hormones); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream, or suppository]) (for females).</p> <p>Part B: Female subject agrees to use one of the following methods of contraception during</p>

Section Number and Title	Original Text:	Changed To:				
		<p>participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause) and/or surgically sterile:</p> <ul style="list-style-type: none">• 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 occlusion.• Vasectomized partner.• Sexual abstinence (no sexual intercourse).				
2. Synopsis, Exclusion Criteria, Section 8.2 Subject Exclusion Criteria	6. Subject has no detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV) antibody at screening.	11. Subject has no detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV) antibody at screening (except if the subject has a documented Hepatitis C antigen test (HCV RNA) with a negative result in their recent medical history).				
2. Synopsis, Duration of participation	<u>Part B</u> : Up to 52 days (up to 7 days for screening; 14 days of treatment; 28-31 days for follow up)	<u>Part B</u> : Up to 52 29 days (up to 7 14 days for screening; 14 days of treatment; 28-31 days for follow up)				
Table 3: Schedule of Events (Part B)	<table><tr><td></td><td>Screening Period</td></tr></table>		Screening Period	<table><tr><td></td><td>Screening Period</td></tr></table>		Screening Period
	Screening Period					
	Screening Period					

Section Number and Title	Original Text:		Changed To:	
	Visits	OUTPATIENT	Visits	OUTPATIENT
	Visit Days	D-7 to -1	Visit Days	D- 7 14 to -1
7.1. Overall Study Design	<p>This study is a two-part, multicenter, Phase 2a study to evaluate the safety, tolerability, PK, and efficacy of SAGE-217 Oral Solution (Part A) and SAGE-217 Capsules (Part B) in approximately 76 adult subjects with MDD. Part A of the study is an open-label design with SAGE-217 Oral Solution dosing for 14 days. Part A will consist of an up to 7 day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 2-week Follow-up Period. Part B of the study is a randomized, double-blind, parallel-group, placebo-controlled design with SAGE-217 Capsule or matching placebo dosing for 14 days. Part B will consist of an up to 7-day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 4-week Follow-up Period. Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B.</p> <p>During the Screening Period (Day -7 to Day -1), after signing the informed consent form (ICF), subjects will be assessed for study eligibility, and the severity of each subject’s MDD will be evaluated using HAM-D. The Screening Period assessments will be conducted on an outpatient basis.</p>		<p>This study is a two-part, multicenter, Phase 2a study to evaluate the safety, tolerability, PK, and efficacy of SAGE-217 Oral Solution (Part A) and SAGE-217 Capsules (Part B) in approximately 76 adult subjects with MDD. Part A of the study is an open-label design with SAGE-217 Oral Solution dosing for 14 days. Part A will consist of an up to 7 day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 2-week Follow-up Period. Part B of the study is a randomized, double-blind, parallel-group, placebo-controlled design with SAGE-217 Capsule or matching placebo dosing for 14 days. Part B will consist of an up to 714-day Screening Period (Days -714 to -1), a 14-day Treatment Period, and a 4-week Follow-up Period. Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B.</p> <p>During the Screening Period (Day -7 to Day -1), after signing the informed consent form (ICF), subjects will be assessed for study eligibility, and the severity of each subject’s MDD will be evaluated using HAM-D. The Screening Period assessments will be conducted on an outpatient basis.</p>	
13.1.6. Laboratory	All required samples in Part A will be analyzed at		All required samples in Part A will be analyzed at	

Section Number and Title	Original Text:	Changed To:
Assessments	local laboratories. All samples in Part B will be analyzed at the central laboratory. Subjects may be considered eligible for the study based on local laboratory results; however, screening samples in Part B must also be sent to the central laboratory.	local laboratories. All samples in Part B will be analyzed at the central laboratory. Subjects may be considered eligible for the study based on local laboratory results; however, screening samples in Part B must also be sent to the central laboratory. Both local and central screening labs must adhere to the visit window provided in the Schedule of Events.

**Summary of Changes to
Protocol 217-MDD-201, Amendment #4
Date of Amendment: 12 July 2017**

The following changes were made in Protocol 217-MDD-201 v5.0, Amendment #4. In addition, minor editorial revisions (eg, formatting, punctuation) that are not listed below may have been made throughout the protocol.

Section Number and Title	Original Text:	Changed To:
Document Header	Amendment 3 Version 4.0	Amendment 34 Version 45.0
Title Page		Date of Amendment Four Version 5.0, 12 July 2017
Protocol Signature Page	Date of Amendment Three: Version 4.0 06 June 2017	Date of Amendment Three Four : Version 45.0 06 June 12 July 2017
2. Synopsis, Number of subjects (planned)	Approximately ten subjects will be enrolled in Part A. Up to 66 subjects may be randomized in Part B.	Approximately ten subjects will be enrolled in Part A. Up to 66 Approximately 88 subjects may be randomized in Part B.
2. Synopsis, Sample Size Calculation; 14.8. Determination of Sample Size	For Part B, assuming a two-sided t-test at an alpha level of 0.05, a sample size of 29 subjects per group would provide 80% power to detect an effect size of 0.75 between the SAGE-217 Capsules and matching placebo groups with regard to the efficacy outcome variable of change from baseline in HAM-D total score. An effect size of 0.75 corresponds to a matching placebo-adjusted difference of 7.5 points in the change from baseline in HAM-D total score at 15 days with an assumed SD of 10 points. By including two treatment groups and using a 1:1 randomization,	For Part B, assuming a two-sided t-test at an alpha level of 0.05, a sample size of 29 40 subjects per group would provide 80 90 % power to detect an effect size of 0.75 between the SAGE-217 Capsules and matching placebo groups with regard to the efficacy outcome variable of change from baseline in HAM-D total score. An effect size of 0.75 corresponds to a matching placebo-adjusted difference of 7.5 points in the change from baseline in HAM-D total score at 15 days with an assumed SD of 10 points. By including two treatment groups and using a 1:1 randomization, a

Section Number and Title	Original Text:	Changed To:
	a total of 58 subjects are required. Assuming a non-evaluability rate of 10%, up to 66 subjects will be randomized. Additional subjects may be enrolled if the drop-out rate is higher than 10%.	total of 58 80 subjects are required. Assuming a non-evaluability rate of 10%, up to 66 approximately 88 subjects will be randomized. Additional subjects may be enrolled if the drop-out rate is higher than 10%.
9.1. Number of Subjects	Approximately ten subjects with MDD will be enrolled into Part A of the study. Up to 66 subjects may be randomized in Part B to ensure at least 58 evaluable subjects for Part B. Evaluable subjects are defined as those subjects receiving study drug with at least one post-baseline HAM-D assessment. Additional subjects may be enrolled if the drop-out rate is higher than 10%.	Approximately ten subjects with MDD will be enrolled into Part A of the study. Up to 66 Approximately 88 subjects may be randomized in Part B to ensure at least 58 80 evaluable subjects for Part B. Evaluable subjects are defined as those subjects receiving study drug with at least one post-baseline HAM-D assessment. Additional subjects may be enrolled if the drop-out rate is higher than 10%.

SAGE THERAPEUTICS, INC.

Statistical Analysis Plan

Methods

Protocol Number SAGE-217-MDD-201

**A Phase 2, Two-Part (Open-Label Followed by Double-Blind) Study
Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of
SAGE-217 in the Treatment of Adult Subjects With Moderate to Severe
Major Depressive Disorder**

Author of SAP: Kelley Wekheye

Version: Version 1.0

Version Date of SAP: 03 FEB 2017

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Authorization Signature Page

A Phase 2, Two-Part (Open-Label Followed by Double-Blind) Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Adult Subjects With Moderate to Severe Major Depressive Disorder

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Date

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2 LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
AUC _∞	area under the concentration-time curve from time zero to infinity
BMI	body mass index
bpm	beats per minute
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
C _{max}	maximum (peak) plasma concentration
CS	clinically significant
C _{ss}	steady-state drug concentration in the plasma during oral intake
C _{avg,ss}	steady-state drug concentration in the plasma
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
FAs-D	fatigue associated with depression
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	17-item Hamilton Rating Scale for Depression
HIV	human immunodeficiency virus
ICF	informed consent form
Kg	kilogram
m	meter
MADRS	Montgomery-Åsberg Depression Rating Scale
Max	maximum
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
mmHg	millimeter of mercury
MMRM	mixed effects model for reported measures
msec	millisecond
n	number
PK	pharmacokinetic(s)
PRO	patient reported outcome
PT	preferred term
SAP	statistical analysis plan
SCID-I	Structured Clinical Interview for DSM-5 Axis I Disorders
SD	standard deviation
SF-36	36-item short form survey
SI	International System of Units
SOC	system organ class
ss	steady state
SSS	Stanford Sleepiness Scale

TEAE	treatment-emergent adverse event
$t_{1/2}$	Elimination half-life
t_{max}	time at maximum (peak) plasma concentration
WHO	World Health Organization
WHO-DD	World Health Organization-Drug Dictionary

3 INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis and is based on the approved clinical study protocol, dated 13 Jan 2017, version 2.0.

The purpose of the SAP is to describe in detail about the statistical methodology and the statistical analyses to be conducted for the above mentioned protocol. The SAP will be approved and finalized before Part A database lock.

All analyses and summary outputs will be generated using SAS® version 9.3 (or higher).

4 STUDY OBJECTIVES

4.1 Part A

4.1.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg.

4.1.2 Secondary Objective

The secondary objective is to determine if treatment with SAGE-217 Oral Solution 30 mg for 14 days reduces depressive symptoms.

4.2 Part B

4.2.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg.

4.2.2 Secondary Objective

The secondary efficacy objective for Part B of the study is to determine if treatment with SAGE-217 Oral Solution 30 mg reduces depressive symptoms in subjects with moderate to severe major depressive disorder (MDD) compared to matching placebo.

4.3 Pharmacokinetic Objective

The Pharmacokinetic (PK) objective is to assess the PK profile of SAGE-217 Oral Solution in plasma samples.

5 STUDY ENDPOINTS

5.1 Part A

5.1.1 Primary

The primary endpoint is the safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); Stanford Sleepiness Scale (SSS) score; physical examination; and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).

5.1.2 Secondary

Reduction in depressive symptoms as assessed by the following:

- Change from baseline in Hamilton Rating Scale for Depression (HAM-D) total score at all time points;
- HAM-D response (defined as having a 50% or greater reduction from baseline in HAM-D total score);
- HAM-D remission (defined as having a HAM-D total score of ≤ 7);
- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at all time points;
- Change from baseline in HAM-D subscale and individual item scores at all time points;
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at all time points; and
- Clinical Global Impression – Improvement (CGI-I) response (defined as a CGI-I score of “very much improved” or “much improved”).

5.2 Part B

5.2.1 Primary

The primary endpoint is the safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS.

5.2.2 Secondary

Reduction in depressive symptoms, compared to placebo, as assessed by the following:

- Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at all time points;
- HAM-D response;
- HAM-D remission;
- Change from baseline in the MADRS total score at all time points;
- Change from baseline in HAM-D subscale and individual item scores at all time points;
- Change from baseline in HAM-A total score at all time points;
- CGI-I response; and
- 36-item short form survey (SF-36) and fatigue associated with depression (FAs-D) patient-reported outcome.

5.3 Other Endpoints

Not applicable.

6 STUDY DESIGN

6.1 Overall Design

This study is a two-part, multicenter, Phase 2a study to evaluate the safety, tolerability, PK, and efficacy of SAGE-217 Oral Solution in approximately 62 adult subjects with MDD. Part A of the study is an open-label design with SAGE-217 Oral Solution dosing for 14 days. Part B of the study is a randomized, double-blind, parallel-group, placebo-controlled design with SAGE-217 Oral Solution or matching placebo dosing for 14 days. Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B.

Part A and B of the study will consist of an up to 7-day Screening Period (Days -7 to -1), a 14-day Treatment Period, and a 2-week Follow-up Period (through Day 28).

During the Screening Period (Day -7 to Day -1), after signing the informed consent form (ICF), subjects will be assessed for study eligibility, and the severity of each subject's MDD will be evaluated using HAM-D. The Screening Period assessments will be conducted on an outpatient basis.

If applicable, standard of care data collected prior to obtaining informed consent may also be included as screening data, if appropriate, such as laboratory tests, ECG, physical examination, and vital signs conducted within the preceding 48 hours, as long as the requirement for the screening assessment to be collected retrospectively is met in full. If applicable, to ensure protocol compliance, any standard of care data eligible for inclusion as screening data must include the precise nature and timing of data collection.

During the 14-day study Treatment Period of Part A and B, subjects must remain inpatient for the first 7 days at minimum and per Investigator's judgement thereafter. The Follow-up Period assessments will be conducted on an outpatient basis.

The study will be conducted in two parts:

- Part A: Beginning on Day 1, subjects will receive open-label SAGE-217 Oral Solution at 8:00 PM (± 15 minutes) with food (as outlined in protocol Section 9.2.1). Subjects will receive SAGE-217 Oral Solution 30 mg from Day 1 to Day 14 as tolerated.
- Part B: Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomized within each stratum in a 1:1 fashion to receive SAGE-217 Oral Solution or placebo for 14 days beginning on Day 1 as tolerated. All doses of study drug will be administered at 8:00 PM (± 15 minutes) with food as outlined in protocol Section 9.2.2.

Enrollment into Part A may be stopped and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed. Alternatively, upon completion of Part A, Part B may begin. The study may be terminated if there is clear lack of activity based on HAM-D scores during Part A.

In Part A and Part B, study drug (SAGE-217 Oral Solution or matching placebo) will be administered at the study center for at least the first 7 days of the Treatment Period, which includes Day 1 of study drug administration through completion of study drug administration on Day 14. Subjects may be discharged after a minimum 7-day inpatient stay, following completion of the Day 7 assessments. If their clinical condition does not allow discharge, the Investigator may keep the subjects as inpatients for a longer period of time. Subjects discharged from the inpatient unit may receive treatment with study drug for the remainder of the 14-day Treatment Period as outpatients. For the outpatient phase, dosing will be done at the clinical site or, if suitable arrangements can be made, via home administration where local regulations allow. Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.

