Official Title:	**A Phase 3, Randomized, Double-Blind Study Comparing the Efficacy and Safety of SAGE-217 Plus an Antidepressant Versus Placebo Plus an Antidepressant in Adults With Major Depressive Disorder**
NCT Number:	NCT04476030
Document Date:	SAP Version 1.0 : 11 January 2022

9. DOCUMENTATION OF STATISTICAL METHODS

The following statistical analysis plan is provided:

Statistical analysis plan Version 1.0, 11 January 2022

STATISTICAL ANALYSIS PLAN METHODS

Protocol Number 217-MDD-305

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

Author of SAP: [redacted] **and** [redacted]

Version: 1.0

Version Date of SAP: 11 Jan 2022

Sponsor:

Sage Therapeutics, Inc.

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Cambridge, Massachusetts 02142

Authorization Signature Page

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

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[redacted], PhD, [redacted]

Date

Sage Therapeutics, Inc.

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1. LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
AE	adverse event
AR	autoregressive
ATC	anatomical therapeutic chemical
ADT	Antidepressant therapy
BMI	body mass index
CGI-I	Clinical Global Impression scale for improvement
CGI-S	Clinical Global Impression scale for severity
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FAS	Full Analysis Set
GEE	generalized estimating equation
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Depression Rating Scale
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
ICF	informed consent form
IP	Investigational product
IRT	interactive response technology
LFT	Liver Function Tests
LLOQ	Lower limit of quantification
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MMRM	mixed effects model for repeated measures
MedDRA	Medical Dictionary for Regulatory Activities
PCS	potentially clinically significant
PCSC	potentially clinically significant change
PHQ-9	Patient Health Questionnaire
[redacted]	[redacted]

Abbreviation or specialist term	Explanation
PRO	patient-reported outcome
PT	preferred term
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
[redacted]	[redacted]
SI	International System of Units
SNRI	serotonin-norepinephrine reuptake inhibitor
SOC	System Organ Class
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
UN	unstructured

2. INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis of data from 217-MDD-305 study, and is based on clinical study protocol, version 4.0, dated 10 Jan 2022.

The purpose of the SAP is to describe in detail the statistical methodology and analyses to be conducted for 217-MDD-305 protocol. The SAP will be finalized and approved before the database lock.

Any changes made to this SAP after the clinical database lock has occurred will be documented and discussed in the clinical study report for this study.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of Study 217-MDD-305 is to evaluate the efficacy of SAGE-217 plus an antidepressant in the treatment of major depressive disorder (MDD) compared to placebo plus an antidepressant.

3.2. Secondary Objective

The secondary objectives of Study 217-MDD-305 are:

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

[redacted]

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 3.

4.1.2. Secondary Efficacy Endpoints

4.1.2.1. Key Secondary Efficacy Endpoint

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

4.1.2.2. Other Secondary Efficacy Endpoints

- Change from baseline in HAM-D total score at Day 15 and Day 42
- Change from baseline in HAM-D total score around end of blinded treatment (using equal weights for the scheduled visits –Day 12, Day 15, Day 18)
- HAM-D response at Day 15 and Day 42
- HAM-D remission at Day 15 and Day 42
- Change from baseline in Clinical Global Impression – Severity at Day 15
- CGI-I response, defined as “much improved” or “very much improved”, at Day 3 and Day 15
- Change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15
- MADRS response at Day 15
- MADRS remission at Day 15
- Change from baseline Hamilton Rating Scale for Anxiety (HAM-A) total score at Day 15
- Time to first HAM-D response
- Change from baseline in depressive symptoms at Day 15, as assessed by the PHQ-9

4.2. Other Endpoints

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

5. STUDY DESIGN

5.1. Overall Design

This is a randomized, double-blind, parallel-group, placebo-controlled study in adults with MDD. The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Clinical Trial Version (SCID 5-CT) performed by a qualified healthcare professional.

The study will consist of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a 28-day Antidepressant (ADT) Continuation Period. Upon meeting the eligibility criteria (including, but not limited to, not having taken any antidepressant within 30 days prior to Day 1 or taken fluoxetine within 60 days prior to Day 1), participants will be randomized to receive blinded investigation product (IP; SAGE-217 or placebo) for administration each evening from Day 1 through 14. In addition, all participants will receive 1 of 2 classes of ADTs: a selective serotonin reuptake inhibitor (SSRI; sertraline, escitalopram, citalopram) or a serotonin-norepinephrine reuptake inhibitor (SNRI; duloxetine or desvenlafaxine) in an open-label manner from Day 1 through the end of the study. The ADT will be administered per labeled prescribing information. The investigator will assign 1 of the 5 ADTs based on clinical standard of care; the participant must not have been previously treated with the assigned ADT within the current depressive episode. Randomization will be stratified by ADT class (SSRI or SNRI). Blinded IP (SAGE-217 or placebo) dosing starts with 50 mg on Day 1; the dose may be reduced for safety/tolerability concerns (at the discretion of the investigator) to 40 mg any time during the 14-day Treatment Period.

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

Participants will self-administer IP once daily at approximately 8 PM with fat-containing food (eg, within 1 hour of an evening meal which contains fat, or with a fat-containing snack), on an outpatient basis, for 14 days. ADT and SAGE-217 or placebo will be administered at the same time during the Treatment Period; participants assigned duloxetine will also administer ADT in the morning (for twice-daily dosing) as part of a divided dose for the first 7 days. Participants will return to the study center as outlined in the Schedule of Assessments. Blinded IP will be administered as 2 capsules per dose each evening. Participants who cannot tolerate the 40-mg blinded IP dose may be discontinued from

blinded IP at the discretion of the investigator. If blinded IP is discontinued, ADT may be continued at the discretion of the investigator.

