Statistical Analysis Plan

Methods

Protocol Number 217-MDD-201 / NCT03000530

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 $\leqslant 7$);
- 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 ($t_{½}$), 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
    - CGII 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}, $t_{½}$, 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 $\geqslant$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 $\geqslant$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 $\geqslant$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 $\geqslant$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
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 effect 3. 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"). 4. 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	1. All physical examinations data in Parts A and B will be listed. 2. 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 3. 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. 4. 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 pro-rating 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 $\geqslant$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 $\leqslant 7$. 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 $\leqslant$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 $\leqslant 7$. 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 ⩾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 / 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/min	>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 ± 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

11 INDEX OF TABLES

11.1 Part A

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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 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 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):

```
proc mi data=&data seed=xxxx nimpute=4 round=. . . . 1 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;
```