Subjects will be monitored for safety during the Treatment and Follow-up Periods including monitoring for adverse events/serious adverse events, routine clinical laboratory assessments, physical examination, vital signs, and ECG.

During the Treatment Period, subjects will be able to receive study drug as long as there are no dose-limiting safety/tolerability concerns. Subjects who experience moderate or severe adverse events that according to the clinical judgement of the Investigator are related to study drug while receiving the 30 mg dose of study drug will receive 20 mg for the remaining of the Treatment Period. Subjects who experience moderate or severe related adverse events while receiving the 20 mg dose of study drug

may not be able to continue receiving study drug based on the evaluation and clinical judgment of the Investigator, and may be terminated from the study.

Dosing may also be modified based on tolerability as assessed with SSS scores. Any SSS score of ≥ 6 will be reassessed within 10 minutes. If a subject is receiving the 30 mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat assessment during normal waking hours, the dose will be decreased to 20 mg for the rest of the Treatment Period. If a subject is receiving the 20 mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat assessment during normal waking hours, then study drug will be discontinued and the subject will be terminated from the study.

See section 15.1 for schedule of events in Part A and Part B.

6.2 Sample Size and Power

The sample size of ten subjects for Part A was selected based on clinical and not statistical considerations.

For Part B, assuming a two-sided t-test at an alpha level of 0.10, a sample size of 23 subjects per group would provide 80% power to detect an effect size of 0.75 between the SAGE-217 Oral Solution and matching placebo groups with regard to the secondary efficacy outcome variable of change from baseline in HAM-D total score. An effect size of 0.75 corresponds to a matching placebo-adjusted difference of 7.5 points in the change from baseline in HAM-D total score at 15 days with an assumed SD of 10 points. By including two treatment groups and using a 1:1 randomization, a total of 46 subjects are required. Assuming a non-evaluability rate of 10%, up to 52 subjects will be randomized.

6.3 Randomization

Part A is open-label with no control group; therefore, there will be no randomization or blinding.

Part B is a double-blind, placebo-controlled study. Subjects who meet the entrance criteria will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 Oral Solution or taste-matched placebo according to a computer-generated randomization schedule. Once it has been determined that a subject meets eligibility criteria, the subject will be sequentially assigned a subject number from the randomization schedule provided to the unblinded pharmacist. Subject identification numbers will consist of the site number (e.g., "01") followed by numbering starting with double zero (e.g., 01-001, 01-002, 01-003 through 01-0xx).

The randomization schedule will be generated using SAS V9.3 or later.

6.4 Blinding and Unblinding

Only the clinic pharmacist or designated pharmacy staff, who is responsible for preparing the solutions, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual solution contents to the Investigator, who should also alert Sage of the emergency. In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the electronic case report form (eCRF). If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study. In addition, an unblinded Monitor will perform drug accountability during the study.

7 MODIFICATIONS

7.1 Modifications to the Approved Clinical Study Protocol

Protocol Text	SAP Text
<ol style="list-style-type: none">1. Physical examinations in Parts A and B will be summarized at the Screening visit, Day 8, Day 15, Day 21, and Day 28 visits.2. Center will be treated as random effect3. The HAM-D total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (i.e., “Not assessed”).	<ol style="list-style-type: none">1. All physical examinations data in Parts A and B will be listed.2. Center will be treated as a fixed effect3. Item 16 mentioned in Section 11 of the protocol corresponds to item 8 (loss of weight) in the structured interview guide and is scored in a range of 0 to 2.

7.2 Modifications to the Approved Statistical Analysis Plan

Not applicable.

7.3 Modifications to the Approved DMC Charter

Not applicable.

8 ANALYSIS SETS

8.1 Efficacy Set

The Efficacy Set for Part A is defined as all subjects who received at least one dose of the study drug and have a baseline and at least one post-baseline efficacy evaluation. The Efficacy Set will be used to analyze efficacy data.

The Efficacy Set for Part B is defined as all subjects who are randomized and who received at least one dose of the double-blind study drug and have a baseline and at least one post-baseline efficacy evaluation. The Efficacy Set will be used to analyze efficacy data.

8.2 Safety Set

The Safety Set for Part A is defined as all subjects who received at least one dose of the study drug. The Safety Set will be used to provide descriptive summaries of safety data.

The Safety Set for Part B is defined as all subjects who received at least one dose of the double-blind study drug. The Safety Set will be used to provide descriptive summaries of safety data.

8.3 Pharmacokinetic (PK) Set

The PK Set (for Part A and Part B) will consist of all subjects in the Safety Set for corresponding part of the study with sufficient plasma concentrations for PK evaluations and without major protocol deviations that affect the PK evaluation, and will be used to summarize PK data.

9 STATISTICAL ANALYSIS

9.1 General Considerations

Unless otherwise specified, continuous endpoints will be summarized with n, mean, standard deviation (SD), median, minimum (min) and maximum (max). If the measurements in the source (raw) data are integers, then the corresponding mean and median will be presented to 1 decimal place and the SD to 2 decimal places; if the measurements are obtained to 1 decimal place, then the mean and median will be presented to 2 decimal places and the SD to 3 decimal places; and so forth. Minimum and maximum will be displayed as reported in the source (raw) data. 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. Percentages will be presented to 1 decimal place unless otherwise specified.

All analyses and summary outputs will be generated using SAS® version 9.3 (or higher).

All subject data, including those derived, will be presented in the subject data listings; listings will display all subjects who were enrolled, regardless of whether or not they received study drug. In general, the subject data listings will be sorted by randomized treatment group (Part B), subject number and assessment visit and date (and time, if applicable). The summary tables will be presented descriptively overall for Part A and by treatment group for Part B.

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

9.1.1 Study Day Definition

Study day will be defined as follows:

- The first dose of study drug is designated as Day 1.
- For visit days after Day 1, study day = visit date – Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date – Day 1 date. Thus, study days for screening visit are negative numbers. There is no “Day 0”.

9.1.2 Missing Data

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

9.2 Background Characteristics

9.2.1 Subject Disposition

For Part A, the summaries of subject disposition will include the number of subjects who were enrolled, who were dosed, who completed Part A of the study, who discontinued from study drug in Part A, and reasons for discontinuation from study drug. Enrolled subject is defined as any screened subject who met the study requirements (inclusion/exclusion criterion) during screening.

For Part B, the summaries of subject disposition will include the number of subjects who were randomized, who were dosed, who completed Part B of the study, who prematurely discontinued, and reasons for premature discontinuation by treatment group.

For both Part A and Part B, the number and percentage of subjects in each analysis set will be summarized.

For screen failure subjects, reasons for screen failure will be summarized separately along with the number of subjects who were screened. A screened subject is defined as any subject who signed the study specific informed consent. A screen failure subject is defined as any subject who is screened but failed to meet study requirements (inclusion/exclusion criterion) during screening.

9.2.2 Demographics and Baseline Characteristics

Demographic data, such as age, gender, race and ethnicity, and baseline characteristics, such as height, weight, and body mass index (BMI, calculated as weight (kg)/ [height (m)²]), will be summarized using the Safety Set.

Hepatitis, human immunodeficiency virus (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 collected at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1.

Medical/family history data will be summarized by system organ class (SOC) and preferred term (PT) and listed by subject for the Safety Set.

9.2.3 Prior and Concomitant Medications

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

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those with a start or stop date during the 30 days prior to informed consent. Concomitant medications are defined as those with a start date on or after informed consent, or those with a start date before informed consent that are ongoing or with a stop date on or after the informed consent. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

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

Medication summaries will be performed by anatomical therapeutic chemical (ATC) level 2 term and PT based on the Safety Set.

9.2.4 Study Drug Exposure

Exposure to study drug is defined as total number of days treated with study drug during the study, with total days calculated as last dose date of study drug - first dose date of study drug + 1. The number and percentage of subjects exposed to 20 mg and 30 mg of study drug and discontinued study drug will be presented. Subjects exposed to 30 mg of study drug will be further summarized by the number of days the study drug was received (<3, 3-7, >7). Study drug exposure will be summarized using the Safety Set.

9.2.5 Protocol Deviations

Protocol deviations identified during site monitoring in consultation with Medical Monitor will be captured in a protocol deviation log and categorized. These deviations data for all subjects that violated the clinical study protocol at anytime during the study will be listed.

9.3 Efficacy Analysis

The secondary objective of Part A of the study is to determine if SAGE-217 Oral Solution 30 mg given for 14 days reduces the depressive symptoms measured by change from baseline at various time points in HAM-D total score, HAM-D subscale and individual item scores, HAM-A total score, MADRS total score. In addition, HAM-D response; HAM-D remission; and CGI-I response will be assessed.

The secondary objective for Part B of the study is to determine if treatment with SAGE-217 Oral Solution 30 mg given for 14 days reduces depressive symptoms in subjects with moderate to severe MDD compared to matching placebo measured by change from baseline at various time points in HAM-D total score, HAM-D subscale and individual item scores, HAM-A total score, MADRS total score. In addition, HAM-D response; HAM-D remission; and CGI-I response will be assessed.

9.3.1 Definition of Efficacy Variable(s)

The efficacy variables are defined as follows:

9.3.1.1 Hamilton Rating Scale for Depression (HAM-D)

HAM-D consists of 17 items that will be used to rate the severity of depression in subjects who are already diagnosed as depressed using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Axis I Disorders (SCID-I).

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. Each item is scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression. Item 16 mentioned in Section 11 of the protocol corresponds to item 8 (loss of weight) in the structured interview guide and is scored in a range of 0 to 2. The score for each item will be summed to compute a total score, which ranges from 0 to 52.

Hamilton Rating Scale for Depression response will be defined as having a 50% or greater reduction from baseline in HAM-D total score. Any subject who met this criterion will be defined as a HAM-D Responder.

Hamilton Rating Scale for Depression remission will be defined as having a HAM-D total score of ≤ 7 . Any subject who met this criterion will be defined as a subject in HAM-D remission.

As a measure of the severity of depression, HAM-D total score will be categorized as: 0-7=Normal, 8-13=Mild Depression, 14-18=Moderate Depression, 19-22=Severe Depression, ≥ 23 Very Severe Depression.

9.3.1.2 Montgomery-Åsberg Depression Rating Scale (MADRS)

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

Higher MADRS scores indicate more severe depression, and each item yields a score of 0 to 6. The MADRS total score will be calculated as the sum of the 10 individual item scores, which ranges from 0 to 60.

9.3.1.3 Hamilton Anxiety Rating Scale (HAM-A)

The 14-item HAM-A will be used to rate the severity of symptoms of 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.

As a measure of the severity of anxiety, HAM-A total score will be categorized as follows in the shift table: 0-13=Normal, 14-17 Mild Anxiety, 18-24 Moderate Anxiety, >=25 Severe Anxiety, per the Psych Congress Network.

9.3.1.4 Clinical Global Impression – Severity (CGI-S)

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

9.3.1.5 Clinical Global Impression – Improvement (CGI-I)

The CGI-I employs a 7-point Likert scale to measure the overall improvement in the subject's condition posttreatment. The Investigator will rate the subject's total improvement whether or not it is due entirely to drug treatment. Response choices include: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse.

CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved."

9.3.1.6 Short Form-36 (SF-36)

The SF-36 Health Survey is a subject-reported 36-item instrument for measuring functional health and well-being. The scores are totaled and higher score will indicate a better state of health.

9.3.1.7 The Fatigue Associated With Depression (FAs-D) Patient-Reported Outcome (PRO)

Fatigue is one of the most common symptoms of MDD. The 13-item patient-reported questionnaire was designed to assess fatigue associated with depression in the past week. Three scores are computed:

- A six-item fatigue experience subscale
- A seven-item fatigue impact subscale

- A total score (all 13 items).

The two subscales and the total score are computed as the mean of all answered items within each scale, and each scale score has a possible range of 1 to 5, with higher scores representing greater fatigue.

9.3.2 Visit Windows

The unscheduled or early termination (ET) visit will be mapped to a scheduled visit for analysis using the date of collection/assessment as a basis to determine study day and then study day will be mapped to the intended visit. The table below contains the visit windows for efficacy analysis.

Once analysis visit windows get assigned, all visits, including scheduled visits, unscheduled visits, and ET visits will be eligible for being flagged as the “analyzed record” within the analysis window, a subject’s individual analysis visit window could potentially contain more than 1 visit. In the event of multiple visits falling within an analysis window or in case of a tie, the following rules will be used in sequence to determine the “analyzed record” for the analysis visit window:

- If there is a scheduled visit/day for the analysis visit window, then the scheduled visit/day data will be used.
- If there is no scheduled visit/day for the analysis visit window, the data closest to the scheduled day/time will be used.
- If there is no scheduled visit/day for the analysis visit window and there is a tie between the data in the number of days/hours before and after the scheduled day, the later data will be used.

The data not flagged as the “analyzed record” will also be listed in subject listings.

Table 1: Visit Windows for Efficacy Analysis, for Both Part A and Part B

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Screening	Day -1	Days (-7) to (-1)
Baseline	Day 1	Day 1
Day 2	Day 2	Day 2
Day 3	Day 3	Day 3
Day 4	Day 4	Day 4
Day 5	Day 5	Day 5
Day 6	Day 6	Day 6
Day 7	Day 7	Day 7
Day 8	Day 8	Day 8
Day 15	Day 15	Day 15
Day 21 (± 1 day)	Day 21	Day 20 - 22
Day 28 (± 3 days)	Day 28	Day 25 - 31

9.3.3 Analysis of Efficacy Variable(s)

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data. For (the open-label) Part A, efficacy data will be summarized descriptively. For Part B, subjects will be analyzed according to randomized treatment. The Efficacy Set will be used for all efficacy summary tables.