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

5.2. Sample Size and Power

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

5.3. Randomization

This is a randomized, double-blind, placebo-controlled study. Participants who meet the eligibility criteria will be randomized in a 1:1 ratio to receive SAGE-217 50 mg plus assigned ADT or matched placebo plus assigned ADT. The randomization is stratified by the class of ADT use – SSRI or SNRI.

Randomization schedules will be generated by an independent statistician. The allocation to treatment group (SAGE-217 50 mg, or placebo) will be based on the randomization schedule. Randomization will be performed centrally via an interactive response technology (IRT) system.

5.4. Blinding and Unblinding

This is a randomized, double-blind, placebo-controlled study. The Sponsor, site personnel and participants will remain blinded until the database lock, after all participants complete the Day 42 visit.

During the study, the blind is to be broken by the Investigator via the IRT system only when the safety of a participant is at risk and the treatment plan is dependent on the blinded IP received. In all cases where the blinded IP allocation for a participant is unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's records and on the electronic case report form (eCRF).

If a participant or site personnel become unblinded to an individual participant's treatment before database lock, the participant will be excluded from the Per Protocol Set (See Section 0), but will be included in the Full Analysis Set (See Section 7.1).

6. MODIFICATIONS

6.1. Modifications to the Approved Clinical Study Protocol

Not applicable

6.2. Modifications to the Approved Statistical Analysis Plan

Not applicable

6.3. Modifications to the Approved DMC Charter

Not applicable

7. ANALYSIS SETS

7.1. Full Analysis Set

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

7.2. Randomized Set

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

7.3. Safety Set

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

7.3.1. Safety Set –ADT Only

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

[redacted]

7.5. Per Protocol Set

The Per Protocol Set is defined as all participants in the FAS without any major protocol deviations related to efficacy. For further details, see Section 8.2.2.

In addition, Per Protocol Set will also exclude FAS participants with any of the following conditions:

- Participants who consumed <22 blinded IP capsules

- Participants who consumed less than 11 days of assigned ADT
- Participants who consumed incorrect blinded IP (i.e., IP other than which a participant was randomized to receive) at any time during the study
- Participant whose treatment blind has been broken before the study database has been unblinded

8. STATISTICAL ANALYSIS

8.1. 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 with the precision as reported in the source (raw) data. In addition, change from baseline values (visit value – baseline value) 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; the denominator of percentages will be the number of participants in the analysis set used unless specified otherwise.

All analyses and summary outputs will be generated using SAS® 9.4 or higher.

All summaries and figures will be provided by treatment group: “placebo + assigned ADT’ or “SAGE-217 + assigned ADT”. Assigned ADT is the ADT that is assigned to each participant at baseline by the investigator as the concomitant, open label ADT; this will be taken from the ADT administration eCRF page irrespective of how the participant was stratified at randomization. Assigned ADT use is derived from the first record of ADT administration available in eCRF. The SAGE-217+ assigned ADT treatment group does not differentiate 50mg or 40mg dose of SAGE-217. These treatment groups do not distinguish between different doses of ADT after the 14-day blinded Treatment Period. Efficacy data are analyzed by the treatment group that the participant is randomized to. Safety data are analyzed by the actual blinded IP treatment received, determined as follows: if a participant received any dose of SAGE-217 at any time, the participant is assigned to actual treatment of SAGE-217 + assigned ADT (irrespective of whether the participant took the ADT); the participant is assigned to actual treatment of Placebo + assigned ADT (irrespective of whether the participant took the ADT) if the participant has taken Placebo and has never taken any dose of SAGE-217.

All participant data, including those derived, to support tables and figures will be presented in the participant data listings. In general, the participant data listings will be sorted by

participant ID and assessment visit and date (and time, if applicable). The treatment will be identified for each participant – either planned or actual – according to the analysis set used.

Adverse event data for participants in Safety Set – ADT Only will be provided in a listing; other data from this analysis set will reside in the database but will not be used in analysis.

For the purpose of all safety and efficacy analyses, baseline is defined as the last non-missing measurement, including unscheduled visits, prior to the first dose of blinded IP, unless stated otherwise. If the time of an assessment is collected, baseline will be the latest assessment prior to first dose of blinded IP administration time; if the time of an assessment is not collected, the assessment on Day 1 is assumed to be prior to dosing if the protocol mentions that this assessment needs to be before dosing or it is collected as "predose".

8.1.1. Study Day Definition

First dose of IP is administered in the evening; assessments at the clinic on Day 1 are hence assumed to be before the first dose of blinded IP.

Study day will be defined as follows:

The day of participant receiving the first dose of blinded IP is designated as Day 1.

For visit/assessment days after Day 1, study day = visit/assessment date – Day 1 date + 1.

For visit/assessment days prior to Day 1, study day = visit/assessment date – Day 1 date.

Thus, study days for screening visit are negative numbers. There is no "Day 0".

8.1.2. Missing Data

All participants will be used in the analyses, as per the analysis populations, using all non-missing data available. Missing scheduled visit values may be replaced by windowing unscheduled visit values (see Section 8.3.2). Efficacy analyses will use sensitivity analyses to assess the impact of missing data. Imputation of missing data in scoring of questionnaires is discussed in respective sections below. Handling of missing or incomplete dates have been discussed in Section 11.3 Appendix C.

8.2. Background Characteristics

All summary tables in this section will be presented under treatment columns of 'placebo + ADT', 'SAGE-217 + ADT', and 'Overall'.

The subgroup (SSRI or SNRI) of assigned ADT will be determined as follows:

- SSRI: the generic term contains "sertraline", "escitalopram", "citalopram" and has a start date on or after the first dose of blinded IP.
- SNRI: the generic term contains "duloxetine", "desvenlafaxine" and has a start date on or after the first dose of blinded IP.

8.2.1. Participant Disposition

The summary of participant disposition will use all participants who provided written informed consent to the study. The disposition summary will also be provided using FAS.

The summary of participant disposition will include the number of participants who were screened, who screen failed, who were randomized, who received IP – either ADT or SAGE-217/Placebo, reasons for not being dosed, the number and percentage of participants who completed the study, who consented to continue in another SAGE-217 follow-up study, who prematurely withdrew from the study, and primary reasons for not completing the study, who completed blinded IP, who completed ADT, who discontinued blinded IP prematurely, who discontinued ADT prematurely, primary reasons for discontinuing blinded IP, and primary reasons for discontinuing ADT. All percentages will be calculated based on the participants who were randomized and received blinded IP; treatment group assignment will use planned treatment.

If a participant was rescreened (because the participant was a screen failure the first time), the status of the participant will be determined from the second screening. In the count of screened participants, this participant will be counted only once.

A completer for the study is defined as one who completed the last follow-up visit (Day 42) based on the study completion CRF page with the completion question answered Yes.

A participant is marked as completing the blinded treatment if the blinded IP completion CRF page indicates treatment completion.

A participant is marked as completing the assigned ADT treatment if the assigned ADT completion CRF page indicates treatment completion.

The number of participants in each analysis set will be provided. Using Randomized Set, the reason for not being included in other analysis sets will be summarized.

A separate data listing will be provided for all participants who prematurely discontinued blinded IP or prematurely withdrew from the study with reasons, number of days on blinded IP, date of withdrawal from the study, using Safety Set. A similar listing will be provided for premature discontinuation from assigned ADT.

8.2.2. Protocol Deviations

Protocol deviations identified during the study will be captured and categorized by the study team review as major or minor deviations in blinded fashion on an ongoing basis until database lock.

The study team will identify the major protocol deviations related to efficacy or which may have an impact on efficacy to determine the participants in FAS to be excluded from the Per Protocol Set prior to database lock in a blinded fashion (ie, it is possible for a participant to have a major protocol deviation and be included in the Per Protocol Set).

In addition, COVID-19 related protocol deviations such as remote telephone/video visit/assessment, home healthcare visit, missed visit/assessment, out of window visit/assessment, safety reporting, IP administration, and others will be documented.

All protocol deviations – major and minor – will be included in a data listing using Randomized set and randomized treatment. Any protocol deviation related to COVID-19 will be provided in a separate data listing using randomized set and randomized treatment. Major protocol deviations will be summarized using randomized treatment and FAS.

Any violation of inclusion/exclusion criteria will be presented by randomized treatment in a separate data listing using Randomized Set.

If a participant received any incorrected blinded IP other than what he/she was randomized to, the details of such inappropriate blinded IP consumption will be provided in a separate listing.

8.2.3. Demographics and Baseline Characteristics

The following analyses will be provided separately for the below sets:

- Safety Set (using actual treatment received),
- FAS (using randomized treatment),
- FAS by the subgroup of Assigned ADT use,
- FAS by US COVID-19 status at time of enrollment.

Demographic data (age at informed consent date, race, sex, ethnicity, employment status, highest education level, marital/civil status) and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized.

Baseline subgroups will be summarized for the following categories whenever appropriate:

- Assigned Antidepressant Use: SSRI, SNRI
- Age:18-24, 25-50, 51-64 years
- Sex: Female, Male
- Race: Black or African American, White, Other
- BMI at baseline: ≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m^2
- COVID-19 History: this will be summarized by COVID-19 related preferred term (PT) coded by Medical Dictionary for Regulatory Activities (MedDRA) in medical history data. For participants without COVID-19 related PT, the participants are categorized as 'Not Impacted'. If a participant had multiple PTs related to COVID-19, then the participant will be counted once under the worst case in the following order: Hospitalization > SARS-CoV-2 test positive > Patient isolation > Suspected COVID-19 > COVID-19.
- Depression with elevated anxiety by HAM-D subscale:
  Baseline HAM-D Anxiety subscale score >=7 (equivalent to normalized score of >=39), Baseline HAM-D Anxiety subscale score <7 (equivalent to normalized score of <39)
- Depression with elevated anxiety by HAM-A total score:

Baseline HAM-A total score >=20, Baseline HAM-A total score <20

- US COVID-19 status at time of enrollment: First informed consent sign date: <=18Mar2021, > 18Mar2021: a new subgroup is defined by the COVID-19 status in the US at the time of a participant's enrolment in the study. This is to investigate any potential impact of COVID-19 on study results using a date of the first informed consent; i.e. pre and during peak vs. post-peak has been determined from CDC report on COVID-19 (see Section 11.4).

Any deviation from the antidepressant stratum recorded at IRT system will be included as a protocol deviation and will be included in the protocol deviation listing.

Diagnostic labs are part of screening. The results of the diagnostic screening tests in Table 1 will be provided in a data listing using the Safety Set.

Table 1: Diagnostic Screening Tests

Diagnostic		
Serum	**Urine**	**Breathalyzer**
Hepatitis B Hepatitis C Reflex HCV RNA HIV-1 and -2 Female participants that are not surgically sterile and do not meet the protocol-defined criteria for being postmenopausal: serum hCG Female participants, if menopause is suspected and not surgically sterile: FSH	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine Female participants that are not surgically sterile and do not meet the protocol-defined criteria for being postmenopausal: urine hCG	Alcohol

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

Child-bearing potential data will be collected at screening and will be listed in a data listing using the Safety Set.

8.2.4. Medical/Surgical History

The following analyses will use the Safety Set.

Years since initial diagnosis of MDD, antidepressant usage, and information about depressive episodes will be summarized. Years since initial diagnosis of MDD, days since start of current episode and years since start of first episode will be calculated using: First dose date of the blinded IP – date of interest. For imputation of incomplete dates in medical history, please see Section 11.3.

Medical/surgical history collected at screening will be coded using the MedDRA, Version 23.0 or higher. Medical/surgical history data will be summarized by system organ class

(SOC) and preferred term (PT). A summary of medical/surgical history that are ongoing at the time of screening will be provided separately.