Descriptive statistics including n, mean, SD, median, minimum, and maximum of actual, change from baseline, and percentage change from baseline values will be presented by assessment time point for the following continuous efficacy variables:

- HAM-D total score;
- MADRS total score;
- HAM-D subscale and individual item scores (Note: percentage change from baseline values will not be presented for HAM-D individual item scores);
- HAM-A total score;
- SF-36 total score (Part B only);
- FAs-D subscales and total score (Part B only).
- CGI-I and CGI-S scale scores.

Descriptive statistics including counts and percentages will be summarized by assessment time point for the following categorical efficacy variables:

- HAM-D response;
- HAM-D remission; CGI-I response.

Shift analysis pre- and post-treatment Day 8 and Day 15/ET respectively will be presented for the following depression categories (0-7 normal, 8-13 mild depression, 14-18 moderate depression, 19-22 severe depression, ≥ 23 very severe depression) based on sum scores from the first 17 items of the HAM-D rating scale. Shift analysis for the following anxiety categories (0-13=Normal, 14-17 Mild Anxiety, 18-24 Moderate Anxiety, ≥ 25 Severe Anxiety) will also be presented based on the 14-item HAM-A rating scale total score.

Change from baseline and percentage change from baseline in HAM-D, HAM-A, and MADRS total score over time will be presented graphically overall for Part A and by treatment group for Part B.

Mixed Effects Model for Repeated Measures:

For Part B, change from baseline on the sum scores from the first 17 items of HAM-D rating scale at the end of the treatment period (Day 15/ET) will be used to measure the effectiveness of SAGE-217 oral solution against placebo using the mixed effect model for repeated measures (MMRM).

The model will include the change from baseline at each visit as the dependent variable. Treatment, baseline total score, center, antidepressant use strata, assessment time point, time point-by-treatment interaction as explanatory variables will be included in the model. All explanatory variables including center will be treated as a fixed effect.

Model-based point estimates (i.e., least squares [LS] means, 95% confidence intervals, and p-values) will be reported. An unstructured covariance structure will be used to model the within-subject errors. Compound symmetry covariance structure will be used if there is a convergence issue with the unstructured covariance model.

See sample SAS code for MMRM in section 15.2.

Similar to those methods described above for Part B, an MMRM will be used for the analysis of the following variables: changes from baseline in MADRS total score and HAM-A total score, and select individual item and subscale scores. For each model, the comparison of interest will be between SAGE 217 Oral Solution and placebo at the 15-day time point. Model-based point estimates (i.e., LS means), 95% confidence intervals, and p-values will be reported.

Logistic Regression:

Logistic regression methods will be used for the analysis of the following binary variables in Part B of the study: HAM-D response, HAM-D remission and CGI-I response.

Hypothesis test:

$$H_0: \theta = 1$$

$$H_1: \theta \neq 1$$

where θ represents the odds that an outcome will occur given SAGE-217 Oral Solution, compared to the odds of the outcome occurring given placebo.

Logistic regression models will include terms for center, treatment, antidepressant use strata, and baseline score. The comparison of interest will be the difference between SAGE-217 Oral Solution and placebo at the 15-day time point in Part B. Model-based point estimates (i.e., odds ratios), 95% confidence intervals, and p-values will be reported. For the CGI-I response analysis, baseline CGI-S score will be included in the model.

See sample SAS code for logistic regression in section 15.2.

Generalized estimating equations:

Generalized estimating equations (GEE) will also be used to analyze the three binary variables. The model will include center, treatment, antidepressant use strata, baseline score and post-baseline time points. Assume exchangeable working correlation structure.

See sample SAS code for GEE model in section 15.2.

9.4 Safety Analysis

The primary endpoint is the safety and tolerability of SAGE-217, as evaluated by adverse events, concomitant medication usage, changes from baseline in physical examination, vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Sedation will be assessed using the SSS. Safety data will be listed by subject and summarized descriptively in Part A and by treatment group in Part B. All safety summaries will be performed on the Safety Set. All safety data will be presented in subject data listings.

The safety endpoints and variables considered in the summary tables for this study are summarized in Table 2.

Table 2: Safety endpoints and variables in the summary tables

Safety Evaluation	Incidence	Actual Value	Change from Baseline	Abnormality/Clinical Significance (CS)
AEs	X			
Con Meds	X	*		
Labs		X	X	*
ECG		X	X	*
Vital Signs		X	X	
PE		*		
C-SSRS	X	*		
SSS		X	X	

X = Safety Assessment will be summarized in tables

* = Safety Assessment will be summarized in individual subject data listings

9.4.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset after the start of study drug, or any worsening of a pre-existing medical condition/adverse event with onset after the start of study drug and until 7 days after the last dose.

All adverse events will be coded using MedDRA version 18.1 or higher and summarized by SOC and PT. Multiple occurrences of an AE are counted only once per subject per SOC and PT for summary tables.

Summary tables of TEAEs will be presented and will summarize the number and percentage of subjects for the following:

- Any TEAE
- TEAEs by relationship to study drug (not related, related)
- TEAEs by severity
- Serious AEs (SAEs)
- TEAEs that resulted in discontinuation of study drug
- Overall summary of the number and percentage of subjects reporting TEAEs, drug-related TEAEs, severe TEAEs, serious AEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death

Subjects will be counted only once within each SOC and PT at the maximum severity in the following order: severe, moderate, and mild. An AE with missing severity will be considered as a severe AE. Subjects will be counted only once within each SOC and PT at the strongest relationship to study drug in the following order: related, not related to study drug. If the relationship between the adverse event and the study drug is determined to be “possible” or “probable”, the event will be considered to be related to the study drug. An AE with missing relationship to study drug will be considered as related to study drug. For Part A, the incidences will be presented by overall

descending frequency of SOC and then, within a SOC, by overall descending frequency of PT based on the subject count in the SAGE-217 column. For Part B, the incidences will be presented in order of decreasing frequency of SOC and then, within a SOC, by overall descending frequency of PT based on the subject count for the SAGE-217 Oral Solution treatment group column.

All adverse events and serious adverse events (including those with onset or worsening before the start of study drug) through the Day 28 follow-up visit will be listed.

9.4.2 Clinical Laboratory

Clinical laboratory results will be listed by subject and timing of collection.

Summary tables will include descriptive statistics for the actual values and changes from baseline by study visit (Day) in hematology, serum chemistry, coagulation and quantitative urinalysis test results and overall in Part A and by treatment group in Part B. Out-of-range values will be flagged as low, high, or abnormal, where applicable, in the subject data listings.

For qualitative urinalysis parameters, test results will be categorized as normal and abnormal. Frequency counts and percentages will be presented over time for these categorical data in Part A and by treatment group in Part B.

All parameters will be converted to consistent units according to the International System of Units (SI) before summarization.

9.4.3 Electrocardiogram

The following ECG parameters will be listed for each subject: heart rate (bpm), PR (msec), QRS (msec), QT (msec), QTc (msec) interval calculated using the Fridericia method (QTcF). Any clinically significant abnormalities or changes in ECGs should be listed as an adverse event. Electrocardiogram findings will be listed by subject and visit.

QTcF (msec) is calculated as: $QT (msec) / RR^{1/3}$, where $RR = 60 / \text{heart rate (bpm)}$.

The actual value at each time point and change from baseline at each post-baseline time point will be summarized overall in Part A and by treatment group in Part B. The number and percentage of subjects with 'normal', 'abnormal, not clinically significant' and 'abnormal, clinically significant' ECG results will be summarized at baseline and each post-baseline time point.

Note: If the assessment is 'Abnormal, clinically significant', the event is reported as adverse event if identified after the date of informed consent; and any clinically significant abnormality at screening as judged by the investigator should be recorded in the medical history.

9.4.4 Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for vital signs (respiratory rate (breaths/minute), oral temperature (degrees C), supine systolic blood pressure (mmHg), supine diastolic blood pressure (mmHg), standing systolic blood pressure (mmHg), and standing diastolic blood pressure (mmHg) by time point. Vital sign results will be listed by subject and timing of collection. The actual value at each time point and change from baseline at each post-baseline time point will be summarized overall in Part A and by treatment group in Part B.

9.4.5 Physical Examination

All physical examinations data in Parts A and B will be listed.

Note: Any abnormalities that are new or worsened are recorded as an adverse event.

9.4.6 Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidality data collected on the C-SSRS at baseline and by visit during the Treatment Period will be listed for all subjects. Listings will include all data collected on the C-SSRS. In addition, the number and percentage of subjects with a response of 'Yes' to any C-SSRS Suicidal Ideation or Suicidal Behavior item will be presented.

9.4.7 Stanford Sleepiness Scale (SSS)

The SSS is subject-rated scale designed to quickly assess how alert a subject is feeling. Degrees of sleepiness and alertness are rated on a scale of 1 to 7, where the lowest score of '1' indicates the subject is 'feeling active, vital, alert, or wide awake' and the highest score of '7' indicates the subject is 'no longer fighting sleep, sleep onset soon; having dream-like thoughts'.

Sedation data collected on the SSS will be listed for all subjects. Actual value and changes from baseline in score over time will be represented graphically. The actual value at each time point and change from baseline at each post-baseline time point will be summarized overall in Part A and by treatment group in Part B. In addition, the number and percentage of subjects at each SSS scale rating will be presented.

9.5 Pharmacokinetic Analysis

PK analyses will be performed for the PK Set.

9.5.1 Collection schedule

Plasma samples for PK analysis in Part A and Part B will be collected predose on Days 2, 3, 4, 5, and 6, predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15.

The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. Plasma samples for PK analysis will be collected per protocol.

9.5.2 Derived PK parameters

Non-compartmental PK parameters for SAGE-217 will be calculated using Phoenix WinNonlin 6.4 or higher version. Actual sampling times will be used in the determination of the individual PK parameters. Linear up log down method will be used for derivation of AUC.

The following PK parameters will be derived (where possible):

Table 3: PK parameters and definitions

AUC_{0-t} (or AUC)	Area under the plasma concentration time curve up to time t
AUC_{∞}	AUC from time 0 to infinity
C_{max}	Maximum (peak) plasma concentration
T_{max}	Time at maximum (peak) plasma concentration
$t_{1/2}$	Elimination half-life (where possible)
C_{ss} (or $C_{avg,ss}$)	Steady-state drug concentration in the plasma during oral intake , the dosing interval will be considered as 24 hours

9.5.3 Handling of dropouts or missing data

Missing concentration data for all subjects who are administered scheduled study treatment will be considered as non-informative missing and will not be imputed.

The following rules will apply for the derivation of all kinds of AUCs:

- Pre-dose concentration values below the assay's limit of quantification (BLQ) will be treated as zero.
- The sampling time relative to dosing for pre-dose samples will also be treated as zero.
- Post-dose BLQ values will be set to missing.

If the actual time of sampling is missing, the planned time may be used.

9.5.4 Summary statistics

The plasma concentrations along with time point deviation from scheduled time will be listed by subject.

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics separately for part A and B. Time at maximum (peak) plasma concentration (t_{max}) will be summarized using n, mean, SD, median, minimum, and maximum. All other PK parameters will be summarized using n, geometric mean, geometric coefficient of variation, coefficient of variation, median, minimum, and maximum and listed by subject.

9.5.5 Data presentation

The descriptive statistics will be generated as discussed above in Section 9.5.4.

The following figures will be produced:

- Mean \pm SD plasma concentration-time profiles for Day 7 will be plotted on linear and semi-log scales separately for part A and B
- Individual subject concentration-time profiles on linear and semi-logarithmic concentration scales
- Spaghetti plots for each treatment on Day 7 separately for part A and B (linear and semi-logarithmic scale)

10 SUMMARY OF INTERIM AND DMC ANALYSES

Not applicable

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15 LIST OF APPENDICES

15.1 Appendix A: Schedule of Assessments

Table 3: Schedule of Events (Part A)

	Screening Period	Open-Label Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D -7 to -1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D30 (±3d)
Study Procedure																		
Informed Consent	X																	
Inclusion/Exclusion	X	X																
Demographics	X																	
Medical/Family History	X																	
SCID-I	X																	
Confinement		X							(X)									
Physical Examination	X								X							X	X	X
Body Weight/Height	X															X (wt only)	X (wt only)	X (wt only)
Clinical Laboratory Assessments ^b	X								X							X	X	X
Drug & Alcohol Screen ^c	X	X																
Pregnancy Test ^d	X	X														X ^e		X
Hepatitis & HIV Screen	X																	
Blood Sample ^f	O								O							O		
Genetic Sample ^g	O																	
Vital Signs ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry		X	X	X	X	X	X	X	X									
12-Lead ECG ⁱ	X	X	X					X							X		X	
C-SSRS ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S ^k	X	X	X	X					X							X	X	X

	Screening Period	Open-Label Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D -7 to -1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D30 (±3d)
Study Procedure																		
CGI-I ^k			X	X					X							X	X	X
HAM-A ^k	X	X	X	X					X							X	X	X
HAM-D ^k	X	X	X	X	X	X	X	X	X							X	X	X
MADRS ^k	X	X	X	X	X	X	X	X	X							X	X	X
SSS ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Plasma PK ^m			X	X	X	X	X	X	X						X	X		
Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse Events	X																	
Prior/Concomitant Medications ⁿ	X																	

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ET = early termination; ECG = electrocardiogram; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; MADRS = Montgomery-Åsberg Depression Rating Scale; PK = pharmacokinetic; SCID-I = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Axis I Disorders; SSS = Stanford Sleepiness Scale

*D1 procedures are to be completed prior to dosing

^a Outpatient visits may take place at the subject's residence or in the clinic.

^b Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning on Days 8 and 15 and during the follow-up visits on Day 21 and Day 28.

^c Urine toxicology for selected drugs of abuse and serum or breath test for alcohol.

^d Serum pregnancy test at screening and urine pregnancy test at Day 1 and Day 28.

^e Female subjects who prematurely discontinue will have a pregnancy test performed at the ET visit.