Participant history of psychiatric disorders and family psychiatric history will be summarized.

8.2.5. Prior and Concomitant Medications

The following analyses will use the Safety Set and will exclude the assigned ADT medication use.

All medications taken during the study will be recorded; in addition, psychotropic medications taken within 6 months prior to screening, and non-psychotropic medications taken within 30 days prior to screening will also be collected. All medications will be coded using World Health Organization-Drug (WHO) Global B3 March 2020 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 initiation of the start of blinded IP. Concomitant medications are defined as those with a start date on or after the first dose of blinded IP or those with a start date before the first dose of blinded IP that are ongoing or with a stop date on or after the first dose of blinded IP. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed concomitant. For imputation of missing concomitant medication dates, please refer to Section 11.3 , Appendix C. Note that it is possible for a medication to be both 'prior' and 'concomitant' when a medication has start date before first dose of blinded IP and end date either missing or after the first dose of blinded IP.

Concomitant medications will be further divided by usage period as follows:

- On-treatment concomitant medications are those that have been used any time from start of first dose to the last dose of blinded IP.
- Post-treatment concomitant medications are those that have been started after the last dose of blinded IP.

Prior and concomitant non-psychotropic medication use will be summarized by anatomical therapeutic chemical (ATC) level 1 and Standard Medication Name. Similar summary tables will be provided for psychotropic medications. Separate but similar summaries will be provided for concomitant medication use for on-treatment and post-treatment periods as defined above.

In addition, for prior and concomitant psychotropic medication separate summaries will be provided by ATC level 1 and ATC level 4.

Prohibited medications are reviewed by the medical monitor in the study team on an ongoing basis in blinded fashion; any medication identified as prohibited medication intake is captured in the protocol deviations list.

8.2.6. Concomitant Procedures

Concomitant procedures are recorded on a separate eCRF page; this will be presented in a listing by participant. The study day for the end date of the procedure will be provided when a complete end date is available.

8.2.7. Investigational Product Exposure

The following analyses will use the Safety Set. Exposure to blinded IP and assigned ADT will be determined separately.

Blinded IP Exposure:

Total drug exposure (in mg) is defined as the total mg for SAGE-217 that was taken during the study. Total drug exposure for participants randomized to placebo is zero, unless the participant has taken SAGE-217 in error, in which case the total exposure comes from SAGE-217 exposure. If the participant missed the dose on any day, the dose taken for that day is 0 mg.

The kit for the 50-mg dose contains two capsules – one for 30 mg, the other for 20 mg. For a participant who took only 1 capsule for a dosing day of 50 mg, it is assumed that the participant took the higher dose (ie, 30 mg) for the day and will be calculated as such for the total drug exposure and percent of the planned exposure received. If a participant takes more than 2 capsules for a planned dosing day of 50 mg, it is assumed that the participant took all capsules for 30 mg.

The kit for the 40-mg dose contains two capsules, 20 mg each; therefore, taking one capsule will unambiguously be assigned to 20 mg. Taking more than 2 capsules is also determined unambiguously counting each capsule as 20 mg.

Total exposure duration to blinded IP (in days) is defined as: date of last dose – date of first dose + 1. Note that this does not exclude days when the dose has been missed.

Percent of the planned exposure received for blinded IP is defined as the total drug exposure, divided by planned exposure, times 100, where planned exposure is defined as follows:

- For participants who complete the blinded treatment period without dose reduction, planned exposure is 14 days of treatment planned, × 50 mg for participants randomized to SAGE-217.
- For participants who discontinue the blinded treatment early without dose reduction, the planned exposure is the number of days (last date of 50 mg – first dose date + 1) × 50 mg. For participants who reduce dose to 40 mg, the planned exposure is the number of days (first date of 40 mg – first dose date) × 50 mg + the number of days (minimum of (end date of 40 mg, 14) – first date of 40 mg + 1) × 40 mg for participants randomized to SAGE-217. The maximum planned exposure is 14 days

For participants randomized to placebo, planned exposure is not applicable.

Total drug exposure, total exposure duration and percent of the planned exposure received will be summarized descriptively. Participants will also be summarized by number of blinded IP capsules administered (<22 capsules, ≥22 capsules).

The number and percent of participants who had a dose adjustment per Investigator (reduced, interrupted, withdrawn) and who had a dose modification (missed dose, took an extra day of dosing, took more than the planned dose for dosing day, took partial dose, other) will also be summarized descriptively.

Total drug exposure, total exposure duration, planned exposure, and percent of the planned exposure received will be listed with details of dates of first and last dose and details of any dose reduction.

Blinded IP administration for each study day will be listed, including the date and time of administration, the number of capsules taken and details of any planned or unplanned dose adjustments. Whether the participant ate fat-containing food within 1 hour of the blinded IP administration will also be included in the blinded IP administration data listing.

Assigned ADT Exposure:

Total drug exposure (in mg) is defined as the total mg for ADT that was taken. Total exposure duration to ADT (in days) is defined as: date of last dose of ADT – date of first dose of ADT + 1. Note that this does not exclude days when the dose was missed. These two measures will be summarized for blinded Treatment Period (the end of period is defined as the last dose of blinded IP), and for the entire study separately, and total drug exposure will be presented separately by each assigned ADT.

Sertraline: 50 mg per day for Week 1 and 100 mg per day for Week 2
Citalopram: 20 mg per day
Escitalopram: 10 mg per day
Duloxetine: 40 or 60 mg per day (divided in two 20 or 30 mg doses for Week 1)
Desvenlafaxine: 50 mg per day

During the assigned ADT Continuation Period, planned exposure may vary for each participant depending on their dose regimen; therefore, planned exposure will not be calculated during the ADT Continuation Period.