^f An optional blood sample for hormone and exploratory biochemistry testing, where consent is given.

^g An optional genetic sample for biomarker testing, where consent is given.

^h Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ±5 minutes of the scheduled time point through 0.5 hours after dosing and ±30 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between the hours of 23:00 h and 06:00 h. From Day 1 through Day 7, vital signs will be completed at the following time points: predose, 0.25, 0.5, 1, 2, and 12 hours after dosing. During the outpatient treatment period, vital signs will be completed prior to dosing and 1 hour after dosing. Vital signs may be repeated at the discretion of the Investigator or Visiting Home Healthcare Provider as clinically indicated.

ⁱ Will be performed 1 hour ±15 minutes after dosing on Days 1, 2, 7, and 14, and during the follow-up visit on Day 21.

- ^j The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- ^k To be completed to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28. The assessment timeframe for HAM-D and HAM-A scales will refer to the past 7 days (1 week) on Screening, Day 1, Day 15/ET, Day 21, and Day 28 visits, and the past 24 hours on visits occurring on Days 2 through 8.
- ^l To be completed within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between 23:00 h and 06:00 h during the inpatient treatment period. From Day 1 through Day 7, SSS will be completed at the following time points: predose, 0.25, 0.5, 1, and 2 hours after dosing. During the outpatient treatment period, SSS will be completed prior to dosing and 1 hour after dosing.
- ^m Plasma samples for PK analysis in Part A and Part B will be collected predose on Days 2, 3, 4, 5, and 6, predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. Plasma samples for PK analysis will be collected per protocol and subjects may need to be awoken for sample collection.
- ⁿ To include those taken within 30 days prior to informed consent and throughout the study.

Table 4: Schedule of Events (Part B)

	Screening Period	Double-Blind, Placebo-Controlled Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D -7 to -1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D30 (±3d)
Study Procedure																		
Informed Consent	X																	
Inclusion/Exclusion	X	X																
Demographics	X																	
Medical/Family History	X																	
SCID-I	X																	
Randomization		X																
Confinement		X							(X)									
Physical Examination	X								X							X	X	X
Body Weight/Height	X															X (wt only)	X (wt only)	X (wt only)
Clinical Laboratory Assessments ^b	X								X							X	X	X
Drug & Alcohol Screen ^c	X	X																
Pregnancy Test ^d	X	X														X ^e		X
Hepatitis & HIV Screen	X																	
Blood Sample ^f	O								O							O		
Genetic Sample ^g	O																	
Vital Signs ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry		X	X	X	X	X	X	X	X									
12-Lead ECG ⁱ	X	X	X					X							X		X	

	Screening Period	Double-Blind, Placebo-Controlled Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D -7 to -1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D30 (±3d)
Study Procedure																		
C-SSRS ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S ^k	X	X	X	X					X							X	X	X
CGI-I ^k			X	X					X							X	X	X
HAM-A ^k	X	X	X	X					X							X	X	X
HAM-D ^k	X	X	X	X	X	X	X	X	X							X	X	X
MADRS ^k	X	X	X	X	X	X	X	X	X							X	X	X
SF-36 ^k	X	X							X							X	X	X
FAs-D ^k	X	X							X							X	X	X
SSS ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Plasma PK ^m			X	X	X	X	X	X	X						X	X		
Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse Events	X																	
Prior/Concomitant Medications ⁿ	X																	

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ET = early termination; ECG = electrocardiogram; FAs-D = fatigue associated with depression; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; MADRS = Montgomery-Asberg Depression Rating Scale; PK = pharmacokinetic; SCID-I = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Axis I Disorders; SSS = Stanford Sleepiness Scale

*D1 procedures are to be completed prior to dosing

^a Outpatient visits may take place at the subject's residence or in the clinic.

^b Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning on Days 8 and 15 and during the follow-up visits on Day 21 and Day 28.

^c Urine toxicology for selected drugs of abuse and serum or breath test for alcohol.

^d Serum pregnancy test at screening and urine pregnancy test at Day 1 and Day 28.

^e Female subjects who prematurely discontinue will have a pregnancy test performed at the ET visit.

^f An optional blood sample for hormone and exploratory biochemistry testing, where consent is given.

- ^g An optional genetic sample for biomarker testing, where consent is given.
- ^h Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 30 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between the hours of 23:00 h and 06:00 h. From Day 1 through Day 7, vital signs will be completed at the following time points: predose, 0.25, 0.5, 1, 2, and 12 hours after dosing. During the outpatient treatment period, vital signs will be completed prior to dosing and 1 hour after dosing. Vital signs may be repeated at the discretion of the Investigator or Visiting Home Healthcare Provider as clinically indicated.
- ⁱ Will be performed 1 hour ± 15 minutes after dosing on Days 1, 2, 7, and 14, and during the follow-up visit on Day 21.
- ^j The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- ^k To be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28. The assessment timeframe for HAM-D and HAM-A scales will refer to the past 7 days (1 week) on Screening, Day 1, Day 15/ET, Day 21, and Day 28 visits, and the past 24 hours on visits occurring on Days 2 through 8.
- ^l To be completed within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between 23:00 h and 06:00 h during the inpatient treatment period. From Day 1 through Day 7, SSS will be completed at the following time points: predose, 0.25, 0.5, 1, and 2 hours after dosing. During the outpatient treatment period, SSS will be completed prior to dosing and 1 hour after dosing.
- ^m Plasma samples for PK analysis in Part A and Part B will be collected predose on Days 2, 3, 4, 5, and 6, predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. Plasma samples for PK analysis will be collected per protocol and subjects may need to be awoken for sample collection.
- ⁿ To include those taken within 30 days prior to informed consent and throughout the study.

15.2 Appendix B: Details of Statistical Methodology

Sample SAS code for MMRM:

```
proc mixed data=&data;  
by param;  
class trtan avisitn siteid usubjid strata;  
model chg=base siteid trtan strata avisitn trtan*avisitn / ddfm=kr s;  
repeated avisitn / subject=usubjid type=un;  
lsmeans trtan*avisitn / cl pdiff e;  
estimate 'SAGE-217 vs PLACEBO at day 15' trtan 1 -1 trtan*avisitn 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 -1 0 0 / cl;  
run;
```

Note: if convergence not met, use type=cs instead

Sample SAS code for Logistic Regression:

```
proc logistic data=&data;  
by param;  
class usubjid trtan siteid strata avisitn;  
model aval (event='1')=base siteid trtan avisitn trtan*avisitn strata; Note: for CGI-S, add cgisbase independent variable as well  
lsmeans trtan*avisitn / diff oddsratio cl exp;  
run;
```

Sample SAS code for Generalized Estimating equation (GEE):

```
proc genmod data=&data;  
by param;  
class usubjid trtan siteid strata avisitn;  
model aval=base siteid trtan strata avisitn trtan*avisitn/dist=bin link=logit;  
repeated subject=usubjid / type=un corr=exch; * if convergence not met, use type=cs;  
lsmeans trtan*avisitn / diff exp cl;  
estimate 'SAGE-217 vs PLACEBO at day 15' trtan 1 -1 trtan*avisitn 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 -1 0 0 / exp cl;  
run;
```




Statistical Analysis Plan

Methods

Protocol Number 217-MDD-201

**A Phase 2, Two-Part (Open-Label Followed by Double-Blind) Study
Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of
SAGE-217 in the Treatment of Adult Subjects with Moderate to Severe Major
Depressive Disorder**

Author of SAP: Kelley Wekheye

Version: Version 3.0

Version Date of SAP: 16 NOV 2017

Sponsor: Sage Therapeutics, Inc.
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Authorization Signature Page

A Phase 2, Two-Part (Open-Label Followed by Double-Blind) Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Adult Subjects with Moderate to Severe Major Depressive Disorder

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2 LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
AUC _∞	area under the concentration-time curve from time zero to infinity
BMI	body mass index
bpm	beats per minute
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
C _{max}	maximum (peak) plasma concentration
CS	clinically significant
C _{ss}	steady-state drug concentration in the plasma during oral/capsule intake
C _{avg,ss}	steady-state drug concentration in the plasma
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
FAs-D	fatigue associated with depression
GEE	Generalized Estimating Equation
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	17-item Hamilton Rating Scale for Depression
HIV	human immunodeficiency virus
HRPQ	Health-Related Productivity Questionnaire
ICF	informed consent form
Kg	kilogram
LOCF	Last Observation Carried Forward
m	meter
MADRS	Montgomery-Åsberg Depression Rating Scale
Max	maximum
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
Min	minimum
mmHg	millimeter of mercury
MMRM	mixed effects model for reported measures
msec	millisecond
n	number
PCS	potentially clinically significant
PCSC	potentially clinically significant change
PK	pharmacokinetic(s)
PRO	patient reported outcome
PT	preferred term
RDQ	Remission in Depression Questionnaire
SAP	statistical analysis plan

SCID-I	Structured Clinical Interview for DSM-5 Axis I Disorders
SD	standard deviation
SF-36	36-item short form survey
SI	International System of Units
SOC	system organ class
ss	steady state
SSS	Stanford Sleepiness Scale
TEAE	treatment-emergent adverse event
$t_{1/2}$	Elimination half-life
t_{max}	time at maximum (peak) plasma concentration
WHO	World Health Organization
WHO-DD	World Health Organization-Drug Dictionary

3 INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis and is based on the approved clinical study protocol, dated 12 Jul 2017, version 5.0. There are two parts to the study. Part A of the study has been completed and Part B was initiated upon completion of Part A.

The purpose of the SAP is to describe in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol. The SAP will be approved and finalized before Part B database lock.

All analyses and summary outputs will be generated using SAS® version 9.3 or higher.

4 STUDY OBJECTIVES

4.1 Part A

4.1.1 Primary Objective

The primary objective of Part A is to evaluate the safety and tolerability of SAGE-217 Oral Solution 30 mg.

4.1.2 Secondary Objective

The secondary objective of Part A is to determine if treatment with SAGE-217 Oral Solution 30 mg for 14 days reduces depressive symptoms.

4.1.3 Pharmacokinetic Objective

The Pharmacokinetic (PK) objective of Part A is to assess the PK profile of SAGE-217 Oral Solution in plasma samples.

4.2 Part B

4.2.1 Primary Objective

The primary objective for Part B of the study is to determine if treatment with SAGE-217 Capsules (30 mg) reduces depressive symptoms in subjects with moderate to severe major depressive disorder (MDD) compared to matching placebo.

4.2.2 Secondary Objective

The secondary objective of Part B is to evaluate the safety, tolerability and efficacy of SAGE-217 Capsule (30 mg).

4.2.3 Exploratory Objective

The exploratory objective for Part B of the study is to assess the patient-reported outcome (PRO) measures as they relate to quality of life, work function, productivity, and depressive symptoms.

4.2.4 Pharmacokinetic Objective

The PK objective of Part B is to assess the PK profile of SAGE-217 Capsules in plasma samples.

5 STUDY ENDPOINTS

5.1 Part A

5.1.1 Primary

The primary endpoint for Part A is the safety and tolerability of SAGE-217 Oral Solution as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); Stanford Sleepiness Scale (SSS) score; physical examination; and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).

5.1.2 Secondary

Reduction in depressive symptoms as assessed by the following:

- Change from baseline in Hamilton Rating Scale for Depression (HAM-D) total score at Day 15 (ET) and all other time points;
- HAM-D response (defined as having a 50% or greater reduction from baseline in HAM-D total score);
- HAM-D remission (defined as having a HAM-D total score of ≤ 7);
- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15 (ET) and all other time points;
- Change from baseline in HAM-D subscale and individual item scores at Day 15 (ET) and all other time points;
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at all time points; and
- Clinical Global Impression - Improvement (CGII) response (defined as a CGI-I score of “very much improved” or “much improved”).

5.1.3 Pharmacokinetic

- Maximum (peak) plasma concentration (C_{\max}), time at maximum (peak) plasma concentration (t_{\max}), plasma elimination half-life ($t_{1/2}$), area under the curve from zero to infinity (AUC_{∞}), and steady-state drug concentration in the plasma during oral intake (C_{ss}).

5.2 Part B

5.2.1 Primary

The primary endpoint for Part B is the reduction in depressive symptoms, compared to placebo, as assessed by the change in the 17-item HAM-D total score from baseline to Day 15.

5.2.2 Secondary

- Reduction in depressive symptoms, compared to placebo, as assessed by the following:
 - Change in the 17-item HAM-D total score from baseline at all time points;
 - HAM-D response;
 - HAM-D remission;
 - Change from baseline in the MADRS total score at Day 15 (ET) and all other time points;
 - Change from baseline in HAM-D subscale and individual item scores at all time points;
 - Change from baseline in HAM-A total score at Day 15 (ET) and all other time points; and
 - CGI-I response.
- The safety and tolerability of SAGE-217 Capsules as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; SSS score; physical examination; and suicidal ideation using the C-SSRS.

5.2.3 Exploratory

Responses to the 36-item short form survey (SF-36), fatigue associated with depression (FAs-D), Remission in Depression Questionnaire (RDQ), and the Health-Related Productivity Questionnaire (HRPQ) will be summarized as exploratory endpoints for Part B.

5.2.4 Pharmacokinetic

- C_{max} , t_{max} , $t_{1/2}$, AUC_{∞} and C_{ss} .

6 STUDY DESIGN

6.1 Overall Design

This study is a two-part, multicenter, Phase 2a study to evaluate the safety, tolerability, PK, and efficacy of SAGE-217 Oral Solution (Part A) and SAGE-217 Capsules (Part B) in approximately 98 adult subjects (approximately 10 subjects in Part A and up to 88 randomized adult subjects in Part B) with MDD. Part A of the study is an open-label design with SAGE-217 Oral Solution dosing for 14 days. Part B of the study is a randomized, double-blind, parallel-group, placebo-controlled design with SAGE-217 Capsule or matching placebo dosing for 14 days. Part B will consist of an up to 14-day Screening Period (Days

-14 to -1), a 14-day Treatment Period, and a 4-week Follow-up Period. Separate cohorts of subjects will be enrolled in Part A and Part B; subjects participating in Part A cannot enroll in Part B.