For participants who complete the blinded treatment period, without discontinuing from the study, the planned exposure of assigned ADT is planned daily dose (in mg) times 14, for ADTs other than sertraline; for sertraline it is 50mg times 7, plus 100 mg times 7. For duloxetine, the first dose taken will be used to determine if the planned dose is 40 mg or 60 mg per day.

For participants who discontinue the study during the blinded Treatment Period, the planned exposure of assigned ADT is:

- For assigned ADTs except sertraline: (minimum of (14, last dose date of blinded IP) – first dose date of ADT +1) × (planned daily dose in mg)
- For sertraline as assigned ADT:

- If last dose date of blinded IP is <= Day 7 then (last dose date of blinded IP) – first dose date of ADT + 1) × 50 mg
- If last dose date of blinded IP > Day 7 then (minimum of (14, last dose date of blinded IP) – 7) × 100 mg + 7 × 50 mg

Percent of the planned exposure received for assigned ADT is defined as the total drug exposure, divided by the planned exposure, times 100.

8.2.8. Investigational Product Adherence

The following analyses will use the FAS. Blinded IP adherence (%) is defined as the number of blinded capsules taken, divided by the number of blinded capsules planned to be taken, times 100.

The schedule of blinded IP is two capsules per day. The number of capsules planned to be taken is defined as follows:

- If the participant discontinues blinded IP within Day 1 and Day 14 (both inclusive), the number of capsules planned to be taken is the last dose day of blinded IP, times 2.
- If the participant does not discontinue blinded IP, the number of capsules planned to be taken is 28.

Blinded IP adherence will be summarized descriptively. Number and percentage of participants with blinded IP adherence in categories - <80%, 80-100%, >100% - will be provided.

For assigned ADT adherence, the number of tablets taken for the same dose may be different for different participants. Without a planned number of tablets to be taken for each dose, ADT adherence based on number of tablets cannot be derived. Percent of planned exposure for the blinded Treatment Period will be used as a measure of ADT adherence.

8.3. Efficacy Analysis

8.3.1. Definition of Efficacy Variables

The efficacy variables are defined as follows:

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

The 17-item HAM-D will be used to rate the severity of depression in participants already diagnosed as depressed. HAM-D is collected during the clinic visit on Screening, Days 1, 3, 8, 12, 15, 18, 21, 28, 35, and 42. The 17-item HAM-D comprises of 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. The score for each item will be summed to compute a total score, which ranges from 0 to 52.

If more than 3 individual items are missing a response, the HAM-D total score will not be calculated and will be left as missing. If less than or equal to 3 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.

Four HAM-D 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. If more than one item is missing or HAM-D total score is missing, the subscale score is left as missing; if one item on a particular subscale is missing but has been imputed for the calculation of total score, the imputed value from total score calculation will be used in subscale score calculation for that item. Table 2 describes the subscale score calculation.

HAM-D response will be defined as having a 50% or greater reduction from baseline in HAM-D total score; only participants who have a non-missing total score of HAM-D at baseline as well as the visit will be considered in HAM-D response evaluations. HAM-D remission will be defined as having a HAM-D total score of ≤7; if HAM-D total score is missing, remission will not be defined. For a sensitivity analysis the worst-case scenario imputation will be used, i.e., missing values for HAM-D response (remission) will be considered as "No response" ("No remission").

Table 2: HAM-D Subscale Calculation

HAM-D Subscales	Items	Calculation
Core	Depressed mood Feeling of guilt Suicide Work and activities Retardation	Sum of the 5-item responses/20 x 100. If more than one item responses are missing or HAM-D total score is missing, leave as missing; otherwise, use the imputed item score used to calculate HAM-D total score to calculate the subscale.
Anxiety	Anxiety psychic Anxiety somatic Somatic symptoms gastrointestinal Somatic symptoms general Hypochondriasis Insight	Sum of the 6-item responses/18 x 100. If more than one item responses are missing or HAM-D total score is missing, leave as missing; otherwise, use the imputed item score used to calculate HAM-D total score to calculate the subscale.
Bech-6	Depressed mood Feeling of guilt Work and activities Retardation	Sum of the 6-item responses/22 x 100. If more than one item responses are missing or HAM-D total score is missing, leave as missing; otherwise, use the imputed item score used to

HAM-D Subscales	Items	Calculation
	Anxiety psychic Somatic symptoms general	calculate HAM-D total score to calculate the subscale.
Maier	Depressed mood Feeling of guilt Work and activities Retardation Agitation Anxiety psychic	Sum of the 6-item responses/24 x 100. If more than one item responses are missing or HAM-D total score is missing, leave as missing; otherwise, use the imputed item score used to calculate HAM-D total score to calculate the subscale.

8.3.1.2. Clinical Global Impression – Improvement (CGI-I)

The Clinical Global Impression – Improvement (CGI-I) employs a 7-point Likert scale to measure the overall improvement in the participant's condition post-treatment. The Investigator will rate the participant's total improvement. Response choices include: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse. The CGI-I is only rated at post-treatment assessments on Days 3, 8, 12, 15, 21, 28, 35, and 42. By definition, all CGI-I assessments are evaluated against baseline conditions. Missing CGI-I score at the visit will not be imputed.

CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved." For a sensitivity analysis the worst-case scenario imputation will be used, i.e. missing values for CHI-I response will be considered as "No response".

8.3.1.3. 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 participant's illness at the time of assessment, relative to the clinician's past experience with participants who have the same diagnosis. Considering total clinical experience, a participant is assessed on severity of mental illness at the time of rating as 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=extremely ill. CGI-S is collected at Screening, Days 1, 3, 8, 12, 15, 21, 28, 35, and 42.