During the Screening Period, after signing the informed consent form (ICF), subjects will be assessed for study eligibility, and the severity of each subject's MDD will be evaluated using HAM-D. The Screening Period assessments will be conducted on an outpatient basis.

If applicable, standard of care data collected prior to obtaining informed consent may also be included as screening data, if appropriate, such as laboratory tests, ECG, physical examination, and vital signs conducted within the preceding 48 hours, as long as the requirement for the screening assessment to be collected retrospectively is met in full. If applicable, to ensure protocol compliance, any standard of care data eligible for inclusion as screening data must include the precise nature and timing of data collection.

During the 14-day study Treatment Period of Part A and B, subjects must remain inpatient for the first 7 days at minimum and per Investigator's judgement thereafter. The Follow-up Period assessments will be conducted on an outpatient basis.

The study will be conducted in two parts:

- Part A: Beginning on Day 1, subjects will receive open-label SAGE-217 Oral Solution at 8:00 PM (± 15 minutes) with food (as outlined in protocol Section 9.2.1). Subjects will receive SAGE-217 Oral Solution 30 mg from Day 1 to Day 14 as tolerated.
- Part B: Based on the results of Part A, eligible subjects will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomized within each stratum in a 1:1 ratio to receive SAGE-217 Capsules (30 mg) or matching placebo for 14 days beginning on Day 1, as tolerated. All doses of study drug will be administered at 8:00 PM (± 15 minutes) with food as outlined in protocol Section 9.2.2.

Enrollment into Part A may be stopped and Part B initiated if there is a clear signal of activity based on the HAM-D scores and/or other scales being assessed. Alternatively, upon completion of Part A, Part B may begin. The study may be terminated if there is clear lack of activity based on HAM-D scores during Part A.

In Part A and Part B, study drug (SAGE-217 Oral Solution in Part A; SAGE-217 Capsule or matching placebo in Part B) will be administered at the study center for at least the first 7 days of the Treatment Period, which includes Day 1 of study drug administration through completion of study drug administration on Day 14. Subjects may be discharged after a minimum 7-day inpatient stay, following completion of the Day 7 assessments. If their clinical condition does not allow discharge, the Investigator may keep the subjects as inpatients for a longer period of time. Subjects discharged from the inpatient unit may receive treatment with study drug for the remainder of the 14-day Treatment Period as outpatients. For the outpatient phase, dosing will be done at the clinical site or, if suitable arrangements can be made, via home administration where local regulations allow. All dosing will be observed, either in the clinical unit or by a healthcare professional at home.

Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.

Subjects will be monitored for safety during the Treatment and Follow-up Periods including monitoring for adverse events/serious adverse events, routine clinical laboratory assessments, physical examination, vital signs, and ECG (only Day 15 during Follow-up).

During the Treatment Period, subjects will be able to receive study drug as long as there are no dose limiting safety/tolerability concerns. Subjects cannot tolerate 30 mg will receive 20 mg for the remaining of the Treatment Period. Subjects who experience intolerable AEs at the 20-mg dose level may be terminated from the study at the discretion of the Investigator.

Dosing may also be modified based on tolerability as assessed with SSS scores. Any SSS score of ≥ 6 will be reassessed within 10 minutes. If a subject is receiving the 30-mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat assessment during normal waking hours, the dose will be decreased to 20 mg for the rest of the Treatment Period. If a subject is receiving the 20-mg dose of study drug and has an SSS score of ≥ 6 that is confirmed on repeat assessment during normal waking hours, then study drug will be discontinued and the subject will be terminated from the study.

Follow-up visits will be conducted on an outpatient basis. Follow-up visits will be conducted weekly for 2 weeks after completion of the Treatment Period in Part A (Day 28 ± 1 day) and weekly for 4 weeks after completion of the Treatment Period in Part B (Day 42 ± 3 days).

See section [15.1](#) for schedule of events in Part A and Part B.

6.2 Sample Size and Power

The sample size of ten subjects for Part A was selected based on clinical and not statistical considerations.

For Part B, assuming a two-sided t-test at an alpha level of 0.05, a sample size of 40 subjects per group would provide 90% power to detect an effect size of 0.75 between the SAGE-217 Capsules and matching placebo groups with regard to the efficacy outcome variable of change from baseline in HAM-D total score. An effect size of 0.75 corresponds to a matching placebo-adjusted difference of 7.5 points in the change from baseline in HAM-D total score at 15 days with an assumed SD of 10 points. By including two treatment groups and using a 1:1 randomization, a total of 80 subjects are required. Assuming a non-evaluability rate of 10%, up to 88 subjects will be randomized. Additional subjects may be enrolled if the drop-out rate is higher than 10%.

6.3 Randomization

Part A is open-label with no control group; therefore, there will be no randomization or blinding.

Part B is a double-blind, placebo-controlled study. Subjects who meet the entrance criteria will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥ 30 days) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 Capsules or matched placebo according to a computer-generated

randomization schedule. Once it has been determined that a subject meets eligibility criteria, the subject will be sequentially assigned a subject number from the randomization schedule provided to the unblinded pharmacist and/or designated pharmacy staff. Subject identification numbers will consist of the site number (e.g., “01”) followed by numbering starting with double zero (e.g., 01-001, 01-002, 01-003 through 01-0xx), for Part A of the study. Moreover, to avoid duplicate patient numbers between Part A and Part B the sequential counter will begin at 201 for all sites in Part B.

The randomization schedule will be computer-generated.

6.4 Blinding and Unblinding

Part A is open-label with no control group; therefore, procedures for blinding and unblinding are not applicable.

Part B is a double-blind, placebo-controlled study. Only the clinic pharmacist and/or designated pharmacy staff, who is responsible for preparing the study drug, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual capsules content to the Investigator, who should also alert Sage of the emergency. In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject’s records and on the electronic case report form (eCRF). If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study. In addition, an unblinded Monitor will perform drug accountability during the study.

7 MODIFICATIONS

7.1 Modifications to the Approved Clinical Study Protocol

Protocol Text	SAP Text
<ol style="list-style-type: none"> Physical examinations in Parts A and B will be summarized at the Screening visit, Day 8, Day 15, Day 21, and Day 28 visits. Center will be treated as random effect The HAM-D total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (i.e., “Not assessed”). The PK Set will consist of all subjects in the Safety Set with sufficient plasma concentrations for PK evaluations, and will be used to summarize PK data 	<ol style="list-style-type: none"> All physical examinations data in Parts A and B will be listed. Center will be treated as a fixed effect in the primary efficacy analysis. As a supportive analysis, the MMRM models will be used to study the heterogeneity of study drug effect by considering center and treatment-by-center effects to be random Item 16 mentioned in Section 11 of the protocol corresponds to item 8 (loss of weight) in the structured interview guide and is scored in a range of 0 to 2. The PK Set will consist of all subjects in the Safety Set with at least 1 post-dose PK assessment in the study, and will be used to summarize PK data

7.2 Modifications to the Approved Statistical Analysis Plan

This SAP has been modified to incorporate protocol version 4.0. Per protocol version 4.0, center should be treated as a random effect.

Summary of changes from SAP V1.0:

- Incorporation of changes due to protocol amendment 2, version 3.0 and protocol amendment 3, version 4.0
- Minor editorial changes
- Prior and concomitant medications: changes in definitions
- HAM-D:
 - Added details on the subscales (Core, Anxiety, Bech-6, and Meier)
 - Separated summary tables for subscale and individual item scores
 - Modified total score categorization

- Additional details for Part B
 - Study drug exposure: added a different categorization for number of days the study drug was received
 - Protocol deviations: added summary table
 - Demographics and Baseline Characteristics: added antidepressant use
 - Rules for determining if missing scores will be replaced and approach to replacement
 - Binary variable analysis (HAM-D response and remission, CGI-I response): removed logistic regression
 - Sensitivity analyses
 - Supportive analyses
 - Statistical methodology (sample SAS code)
 - Safety:
 - Labs, ECGs, and vital signs: added potentially clinically significant criterion and summaries/listings
 - AEs:
 - Added summary table for TEAEs resulting in dose adjustment
 - Changed types of TEAEs summarized for the overall summary table
 - Labs:
 - Listed lab tests
 - added shift tables
 - Stanford sleepiness scale: changed figure display to spaghetti plots for Day 1 through 7
 - PK:
 - Added mean and SD as summary statistics for all parameters
 - Re-numbered the concentration and parameter listings

Summary of changes from SAP V2.0:

- Incorporation of changes due to protocol amendment 4, version 5.0
- HAM-D
 - Modified total score categorization for Part A and Part B
 - Subset analysis
- Added summary table for TEAEs by preferred term
- Changed PK Set definition
- For Part B, modified text on subject data to be displayed in listings
- For Part B, changed sort order for adverse event SOC
- Added note regarding modifications to GEE model for HAM-D Remission.

7.3 Modifications to the Approved DMC Charter

Not applicable.

8 ANALYSIS SETS

8.1 Efficacy Set

The Efficacy Set for Part A is defined as all subjects who received at least one dose of the study drug and have a baseline and at least one post-baseline efficacy evaluation. The Efficacy Set will be used to analyze efficacy data.

The Efficacy Set for Part B is defined as all subjects who are randomized and who received at least one dose of the double-blind study drug and have a baseline and at least one post-baseline efficacy evaluation. The Efficacy Set will be used to analyze efficacy data.

8.2 Safety Set

The Safety Set for Part A is defined as all subjects who received at least one dose of the study drug. The Safety Set will be used to provide descriptive summaries of safety data.

The Safety Set for Part B is defined as all subjects who received at least one dose of the double-blind study drug. The Safety Set will be used to provide descriptive summaries of safety data.

8.3 Pharmacokinetic (PK) Set

The PK Set (for Part A and Part B) will consist of all subjects in the Safety Set with at least 1 post-dose PK assessment in the study, and will be used to summarize PK data.

9 STATISTICAL ANALYSIS

9.1 General Considerations

Unless otherwise specified, continuous endpoints will be summarized with n, mean, standard deviation (SD), median, minimum (min) and maximum (max). If the measurements in the source (raw) data are integers, then the corresponding mean and median will be presented to 1 decimal place and the SD to 2 decimal places; if the measurements are obtained to 1 decimal place, then the mean and median will be presented to 2 decimal places and the SD to 3 decimal places; and so forth. Minimum and maximum will be displayed as reported in the source (raw) data. 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. Percentages will be presented to 1 decimal place unless otherwise specified.

All analyses and summary outputs will be generated using SAS® version 9.3 (or higher).

All subject data, including those derived, will be presented in the subject data listings; listings will display subjects in analysis sets for Part A and all subjects for Part B, regardless of whether or not they received study drug. In general, the subject data listings will be sorted by randomized treatment group (Part B), subject number and assessment visit and date (and

time, if applicable). The summary tables will be presented descriptively overall for Part A and by treatment group for Part B.

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

9.1.1 Study Day Definition

Study day will be defined as follows:

- The day of subject receiving the first dose of study drug is designated as Day 1.
- For visit days after Day 1, study day = visit date – Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date – Day 1 date. Thus, study days for screening visit are negative numbers. There is no “Day 0”.

9.1.2 Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis sets, using all non-missing data available. For Part A, no imputation process will be used to estimate missing data.

For Part B, SF-36 subscales will be calculated and missing responses will be handled using the built-in scoring software. For all the other efficacy and exploratory endpoints, the prorating approach will be considered when calculating the total scores. If no more than 20% of item responses are missing for a given subject on the scale, the missing scores will be replaced with the mean score on all other non-missing scores, or the maximum possible values for the missing responses, whichever is smaller. Otherwise, if more than 20% of item scores are missing for a given subject on the scale, the total score will not be calculated and will be left as missing. See section 9.3.1 for the details of this approach on each endpoint.

A sensitivity analysis will be used to investigate the impact of missing data if $\geq 5\%$ of subjects have missing data in primary efficacy endpoint assessment (i.e., HAM-D total score) or key secondary endpoint assessment (i.e., MADRS total score). Two techniques will be considered for the sensitivity analysis: 1) Multiple Imputation (MI) technique, i.e. by replacing each missing value with a set of plausible values that represent the uncertainty about the right value to impute; 2) Last Observation Carried Forward (LOCF) Imputation technique, i.e. the last observed non-missing value is used to fill in missing values at a later point in the study. See section 9.3.5 for details.

Safety data will not be subject to any imputation and will be summarized on an observed case basis.

9.2 Background Characteristics

9.2.1 Subject Disposition

For Part A, the summaries of subject disposition will include the number of subjects who were enrolled, who were dosed, who completed Part A of the study, who discontinued from study drug in Part A, and reasons for discontinuation from study drug. Enrolled subject is defined as any screened subject who met the study requirements (inclusion/exclusion criterion) during screening.

For Part B, the summaries of subject disposition will include the number of subjects who were randomized, who were dosed, who completed Part B of the study, who prematurely discontinued, and reasons for premature discontinuation by treatment group. The summary will also be provided by site.

For both Part A and Part B, the number and percentage of subjects in each analysis set will be summarized.

For screen failure subjects, reasons for screen failure will be summarized separately along with the number of subjects who were screened. A screened subject is defined as any subject who signed the study specific informed consent. A screen failure subject is defined as any subject who is screened but failed to meet study requirements (inclusion/exclusion criterion) during screening.

A listing of subject randomization will also be presented.

9.2.2 Demographics and Baseline Characteristics

Demographic data, such as age, gender, race and ethnicity, and baseline characteristics, such as antidepressant use, height, weight, and body mass index (BMI, calculated as weight (kg)/[height (m)²]), will be summarized using the Safety Set.

Hepatitis, human immunodeficiency virus (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 collected at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1 or higher.