8.3.1.4. Hamilton Anxiety Rating Scale (HAM-A)

The 14-item HAM-A will be used to rate the severity of symptoms of anxiety. HAM-A is collected during the clinic visit at Days 1, 8, 15, 28, and 42. Each of the 14 items is defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Scoring for HAM-A is calculated by assigning scores of 0 (not present) to 4 (very severe), with a total score range of 0 to 56, where <17 indicates mild severity, 18 to 24, mild to moderate severity, and 25 to 30, moderate to severe severity. The HAM-A total score will be calculated as the sum of the 14 individual item scores. If more than 3 individual items are missing a response, the HAM-A total score will not be calculated and will be left as missing. If less

than or equal to 3 individual item scores are missing, the missing item scores will be imputed by the mean of all other available item scores.

8.3.1.5. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in participants with mood disorders. MADRS is collected at Screening, during the clinic visit on Days 1, 8, 15, 28, and 42.

Each MADRS item ranges from 0 to 6; higher MADRS scores indicate more severe depression. 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.

MADRS response will be defined as having a 50% or greater reduction from baseline in MADRS total score; only participants who have a non-missing total score of MADRS at baseline as well as the visit will be considered in MADRS response evaluations. MADRS remission will be defined as having a MADRS total score of ≤10; if MADRS total score is missing, remission will not be defined. For a sensitivity analysis the worst-case scenario imputation will be used, i.e., missing values for MADRS response (remission) will be considered as "No response" ("No remission").

8.3.1.6. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a 9-item participant-rated depressive symptom severity scale. It is collected during the clinic visit on Days 1, 3, 8, 15, 28, and 42. Scoring is based on responses to specific questions, as follows: 0=not at all; 1=several days; 2=more than half the days; and 3=nearly every day.

The PHQ-9 total score will be calculated as the sum of the 9 individual item scores. If more than 1 individual item is missing, the PHQ-9 total score will not be calculated and will be left as missing. If 1 individual item score is missing, the missing item score will be imputed by the mean of all other available item scores to calculate the PHQ-9 total score. The PHQ-9 total score will be categorized as follows: 0 to 4=minimal depression, 5 to 9=mild depression, 10 to 14=moderate depression, 15 to 19=moderately severe depression; and 20 to 27=severe depression. Improvement since baseline is defined as having a lower category from baseline.

8.3.2. Visit Windows

The blinded treatment period scheduled visits (Day 3, Day 8, Day 12, and Day 15) will not be windowed and will be used at nominal visit value for analysis purposes. However, unscheduled, end-of-double blind treatment, and early termination (ET) visits will be included for the analyses by mapping to a blinded treatment period scheduled visit only if there is no measurement available from the scheduled visit. For ADT Continuation period visits (Day 21, Day 28, Day 35, and Day 42), including unscheduled, end-of-double blind

treatment, and ET visits will be mapped to a scheduled visit for analysis. Day 18 visit will not use a window visit but nominal visit, so no window is identified for Day 18. The windows outlined in Table 3 for each scheduled visit have been widened compared to protocol-specified operational window, to have no gap between them; these windows are used for analysis purposes only. Once analysis visit windows are assigned, all visits, including scheduled visits and windowed visits will be eligible for being flagged as the "analyzed record" within the analysis window; a participant'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 the data from the scheduled visit within the blinded treatment period is available, then the scheduled visit data will be used.
  - If there is no data from the scheduled visit within the blinded treatment period is available, the data closest to the target day for that window will be used.
- For ADT Continuation period the windowed visit will be used.
  - In case there is more than one windowed visit within a window, the data closest to the target day for that window will be used.

  –If there is a tie between the data in the number of days before and after the target day, the later data will be used.

  –If there is a tie on the same day with different times, the later time data will be used.

The summary by visit will use the "analyzed records" only – at most one per participant. The data not flagged as the "analyzed record" will be included in listings. An unscheduled visit that does not fall under any analysis window will remain in the database and will be included in the listings.

Table 3 displays windows for efficacy analysis.

Table 3: Visit Windows for Efficacy Analysis

Scheduled Visit (+/1 window days) in protocol	**Target Study Day**	**Study Day Window for Visit in Analysis[a]**
Day 1	Day 1 (pre-dose)	Day 1 (pre-dose) or last non-missing assessment before first dose of blinded IP
Day 3 (±1 day)	Day 3	Day 2 – Day 5
Day 8 (+1 day)	Day 8	Day 6 – Day 9
Day 12 (±1 day)	Day 12	Day 10 – Day 13
Day 15 (+1 day)	Day 15	Day 14 – Day 17
Day 21 (±3 day)	Day 21	Day 18 – Day 23

Scheduled Visit (+/1 window days) in protocol	Target Study Day	Study Day Window for Visit in Analysis[a]
Day 28 (±3 day)	Day 28	Day 24 – Day 31
Day 35 (±3 day)	Day 35	Day 32 – Day 38
Day 42 (±3 day)	Day 42	>=Day 39

a. For blinded treatment period (Day 3, Day 8, Day 12, and Day 15), the study day window will be used for unscheduled, end-of- double blind treatment, and ET visit only if there is no measurement available from the scheduled visit.

8.3.3. Analysis of Efficacy Variable(s)

The FAS will be used for efficacy analyses. Participants will be analyzed according to randomized treatment.