Medical/family history data will be summarized by system organ class (SOC) and preferred term (PT) and listed by subject for the Safety Set.

9.2.3 Prior and Concomitant Medications

Concomitant Medications will be recorded throughout the study and will be coded using World Health Organization-Drug dictionary (WHO-DD) September 1, 2016, or later.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken prior to the first dose of study drug. Concomitant medications are defined as those with a start date on or after the first dose of study drug, or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

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

Medication summaries will be performed by anatomical therapeutic chemical (ATC) level 2 term and PT based on the Safety Set.

9.2.4 Study Drug Exposure

Exposure to study drug is defined as total number of days treated with study drug during the study, with total days calculated as last dose date of study drug - first dose date of study drug + 1. The number and percentage of subjects exposed to 20 mg and 30 mg of study drug and discontinued study drug will be presented. Subjects exposed to 30 mg of study drug will be further summarized by the number of days the study drug was received (Part A: <3, 3-7, >7; Part B: 1-14 by day). Study drug exposure will be summarized using the Safety Set.

For Part B, summary of study drug exposure will also be performed based on the subgroup by current antidepressant use status for the Safety Set.

9.2.5 Protocol Deviations

Protocol deviations identified during site monitoring in consultation with Medical Monitor will be captured in a protocol deviation log and categorized. These deviations data for all subjects that violated the clinical study protocol at any time during the study will be listed.

Protocol deviation data for Part B will be summarized by site and treatment group for All Randomized Subjects. Number and percentage of subjects with each protocol deviation type will be presented.

9.3 Efficacy Analysis

The secondary objective of Part A of the study is to determine if SAGE-217 Oral Solution 30 mg given for 14 days reduces the depressive symptoms measured by change from baseline at various time points in HAM-D total score, HAM-D subscale and individual item scores, HAM-A total score, MADRS total score. In addition, HAM-D response; HAM-D remission; and CGI-I response will be assessed.

The secondary objective for Part B of the study is to determine if treatment with SAGE-217 Capsules 30 mg reduces depressive symptoms in subjects with moderate to severe MDD compared to matching placebo measured by change from baseline at various time points in HAM-D total score, HAM-D subscale and individual item scores, HAM-A total score, MADRS total score. In addition, HAM-D response; HAM-D remission; and CGI-I response will be assessed.

9.3.1 Definition of Efficacy Variable(s)

The efficacy variables are defined as follows:

9.3.1.1 Hamilton Rating Scale for Depression (HAM-D)

HAM-D consists of 17 items that will be used to rate the severity of depression in subjects who are already diagnosed as depressed using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Axis I Disorders (SCID-I).

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. Each item is scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression. Item 16 mentioned in Section 11 of the protocol corresponds to item 8 (loss of weight) in the structured interview guide and is scored in a range of 0 to 2. The score for each item will be summed to compute a total score, which ranges from 0 to 52. For Part B, if more than 3.4 individual items are missing, the HAM-D total score will not be calculated and will be left as missing. If less than or equal to 3.4 individual item scores are missing, the missing item scores will be imputed by the mean of all other available item scores, or the maximum possible values for the missing responses, whichever is smaller, to calculate the HAM-D total score.

The HAM-D subscales are Core, Anxiety, Bech-6, and Meier. The Core subscale comprises individual ratings related to the following symptoms: depressed mood, feelings of guilt, suicide, work and activities, and retardation. The Anxiety subscale comprises individual ratings related to the following symptoms: anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), hypochondriasis, and loss of weight. The Bech-6 subscale comprises individual ratings related to the following symptoms: depressed mood, feelings of guilt, work and activities, retardation, anxiety psychic, and somatic symptoms general. The Meier subscale comprises individual ratings related to the following symptoms: depressed mood, feelings of guilt, work and activities, retardation, agitation, and anxiety psychic. The subscale scores will be calculated as the sum of the individual rating scores related to each subscale, divided by the total possible score within the subscale, multiplied by 100, and rounded to a whole number.

Hamilton Rating Scale for Depression response will be defined as having a 50% or greater reduction from baseline in HAM-D total score. Any subject who met this criterion will be defined as a HAM-D Responder.

Hamilton Rating Scale for Depression remission will be defined as having a HAM-D total score of ≤ 7 . Any subject who met this criterion will be defined as a subject in HAM-D remission.

As a measure of the severity of depression, HAM-D total score will be categorized as: 0-7=Normal, 8-16=Mild Depression, 17-23=Moderate Depression, ≥ 24 =Severe Depression.

9.3.1.2 Montgomery-Åsberg Depression Rating Scale (MADRS)

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

Higher MADRS scores indicate more severe depression, and each item yields a score of 0 to 6. The MADRS total score will be calculated as the sum of the 10 individual item scores, which ranges from 0 to 60. If more than two individual items are missing, the MADRS total score will not be calculated and will be left as missing. If less than or equal to two individual item scores are missing, the missing item scores will be imputed by the mean of all other

available item scores, or the maximum possible values for the missing responses, whichever is smaller, to calculate the MADRS total score.

9.3.1.3 Hamilton Anxiety Rating Scale (HAM-A)

The 14-item HAM-A will be used to rate the severity of symptoms of anxiety. Scoring for HAM-A is calculated by assigning scores of 0 (not present) to 4 (very severe). The HAM-A total score will be calculated as the sum of the 14 individual item scores. If more than 2.8 individual items are missing, the HAM-A total score will not be calculated and will be left as missing. If less than or equal to 2.8 individual item scores are missing, the missing item scores will be imputed by the mean of all other available item scores, or the maximum possible values for the missing responses, whichever is smaller, to calculate the HAM-A total score.

As a measure of the severity of anxiety, HAM-A total score will be categorized as follows in the shift table: 0-13=Normal, 14-17 Mild Anxiety, 18-24 Moderate Anxiety, >=25 Severe Anxiety, per the Psych Congress Network.

9.3.1.4 Clinical Global Impression – Severity (CGI-S)

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

9.3.1.5 Clinical Global Impression – Improvement (CGI-I)

The CGI-I employs a 7-point Likert scale to measure the overall improvement in the subject's condition posttreatment. The Investigator will rate the subject's total improvement whether or not it is due entirely to drug treatment. Response choices include: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse.

CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved."

9.3.1.6 Short Form-36 (SF-36)

The SF-36 Health Survey is a subject-reported 36-item instrument for measuring functional health and well-being. The scores are totaled and higher score will indicate a better state of health.

9.3.1.7 The Fatigue Associated with Depression (FAs-D) Patient-Reported Outcome (PRO)

Fatigue is one of the most common symptoms of MDD. The 13-item patient-reported questionnaire was designed to assess fatigue associated with depression in the past week. Three scores are computed:

- A six-item fatigue experience subscale

- A seven-item fatigue impact subscale
- A total score (all 13 items).

The two subscales and the total score are computed as the mean of all answered items within each scale, and each scale score has a possible range of 1 to 5, with higher scores representing greater fatigue.

9.3.1.8 Remission in Depression Questionnaire (RDQ)

The Remission from Depression Questionnaire (RDQ) was developed to capture the broader array of domains considered by subjects to be relevant to the construct of remission symptoms of depression, non-depressive symptoms, features of positive mental health, coping ability, functioning, life satisfaction, and a general sense of well-being. The RDQ is a reliable and valid measure that evaluates the multiple domains that depressed patients consider important in determining remission.

Each item ranges from 0 (not at all or rarely true) to 2 (often or almost always true). Each of the seven subscales is scored separately by taking the sum of scores that are within the same subscale. The score for each item will be summed to compute a total score, which ranges from 0 to 82, where ≤ 27 indicates remission, per the Psych Congress Network. The total score is calculated as the sum of the 41 items.

9.3.1.9 Health-Related Productivity Questionnaire (HRPQ)

The Health-Related Productivity Questionnaire (HRPQ) is a generic measure developed to measure health-related work productivity in patients with a particular disease and/or being treated for the disease. The instrument collects productivity data in terms of absenteeism, presenteeism, and combined lost productivity for three work venues: work outside home, housework, and classes/homework.

9.3.2 Visit Windows

The unscheduled or early termination (ET) visit will be mapped to a scheduled visit for analysis using the date of collection/assessment as a basis to determine study day and then study day will be mapped to the intended visit. The table below contains the visit windows for efficacy analysis.

Once analysis visit windows get assigned, all visits, including scheduled visits, unscheduled visits, and ET visits will be eligible for being flagged as the “analyzed record” within the analysis window, a subject’s individual analysis visit window could potentially contain more than 1 visit. In the event of multiple visits falling within an analysis window or in case of a tie, the following rules will be used in sequence to determine the “analyzed record” for the analysis visit window:

- If there is a scheduled visit/day for the analysis visit window, then the scheduled visit/day data will be used.
- If there is no scheduled visit/day for the analysis visit window, the data closest to the scheduled day/time will be used.

- If there is no scheduled visit/day for the analysis visit window and there is a tie between the data in the number of days/hours before and after the scheduled day, the later data will be used.

The data not flagged as the “analyzed record” will also be listed in subject listings.

Table 1: Visit Windows for Efficacy Analysis, for Both Part A and Part B

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Screening	Day -1	Days (-14) to (-1)
Baseline	Day 1	Day 1
Day 2	Day 2	Day 2
Day 3	Day 3	Day 3
Day 4	Day 4	Day 4
Day 5	Day 5	Day 5
Day 6	Day 6	Day 6
Day 7	Day 7	Day 7
Day 8	Day 8	Day 8
Day 15	Day 15	Day 15
Day 21 (± 1 day)	Day 21	Day 20 - 22
Day 28 (± 3 days)	Day 28	Day 25 - 31
Day 35 (± 3 days)	Day 35	Day 32 - 38
Day 42 (± 3 days)	Day 42	Day 39 - 45

9.3.3 Analysis of Efficacy Variable(s)

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data. For (the open-label) Part A, efficacy data will be summarized descriptively. For Part B, subjects will be analyzed according to randomized treatment group. The Efficacy Set will be used for all efficacy summary tables.

Descriptive statistics including n, mean, SD, median, minimum, and maximum of actual, change from baseline, and percentage change from baseline values will be presented by assessment time point for the following continuous efficacy variables:

- HAM-D total score;
- MADRS total score;
- HAM-D subscale and individual item scores (Note: percentage change from baseline values will not be presented for HAM-D individual item scores);
- HAM-A total score;
- RDQ subscale and total score;

Summaries using descriptive statistics described above will also be performed based on the subgroup by current antidepressant use status for HAM-D total score, MADRS total score and HAM-A total score for Part B.

Descriptive statistics including n, mean, SD, median, minimum, and maximum of actual values and change from baseline will be presented by assessment time point for the following continuous efficacy variables:

- CGI-I (actual value only) and CGI-S scale scores;
- SF-36 subscale scores (Part B only);
- FAs-D subscales and total score (Part B only);

Descriptive statistics including counts and percentages will be summarized by assessment time point for the following categorical efficacy variables:

- HAM-D response;
- HAM-D remission;
- CGI-I response;
- HRPQ response.

Shift analysis pre- and post-treatment will be presented for the following depression categories (0-7 normal, 8-16 mild depression, 17-23 moderate depression, ≥ 24 severe depression) based on sum scores from the first 17 items of the HAM-D rating scale. Shift analysis for the following anxiety categories (0-13=Normal, 14-17 Mild Anxiety, 18-24 Moderate Anxiety, ≥ 25 Severe Anxiety) will also be presented based on the 14-item HAM-A rating scale total score.

Change from baseline and percentage change from baseline in HAM-D, HAM-A, and MADRS total score over time will be presented graphically overall for Part A and by study treatments for Part B. Plots of change from baseline in HAM-D, MADRS and HAM-A total score over time will also be performed based on the subgroup by current antidepressant use status for Part B.

9.3.3.1 Mixed Effects Model for Repeated Measures

For Part B of the study, the change from baseline for HAM-D total score will be analyzed using a mixed effects model for repeated measures (MMRM).

The model will include the change from baseline at each visit as the dependent variable. Treatment, baseline HAM-D total score, center, antidepressant use strata, assessment time point, and time point-by-treatment interaction will be included as explanatory variables in the model. All explanatory variables including center will be treated as a fixed effect. The main comparison will be (difference in least mean square [LSMEAN]) between SAGE-217 Capsules and placebo at the 15-day timepoint.

Model-based point estimates (i.e, LSMEAN, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. Compound symmetry covariance structure will be used if there is a convergence issue with the unstructured covariance model.

See sample SAS code for MMRM in section [15.2](#).

Similarly, an MMRM will be used for the analysis of the following variables: changes from baseline in MADRS total score and HAM-A total score, and select individual item and subscale scores. For each model, the comparison of interest will be between SAGE 217 Capsules and matching placebo at the 15-day time point. However, model-based point estimates (i.e, LS means), 95% confidence intervals, and p-values will be reported for all time points.

9.3.3.2 HAM-D Response and HAM-D Remission Analyses

At each visit during the treatment period (Day 2 - Day 8) and at the first follow-up visit (Day15/ET), a subject will be classified as a responder to the study drug if the subject is having a 50% or greater reduction from baseline in HAM-D total score. These binary outcome variables are expected to be correlated rather than independent. The correlated binary outcome variables will be analyzed using the SAS GENMOD procedure that implemented the generalized estimating equations (GEE) approach.

The models will include the response at each of the 8 visits as the dependent variable. The center, treatment, antidepressant use strata, baseline HAM-D total score, assessment time point, and time point-by-treatment will be included as explanatory variables.

The GEE marginal model approach allows to estimate the odds ratio of a response for the subjects who receive SAGE-217 versus the placebo. Odds ratios, 95% confidence intervals, and p-values will be reported. For the model parameters estimation, the following working correlation structures for the binary outcome variables will be assumed: Independence, exchangeable, and unstructured.

At each visit during the treatment period (Day 2 - Day 8) and at Day 15/ET, a subject will be classified as a HAM-D remitter to the study drug if the subject is having a HAM-D total score of ≤ 7 . This correlated binary outcome variable will be analyzed using the SAS GENMOD procedure that implemented the GEE approach as described above.