The following efficacy endpoints will be summarized descriptively by scheduled assessment time point:

- HAM-D total score – observed, change from baseline, percent change from baseline
- HAM-D subscale scores – observed, change from baseline, percent change from baseline
- HAM-D individual item score – observed, change from baseline
- HAM-D response
- HAM-D response – missing response counted as No response
- HAM-D remission
- HAM-D remission – missing remission counted as No remission
- CGI-S score – observed and change from baseline
- CGI-I score - observed
- CGI-I response
- CGI-I response – missing response counted as No response
- HAM-A total score – observed, change from baseline, percent change from baseline
- HAM-A individual item score – observed, change from baseline
- MADRS total score – observed, change from baseline, percent change from baseline
- MADRS individual item score – observed, change from baseline
- MADRS response

- MADRS response – missing response counted as No response
- MADRS remission
- MADRS remission – missing remission counted as No response
- PHQ-9 score – observed (including categories), change from baseline

The summaries of HAM-D change from baseline in total score will also be presented by the following subgroups:

- Assigned Antidepressant Use: SSRI, SNRI
- Age group: 18-24, 25-50, 51-64 years
- Sex: Male, Female
- Race: White, Black, or African American, Other
- BMI at baseline: ≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m^2
- COVID-19 History: this will be summarized by worst case COVID-19 related preferred term (PT) coded by MedDRA in medical history data. For participants without COVID-19 related PT, the participants are categorized as 'Not Impacted'.
- Depression with elevated anxiety by HAM-D subscale:

  Baseline HAM-D Anxiety subscale score >=7 (equivalent to normalized score of >=39), Baseline HAM-D Anxiety subscale score <7(equivalent to normalized score of <39)
- Depression with elevated anxiety by HAM-A total score:

  Baseline HAM-A total score >=20, Baseline HAM-A total score <20
- US COVID-19 status at time of enrollment: First informed consent sign date:

  <= 18Mar2021, > 18Mar2021

In addition, post-baseline percentage improvement in HAM-D total score will be presented in histogram over scheduled visits by treatment group under the following categories: < 0% (worsened), ≥0% but < 25%, ≥25% but < 50%, ≥ 50% but <75%, ≥75%. Post baseline HAM-D total score will also be presented in histogram over scheduled visits: ≤7, >7 but ≤15, >15 but ≤ 23, ≥ 24 but <26, >=26. Corresponding data will be presented in summary tables.

As part of supportive analyses, the summaries (observed, change from baseline, percent change from baseline) and model-based estimates on HAM-D total scores and CGI-S scores will be summarized for Per Protocol Set.

8.3.3.1. Mixed Effects Model for Repeated Measures

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

1) The treatment regimens for participants are: SAGE-217 + ADT and placebo + ADT for 14 days.

2) The target population is adult participants with a diagnosis of major depressive disorder and within a current depressive episode of severity (baseline HAM-D total score >=24).

3) The variable of interest is the change from baseline in HAM-D total score.

4) The intercurrent events could be:

a. The premature discontinuation of treatment for any reason

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

5) The population summary level is the model-based estimate of the difference between SAGE-217 + ADT and placebo + ADT treatments in change from baseline in HAM-D total score.

a. The population summary level for the primary endpoint is the model-based estimate of the difference between SAGE-217 + ADT and placebo + ADT in change from baseline in HAM-D total score at Day 3.

b. The population summary level for the key secondary endpoint is the model-based estimate of the difference between SAGE-217 + ADT and placebo + ADT in change from baseline in HAM-D total score over the blinded treatment period using equal weight to days 3, 8, 12 and 15.

Data from SAGE-217 + ADT group versus Placebo + ADT group will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include randomized treatment (SAGE-217 + ADT or placebo + ADT), baseline HAM-D total score, assigned ADT based on ADT use in ADT administration page of CRF (SSRI/SNRI), assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 + ADT and Placebo + ADT.at Day 3. Model-based point estimates (i.e., treatment difference in least squares [LS] mean is the estimate of the effect) will be reported along with 95% confidence intervals, and p-values. An unstructured (UN) covariance structure (with the default Newton-Raphson algorithm used by SAS PROC MIXED) will be used to model the within-participant errors. If there is a convergence issue with the unstructured covariance model, the Fisher Scoring algorithm (via the SCORING option of the PROC MIXED statement), the no-diagonal factor analytic structure (via the TYPE=FA0(*T*) option of the REPEATED statement, where *T* is the total number of time points), Toeplitz, or Autoregressive (1) [AR (1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR (1) structure, no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS. Observed Margins (OM)

option will be used in SAS with LSMEAN statement. The p-value will be interpreted at two-sided 5% level of significance.

Within the MMRM model of HAM-D total score over time, change from baseline in HAM-D total scores over the blinded treatment period using equal weights for (Day 3, Day 8, Day 12, Day 15), as well as over the time around end of blinded treatment, using equal weights for (Day 12, Day 15, Day 18) will be tested. LSMESTIMATE statement in SAS code will be used to estimate the difference in LS mean between treatment groups, 95% confidence intervals, and p-values.

If the comparison of SAGE-217 + ADT versus Placebo + ADT at Day 3 is significant at a two-sided 0.05 level, the hypothesis testing for the key secondary endpoint will be followed with multiplicity adjustment, as described in Section 8.3.3.5. Similar to those methods described above for the primary endpoint, a MMRM will be used for the analysis of the change from baseline in other time points in HAM-D total score, all time points in HAM-D subscale scores (Core Subscale score, Anxiety Subscale score, Bech-6 Subscale score and Maier Subscale score), HAM-D individual item scores, CGI-S score, HAM-A total score, HAM-A individual item score, MADRS total score, MADRS individual item scores, and PHQ-9 total score.

For each model, the comparison of interest will be between SAGE-217 + ADT and Placebo + ADT; model-based point estimates (i.e., LS means), 95% confidence intervals, and p-values will be reported for all assessment time points.

The MMRM analyses will also be provided for change from baseline in HAM-D total score within each baseline subgroup level (see Section 8.2.3 and 8.3.3) separately; if any treatment group for any level of subgroup has <=15 participants, the subgroup level will not be used in the analysis. The model for subgroup analysis of assigned ADT will not use assigned ADT as explanatory variable.

Line plot of model-based LS Mean and standard error (SE) over time will be prepared for change from baseline in HAM-D total score, CGI-S score, HAM-A total score, and MADRS total score. Forest plot for baseline subgroup analysis for change from baseline in HAM-D total score at Day 3, Day 8, Day 15, and Day 42 – LS mean, 95% confidence interval, and p-value – will be provided.