At Day 2, Day 3, Day 8 and at Day 15/ET, a subject will be classified as a CGI-I responder to the study drug if the subject is having a CGI-I score of “very much improved” or “much improved.” The correlated binary outcome variable will be analyzed similarly as HAM-D responder and HAM-D remitter. For the CGI-I response analysis, baseline CGI-S score will be included in the model.

See sample SAS code for GEE model in section [15.2](#).

9.3.4 Supportive Analysis

A MMRM methods similar to those described in section 9.3.3.1 will be used to study the heterogeneity of study drug effect by considering center and treatment-by-center effects to be random. This supportive analysis applies to HAM-D total score and MADRS total score.

A subset analysis based on subjects that had negative serum drug screening results will be performed for HAM-D total score, HAM-D response and HAM-D remission. The subset analysis will include:

- Descriptive statistics including n, mean, SD, median, minimum, and maximum of actual, change from baseline, and percentage change from baseline values for HAM-D total score;
- MMRM methods similar to those described in section 9.3.3.1 for HAM-D total score;
- Descriptive statistics including counts and percentages for HAM-D response and HAM-D remission.

9.3.5 Sensitivity Analysis

A sensitivity analysis will be used to investigate the impact of missing data if $\geq 5\%$ of subjects have missing data in primary efficacy endpoint assessment (i.e., HAM-D total score) or key secondary endpoint assessment (i.e., MADRS total score). Two techniques will be considered for the sensitivity analysis:

1) Multiple Imputation (MI) technique, i.e. by replacing each missing dependent value with a set of plausible values that represent the uncertainty about the right value to impute, will be considered for the sensitivity analyses. In our case, since we assume arbitrary missing pattern and the variables to be imputed are continuous, a fully conditional specification (FCS) regression method that is available in SAS will be used.

The imputed datasets generated with the approach described above do contain only non-missing value and are used as input in the model for the sensitivity analysis. MMRM similar as described in section 9.3.3.1 will thus be run on each of the generated imputed datasets and the treatment difference between SAGE-217 Capsules and matching placebo at the end of the treatment period (Day 15/ET) will be estimated. Finally, the results will be combined from these several imputed datasets to derive overall estimates. In addition to the estimates, corresponding 95% confidence intervals and p-values will be calculated.

2) Last Observation Carried Forward (LOCF) Imputation technique, i.e., the last observed non-missing value will be used to fill in missing values at a later point in the study, regardless of when the missing value occurred.

The imputed dataset generated with the LOCF technique will be used as input data in the MMRM similarly as described in section 9.3.3.1. The treatment difference between SAGE-217 Capsules and matching placebo at the end of the treatment period (Day 15/ET) will be estimated. Model-based point estimates (i.e., LS means), 95% confidence intervals, and p-values will be reported.

The Efficacy Set will be used for the sensitivity analyses. See sample SAS code for MI in section 15.2.

9.4 Safety Analysis

The primary endpoint is the safety and tolerability of SAGE-217, as evaluated by adverse events, concomitant medication usage, changes from baseline in physical examination, vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Sedation will be assessed using the SSS. Safety data will be listed by subject and

summarized descriptively in Part A and by study drug in Part B. All safety summaries will be performed on the Safety Set. All safety data will be presented in subject data listings.

The safety endpoints and variables considered in the summary tables for this study are summarized in Table 2.

Table 2: Safety endpoints and variables in the summary tables

Safety Evaluation	Incidence	Actual Value	Change from Baseline	Abnormality/Clinical Significance (CS)	Potentially Clinical Significance (PCS)
AEs	X				
Con Meds	X	*			
Labs		X	X	*	X
ECG		X	X	*	X
Vital Signs		X	X		X
PE		*			
C-SSRS	X	*			
SSS		X	X		

Note: PCS criteria are outlined in sections 9.4.2-9.4.4

X = Safety Assessment will be summarized in tables

* = Safety Assessment will be presented in individual subject data listings

9.4.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset after the start of study drug, or any worsening of a pre-existing medical condition/adverse event with onset after the start of study drug and until 7 days after the last dose.

All adverse events will be coded using MedDRA version 19.1 or higher and summarized by SOC and PT. Multiple occurrences of an AE are counted only once per subject per SOC and PT for summary tables.

Summary tables of TEAEs will be presented and will summarize the number and percentage of subjects for the following:

- Any TEAE
- TEAEs by relationship to study drug (not related, related)
- TEAEs by severity
- Serious AEs (SAEs)
- TEAEs that resulted in discontinuation of study drug
- TEAEs that resulted in discontinuation of study drug based on the subgroup by current antidepressant use status (Part B only)
- TEAEs that resulted in dose adjustment (Part B only)
- TEAEs that resulted in dose adjustment based on the subgroup by current antidepressant use status (Part B only)

- Overall summary of the number and percentage of subjects reporting TEAEs, drug-related TEAEs, severe TEAEs, serious AEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death
- Summary of the number and percentage of subjects reporting one event, moderate or severe events, severe events, related events, serious events, drug-related serious events, events leading to dose adjustments, and events leading to study drug discontinuation (Part B only).

Subjects will be counted only once within each SOC and PT at the maximum severity in the following order: severe, moderate, and mild. An AE with missing severity will be considered as a severe AE. Subjects will be counted only once within each SOC and PT at the strongest relationship to study drug in the following order: related, not related to study drug. If the relationship between the adverse event and the study drug is determined to be “possible” or “probable”, the event will be considered to be related to the study drug. An AE with missing relationship to study drug will be considered as related to study drug. For Part A, the incidences will be presented by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT based on the subject count in the SAGE-217 column. For Part B, the incidences will be presented in alphabetical order of SOC and then, within a SOC, by overall descending frequency of PT based on the subject count for the SAGE-217 Capsules study drug column. Incidences will also be presented in order of decreasing frequency of the SAGE-217 Capsules group by PT only.

All adverse events and serious adverse events (including those with onset or worsening before the start of study drug) through the Day 28 follow-up visit (Part A) or Day 42 follow-up visit (Part B) will be listed.

9.4.2 Clinical Laboratory

Clinical laboratory results will be listed by subject and timing of collection.

Hematology tests will include complete blood count, including red blood cells, white blood cells with differentiation, hemoglobin, hematocrit, reticulocytes, and platelets. The coagulation panel will include activated partial thromboplastin time, prothrombin time, and international normalized ratio. Serum chemistry tests will include serum electrolytes; renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide; liver function tests, including alkaline phosphatase, total bilirubin, aspartate aminotransferase, and alanine aminotransferase; total protein; albumin; and thyroid stimulating hormone. Urinalysis will include assessment of protein, blood, glucose, ketones, bilirubin, urobilinogen, hemoglobin, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity.

Summary tables will include descriptive statistics for the actual values and changes from baseline by study visit (Day) in hematology, serum chemistry, coagulation and quantitative urinalysis test results and overall in Part A and by study treatments in Part B. Out-of-range values will be flagged as low, high, or abnormal, where applicable, in the subject data listings.

For qualitative urinalysis parameters, test results will be categorized as normal and abnormal. Frequency counts and percentages will be presented over time for these categorical data in Part A and by treatment group in Part B.

The number and percentage of subjects with PCS values in hematology, serum chemistry and quantitative urinalysis tests will be summarized by treatment and visit and listed in Part B. Potentially clinically significant values will be identified for specific laboratory parameters as outlined in the following table.

Laboratory Parameter	Gender	Units	Criteria for PCS Values (Actual values)	
			High	Low
Hemoglobin	Male	g/L	>185	<125
	Female	g/L	>165	<110
Hematocrit	Male	Fraction of 1	>0.504	<0.415
	Female	Fraction of 1	>0.446	<0.359
Platelet count		10 ⁹ /L	>600	<125
WBC		10 ⁹ /L	>15	<2.5
Basophils		10 ⁹ /L	>0.5	NA
Eosinophils		10 ⁹ /L	>1.5	NA
Neutrophils		10 ⁹ /L	NA	<1.5
Lymphocytes		10 ⁹ /L	>6.0	<0.5
Monocytes		10 ⁹ /L	>1.4	NA
Bilirubin		μ/L	>2xULN	NA
Albumin		g/L	>70	<28
Aspartate Aminotransferase		U/L	>3xULN	NA
Alanine Aminotransferase		U/L	>3xULN	NA
Alkaline Phosphatase		U/L	>1.5xULN	NA
Creatinine (μmol/L)		μmol/L	>141.4	NA
Sodium		mmol/L	>145	<132
Potassium		mmol/L	>5.2	<3.5
Carbon dioxide		mmol/L	>30	<18
Chloride		mmol/L	>120	<90
Occult Blood			>=2+	NA
Urine Glucose			>=1+	NA
Urine Protein			>=1+	NA

Shift analysis pre- and post-treatment will be presented for the following laboratory categories: low, normal and high.

All parameters will be converted to consistent units according to the International System of Units (SI) before summarization.

9.4.3 Electrocardiogram

The following ECG parameters will be listed for each subject: heart rate (bpm), PR (msec), QRS (msec), QT (msec), QTc (msec) interval calculated using the Fridericia method (QTcF). Any clinically significant abnormalities or changes in ECGs should be listed as an adverse event. Electrocardiogram findings will be listed by subject and visit.

QTcF (msec) is calculated as: $QT (msec) / RR^{1/3}$, where $RR (msec) = 60000 / \text{heart rate (bpm)}$.

The actual value at each time point and change from baseline at each post-baseline time point will be summarized overall in Part A and by study drug in Part B. The number and percentage of subjects with 'normal', 'abnormal, not clinically significant' and 'abnormal, clinically significant' ECG results will be summarized at baseline and each post-baseline time point.

QT and QTcF will be categorized into the following groups:

- Maximum value > 450 msec
- Maximum value > 480 msec
- Maximum value > 500 msec

The maximum positive change from baseline in QTcF and QT will be categorized into following groups:

- >30 msec increase
- >60 msec increase

The number and percent of subjects who meet the above threshold criteria will be tabulated. Additionally, the number and percentage of subjects with PCS and potentially clinically significant change (PCSC) values will be summarized by treatment and visit and listed in Part B. Potentially clinically significant values will be identified for ECG parameters as outlined in the following table.

ECG	Units	Criteria for PCS Values (Actual values)		Criteria for PCSC values (Change from Baseline)	
		High	Low	Increase	Decrease
QT Interval	msec	>450 >480 >500	NA	>30 >60	NA
QTcF Interval	msec	>450 >480 >500	NA	>30 >60	NA

Note: If the assessment is ‘Abnormal, clinically significant’, the event is reported as adverse event if identified after the date of informed consent; and any clinically significant abnormality at screening as judged by the investigator should be recorded in the medical history.

9.4.4 Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for vital signs (respiratory rate (breaths/minute), oral temperature (degrees C), supine systolic blood pressure (mmHg), supine diastolic blood pressure (mmHg), standing systolic blood pressure (mmHg), and standing diastolic blood pressure (mmHg) by time point. Vital sign results will be listed by subject and timing of collection. The actual value at each time point and change from baseline at each post-baseline time point will be summarized overall in Part A and by study drug in Part B.

Blood pressure and heart rate will be categorized into the following groups:

- Systolic blood pressure:
 - Minimum value < 90 mmHg
- Diastolic blood pressure:
 - Minimum value < 50 mmHg
- Heart rate:
 - Minimum value < 40 bpm
 - Maximum value >120 bpm
 -

Change from baseline in blood pressure and heart rate will be categorized into following groups:

- Systolic blood pressure:
 - Maximum increase from Baseline ≥ 30 mmHg
 - Maximum decrease from Baseline ≥ 30 mmHg
- Diastolic blood pressure:
 - Maximum increase from Baseline ≥ 20 mmHg
 - Maximum decrease from Baseline ≥ 20 mmHg

The number and percent of subjects who meet the above threshold criteria will be tabulated. Additionally, the number and percentage of subjects with PCS and PCSC values will be summarized by treatment and visit and listed in Part B. Potentially clinically significant values will be identified for vital sign parameters as outlined in the following table.

Vital Sign	Units	Criteria for PCS Values (Actual values)		Criteria for PCSC values (Change from Baseline values)	
		High	Low	Increase	Decrease
Heart rate	Beats/m in	>120	<40	NA	NA
Systolic Blood Pressure (supine and standing)	mmHg	NA	<90	≥30	≥30
Diastolic Blood pressure (supine and standing)	mmHg	NA	<50	≥20	≥20

9.4.5 Physical Examination

All physical examinations data in Parts A and B will be listed.

Note: Any clinically significant abnormalities that are new or worsened are recorded as an adverse event.

9.4.6 Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidality data collected on the C-SSRS at baseline and by visit during the Treatment Period will be listed for all subjects. Listings will include all data collected on the C-SSRS. In addition, the number and percentage of subjects with a response of ‘Yes’ to any C-SSRS Suicidal Ideation or Suicidal Behavior item will be presented in a table.

9.4.7 Stanford Sleepiness Scale (SSS)

The SSS is subject-rated scale designed to quickly assess how alert a subject is feeling. Degrees of sleepiness and alertness are rated on a scale of 1 to 7, where the lowest score of ‘1’ indicates the subject is ‘feeling active, vital, alert, or wide awake’ and the highest score of ‘7’ indicates the subject is ‘no longer fighting sleep, sleep onset soon; having dream-like thoughts’.

Sedation data collected on the SSS will be listed for all subjects. Spaghetti plots of actual value over time during inpatient days (Day 1 through Day 7) will be represented graphically. The actual value at each time point and change from baseline at each post-baseline time point will be summarized overall in Part A and by treatment group in Part B. In addition, the number and percentage of subjects at each SSS scale rating will be presented. Spaghetti plots and summary table will also be performed based on the subgroup by current antidepressant use status for Part B.

9.5 Pharmacokinetic Analysis

PK analyses will be performed for the PK Set.

9.5.1 Collection schedule

Plasma samples for PK analysis in Part A and Part B will be collected predose on Days 2, 3, 4, 5, and 6, predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15.

The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. Plasma samples for PK analysis will be collected per protocol.

9.5.2 Derived PK parameters

Non-compartmental PK parameters for SAGE-217 will be calculated using Phoenix WinNonlin 6.4 or higher version. Actual sampling times will be used in the determination of the individual PK parameters. Linear up log down method will be used for derivation of AUC.

The following PK parameters will be derived (where possible):

Table 3: PK parameters and definitions

AUC_{0-t} (or AUC)	Area under the plasma concentration time curve up to time t
AUC_{∞}	AUC from time 0 to infinity
C_{max}	Maximum (peak) plasma concentration
T_{max}	Time at maximum (peak) plasma concentration
$t_{1/2}$	Elimination half-life (where possible)
C_{ss} (or $C_{avg,ss}$)	Steady-state drug concentration in the plasma during oral intake, the dosing interval will be considered as 24 hours

9.5.3 Handling of dropouts or missing data

Missing concentration data for all subjects who are administered scheduled study treatment will be considered as non-informative missing and will not be imputed.

The following rules will apply for the derivation of all kinds of AUCs:

- Pre-dose concentration values below the assay's limit of quantification (BLQ) will be treated as zero.
- The sampling time relative to dosing for pre-dose samples will also be treated as zero.

- Post-dose BLQ values will be set to missing.

If the actual time of sampling is missing, the planned time may be used.

9.5.4 Summary statistics

The plasma concentrations along with time point deviation from scheduled time will be listed by subject.

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics separately for Part A and B. Time at maximum (peak) plasma concentration (t_{\max}) will be summarized using n, mean, SD, median, minimum, and maximum. All other PK parameters will be summarized using n, mean, SD, geometric mean, geometric coefficient of variation, coefficient of variation, median, minimum, and maximum and listed by subject. For Part B, summary analysis using descriptive statistics will also be performed based on the subgroup by current antidepressant use status.

9.5.5 Data presentation

The descriptive statistics will be generated as discussed above in Section 9.5.4.

The following figures will be produced:

- Mean \pm SD plasma concentration-time profiles for Day 7 will be plotted on linear and semi-log scales separately for Part A and B
- Individual subject concentration-time profiles on linear and semi-logarithmic concentration scales separately for Part A and B
- Individual subject concentration-time profiles on linear scale based on the subgroup by current antidepressant use status for Part B
- Spaghetti plots for each study drug on Day 7 separately for Part A and B (linear and semi-logarithmic scale)
- Spaghetti plots for each study drug on Day 7 on linear scale based on the subgroup by current antidepressant use status for Part B

10 SUMMARY OF INTERIM AND DMC ANALYSES

Not applicable

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15 LIST OF APPENDICES

15.1 Appendix A: Schedule of Assessments

Table 3: Schedule of Events (Part A)

	Screening Period	Open-Label Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D -7 to -1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)
Study Procedure																		
Informed Consent	X																	
Inclusion/Exclusion	X	X																
Demographics	X																	
Medical/Family History	X																	
SCID-I	X																	
Confinement		X							(X)									
Physical Examination	X								X							X	X	X
Body Weight/Height	X															X (wt only)	X (wt only)	X (wt only)
Clinical Laboratory Assessments ^b	X								X							X	X	X
Drug & Alcohol Screen ^c	X	X																
Pregnancy Test ^d	X	X														X ^e		X
Hepatitis & HIV Screen	X																	
Blood Sample ^f	O								O							O		
Genetic Sample ^g	O																	
Vital Signs ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry		X	X	X	X	X	X	X	X									
12-Lead ECG ⁱ	X	X	X					X							X		X	
C-SSRS ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S ^k	X	X	X	X					X							X	X	X

	Screening Period	Open-Label Treatment Period														Follow-up Period		
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT		
Visit Days	D -7 to -1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)
Study Procedure																		
CGI-I ^k			X	X					X							X	X	X
HAM-A ^k	X	X	X	X					X							X	X	X
HAM-D ^k	X	X	X	X	X	X	X	X	X							X	X	X
MADRS ^k	X	X	X	X	X	X	X	X	X							X	X	X
SSS ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Plasma PK ^m			X	X	X	X	X	X	X						X	X		
Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse Events	X																	
Prior/Concomitant Medications ⁿ	X																	

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ET = early termination; ECG = electrocardiogram; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; MADRS = Montgomery-Åsberg Depression Rating Scale; PK = pharmacokinetic; SCID-I = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Axis I Disorders; SSS = Stanford Sleepiness Scale; wt = weight

*D1 procedures are to be completed prior to dosing

^a Outpatient visits may take place at the subject's residence or in the clinic.

^b Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning on Days 8 and 15 and during the follow-up visits on Day 21 and Day 28.

^c Urine toxicology for selected drugs of abuse and serum or breath test for alcohol.

^d Serum pregnancy test at screening and urine pregnancy test at Day 1 and Day 28.

^e Female subjects who prematurely discontinue will have a pregnancy test performed at the ET visit.

^f An optional blood sample for hormone and exploratory biochemistry testing, where consent is given.

^g An optional genetic sample for biomarker testing, where consent is given.

^h Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ±5 minutes of the scheduled time point through 0.5 hours after dosing and ±30 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between the hours of 23:00 h and 06:00 h. From Day 1 through Day 7, vital signs will be completed at the following time points: predose, 0.25, 0.5, 1, 2, and 12 hours after dosing. During the outpatient treatment period, vital signs will be completed prior to dosing and 1 hour after dosing. Vital signs may be repeated at the discretion of the Investigator or Visiting Home Healthcare Provider as clinically indicated.

ⁱ Will be performed 1 hour ±15 minutes after dosing on Days 1, 2, 7, and 14, and during the follow-up visit on Day 21.

- ^j The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- ^k To be completed to be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28. The assessment timeframe for HAM-D and HAM-A scales will refer to the past 7 days (1 week) on Screening, Day 1, Day 15/ET, Day 21, and Day 28 visits, and the past 24 hours on visits occurring on Days 2 through 8.
- ^l To be completed within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between 23:00 h and 06:00 h during the inpatient treatment period. From Day 1 through Day 7, SSS will be completed at the following time points: predose, 0.25, 0.5, 1, and 2 hours after dosing. During the outpatient treatment period, SSS will be completed prior to dosing and 1 hour after dosing.
- ^m Plasma samples for PK analysis in Part A and Part B will be collected predose on Days 2, 3, 4, 5, and 6, predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. Plasma samples for PK analysis will be collected per protocol and subjects may need to be awoken for sample collection.
- ⁿ To include those taken within 30 days prior to informed consent and throughout the study.

Table 4: Schedule of Events (Part B)

	Screening Period	Double-Blind, Placebo-Controlled Treatment Period														Follow-up Period				
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT				
Visit Days	D -14 to -1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)	D35 (±3d)	D42 (±3d)
Study Procedure																				
Informed Consent	X																			
Inclusion/Exclusion	X	X*																		
Demographics	X																			
Medical/Family History	X																			
SCID-I	X																			
Randomization		X*																		
Confinement		X							(X)											
Physical Examination	X								X							X				X
Body Weight/Height	X															X (wt only)	X (wt only)	X (wt only)	X (wt only)	X (wt only)
Clinical Laboratory Assessments ^b	X								X							X	X	X	X	X
Drug & Alcohol Screen ^c	X	X*																		
Pregnancy Test ^d	X	X*														X ^e				X
Hepatitis & HIV Screen	X																			
Blood Sample ^f	O								O							O				
Genetic Sample ^g	O																			
Vital Signs ^h	X	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry		X*	X	X	X	X	X	X	X											
12-Lead ECG ⁱ	X	X	X					X							X		X			

	Screening Period	Double-Blind, Placebo-Controlled Treatment Period														Follow-up Period				
Visits	OUTPATIENT	INPATIENT							INPATIENT or OUTPATIENT ^a							OUTPATIENT				
Visit Days	D -14 to -1	D1*	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15/ ET	D21 (+1d)	D28 (±3d)	D35 (±3d)	D42 (±3d)
Study Procedure																				
C-SSRS ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S ^k	X	X*	X	X					X							X	X	X	X	X
CGI-I ^k			X	X					X							X	X	X	X	X
HAM-A ^k	X	X*	X	X					X							X	X	X	X	X
HAM-D ^k	X	X*	X	X	X	X	X	X	X							X	X	X	X	X
MADRS ^k	X	X*	X	X	X	X	X	X	X							X	X	X	X	X
SF-36 ^k		X*							X							X				X
FAs-D ^k		X*							X							X				X
RDQ ^k		X*														X				X
HRPQ ^k		X*														X				X
SSS ^l	X	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Plasma PK ^m			X	X	X	X	X	X	X						X	X				
Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Adverse Events	X																			
Prior/Concomitant Medications ⁿ	X																			

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ET = early termination; ECG = electrocardiogram; FAs-D = fatigue associated with depression; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; HRPQ = Health-Related Productivity Questionnaire; MADRS = Montgomery-Asberg Depression Rating Scale; PK = pharmacokinetic; RDQ = Remission in Depression Questionnaire; SCID-I = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Axis I Disorders; SF-36 = 36-item short form survey; SSS = Stanford Sleepiness Scale; wt = weight

*D1 procedures are to be completed prior to dosing

^a Outpatient visits may take place at the subject's residence or in the clinic.

- ^b Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning on Days 8 and 15 and during the follow-up visits on Day 21, Day 28, Day 35, and Day 42.
- ^c Urine toxicology for selected drugs of abuse and serum or breath test for alcohol.
- ^d Serum pregnancy test at screening and urine pregnancy test at Day 1 and Day 42.
- ^e Female subjects who prematurely discontinue will have a pregnancy test performed at the ET visit.
- ^f An optional blood sample for hormone and exploratory biochemistry testing, where consent is given.
- ^g An optional genetic sample for biomarker testing, where consent is given.
- ^h Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 30 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between the hours of 23:00 h and 06:00 h. From Day 1 through Day 7, vital signs will be completed at the following time points: predose, 0.25, 0.5, 1, 2, and 12 hours after dosing. During the outpatient treatment period, vital signs will be completed prior to dosing and 1 hour after dosing. Vital signs may be repeated at the discretion of the Investigator or Visiting Home Healthcare Provider as clinically indicated.
- ⁱ Will be performed 1 hour ± 15 minutes after dosing on Days 1, 2, 7, and 14, and during the follow-up visit on Day 21.
- ^j The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at any time of day at all subsequent time points.
- ^k To be completed at 8:00 AM (± 30 minutes) at each scheduled time point during the Treatment Period, and in the morning on Day 15, Day 21, and Day 28. The assessment timeframe for HAM-D and HAM-A scales will refer to the past 7 days (1 week) on Screening, Day 1, Day 15/ET, Day 21, Day 28, Day 35 and Day 42 visits, and the past 24 hours on visits occurring on Days 2 through 8.
- ^l To be completed within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater, unless the subject is asleep between 23:00 h and 06:00 h during the inpatient treatment period. From Day 1 through Day 7, SSS will be completed at the following time points: predose, 0.25, 0.5, 1, and 2 hours after dosing. During the outpatient treatment period, SSS will be completed prior to dosing and 1 hour after dosing.
- ^m Plasma samples for PK analysis in Part A and Part B will be collected predose on Days 2, 3, 4, 5, and 6, predose and 0.25, 0.5, 1, 2, 10, and 12 hours postdose on Day 7 (within ± 5 minutes of the scheduled time point through 0.5 hours after dosing and ± 15 minutes of the scheduled time point from 1 hour after dosing and greater), prior to discharge on Day 8 for subjects being discharged or 16 hours postdose for subjects remaining as inpatients, predose on Day 14, and in the morning on Day 15. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. In the event of a dose adjustment, an unscheduled PK sample should be collected just prior to the dose change. Plasma samples for PK analysis will be collected per protocol and subjects may need to be awoken for sample collection.
- ⁿ To include those taken within 30 days prior to informed consent and throughout the study.

15.2 Appendix B: Details of Statistical Methodology

Sample SAS code for Mixed Effects Model for Repeated Measures (MMRM):

```
proc mixed data=&data;  
by param;  
class trtan avisitn siteid usubjid strata;  
model chg=base siteid trtan strata avisitn trtan*avisitn / ddfm=kr s;  
repeated avisitn / subject=usubjid type=un;  
lsmeans trtan*avisitn /cl pdiff e;  
estimate 'SAGE-217 vs PLACEBO at day 15' trtan 1 -1 trtan*avisitn 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 / cl;  
run;
```

Note: if convergence not met, use type=cs instead

Sample SAS code for Generalized Estimating Equation (GEE):

```
proc genmod data=&data;  
by param;  
class usubjid trtan siteid strata avisitn;  
model aval=base siteid trtan strata avisitn trtan*avisitn/dist=bin link=logit;  
repeated subject=usubjid / type=un; * if convergence not met, use type=exch;  
lsmeans trtan*avisitn / diff exp cl;  
estimate 'SAGE-217 vs PLACEBO at day 15' trtan 1 -1 trtan*avisitn 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 / exp cl;  
run;
```

Note: for HAM-D Remission, the Day 2 visit and siteid will be excluded from the model due to too few subjects for model convergence.

Sample SAS code for Multiple Imputation (MI):

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```
proc mi data=&data seed=xxxx nimpute=4 round=. . . 1 1 1 1 1 1 1 1 1 1 1 1 out=fcs_reg;  
class trtan strata;  
fcs discrim (trtan strata /details classeffects=include);  
fcs nbiter=20 reg (base day2 day3 day4 day5 day6 day7 day8 day15 day21 day28 day35 day42/details);  
var trtan strata base day2 day3 day4 day5 day6 day7 day8 day15 day21 day28 day35 day42;  
run;
```