The estimate of change from baseline in HAM-D total scores over the treatment period will be tested for the following subgroups:

1. Assigned ADT use (the term for assigned ADT will be skipped in the model)
2. US COVID-19 status at time of enrollment: First informed consent date: <= 18Mar2021, > 18Mar2021

In addition, the MMRM analyses will be provided for change from baseline in HAM-D subscale scores, HAM-D individual item scores, CGI-S score, HAM-A total score and MADRS total score for the above two subgroups.

A Forest plot for individual items in HAM-D, and for subscales of HAM-D will also be provided. These plots along with supporting tables will also be produced for the above two subgroups.

Summary of the model-based estimates for HAM-D total score and CGI-S score will be provided separately for Per Protocol Set. Line plot of model-based LS Mean and standard error (SE) over time will be prepared for change from baseline in HAM-D total score, and CGI-S score will be provided separately for Per Protocol Set.

8.3.3.2. Generalized Estimating Equation (GEE) Models

Generalized estimating equation (GEE) methods will be used for the analysis of HAM-D response and HAM-D remission. GEE models will include terms for randomized treatment (SAGE-217 + ADT, or Placebo + ADT), baseline HAM-D score, assigned ADT (SSRI/SNRI), assessment time point, and time point-by-treatment as explanatory variables.

An unstructured (UN) covariance structure will be used to model. If there is a convergence issue with the unstructured covariance model, then exchangeable covariance structure will be used. If the model still does not converge with exchangeable structure, no results will be reported.

Model-based point estimates (i.e., odds ratios), 95% confidence intervals, and p-values will be reported.

Similar GEE method will be used for the analysis of MADRS response and remission.

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

For a sensitivity analysis the worst-case scenario imputation will be used, GEE methods will be repeated for the analysis of HAM-D response with missing values considered as “No response”. This sensitivity analysis will be performed similarly for HAM-D remission with missing values considered as “No remission”. This sensitivity analysis will be also performed for MADRS response, MADRS remission, and CGI-I response.

Model diagnostics to access the goodness of fit for the GEE models will be examined. In the event of poor goodness of fit, logistic regression will be performed separately for each visit, including baseline score, and assigned ADT (SSRI/SNRI) as explanatory variables.

Similar GEE method will be used for the analysis of HAM-D response/remission and MADRS response/remission for the following subgroups:

1. Assigned ADT use (the term for assigned ADT will be skipped in the model)
2. US COVID-19 status at time of enrollment at time of enrollment: First informed consent date: <= 18Mar2021, > 18Mar2021

If the model does not converge due to 0 frequency at certain visits, a new model will be run without these visits and the results will be reported.

This analysis will also be provided for the above two subgroups for CGI-I response.

Bar charts over scheduled visits by treatment for HAM-D response/remission, MADRS response/remission, and CGI-I response will be provided. In addition, theses bar charts will be also provided above sensitivity analyses, as well as for the above subgroups, separately. A GEE method will also be used for the analysis of HAM-D response, HAM-D remission, CGI-I response by scheduled assessment time point for anxious subgroup 1 and 2 in Section 8.3.3, respectively.

8.3.3.3. Sensitivity Analysis

8.3.3.3.1. Imputation Based on Study Withdrawal Reasons

A sensitivity analysis will be used to investigate the impact of missing data in HAM-D total score at each study visit.

Imputation based on study withdrawal reason will be used. The missing HAM-D total scores will be imputed using multiple imputation (MI) methods. The MMRM model will use the dataset (all observed and imputed values included) to estimate the treatment difference in change from baseline in HAM-D total score. The FAS will be used for sensitivity analyses. Sample SAS code for MI is provided in Section 11.2 Appendix B.

Imputation distribution:

All randomized participants will be classified as missing category 1, or missing category 2, based on the following rules:

- Missing category 1: Participant discontinued due to adverse events, physician decision, protocol deviation, non-compliance with IP, lost to follow-up, participant decision, withdrawal by subject, sponsor request, or other.
- Missing category 2: Participant discontinued due to pregnancy, or due to COVID-19

Imputation algorithm:

Missing values of HAM-D total score at all visits will be imputed using the fully conditional specification (FCS) models. Two different imputation models will be used based on reasons of missing:

- **Missing category 1:** simulate missing values of HAM-D total score using an imputation model based on the non-missing HAM-D total scores for placebo group ("Jump to Reference"). This represents a conservative approach as it tends to reduce the difference between treatment and placebo group.
- **Missing category 2:** simulate missing values of HAM-D total score using an imputation model based on the non-missing HAM-D total scores within the same treatment group.

Analysis model:

The complete multiple imputation method is described below:

- Repeat the process K (K=100) times, using the procedure described above to form K imputed complete datasets with the same variance structure.

- Fit the MMRM model including treatment, baseline antidepressant use, baseline HAM-D total score, assessment time point, and time point-by-treatment to each imputed dataset, to estimate the treatment effect and its variance.
- Combine the results from the K imputed datasets using the SAS procedure MIANALYZE, to derive the MI estimator.

We fit the analysis model (MMRM model specified before) to the kth completed dataset, denoting the estimate of the treatment difference θ by θ_k from the kth completed dataset and denoting the corresponding estimate of the variance V_k. The MI estimator of θ, $\tilde{\theta}_{MI}$, is the average of the K individual estimators:

$$\tilde{\theta}_{MI} = \frac{1}{K}\sum_{k=1}^{K}\theta_k$$

The estimated variance of $\tilde{\theta}_{MI}$ is a combination of the between- and within-imputation variability as follows:

$$V_{MI} = W + \left(1 + \frac{1}{K}\right)B$$

where $W = \frac{1}{K}\sum_{k=1}^{K} V_K$ is the within-imputation variability and $B = \frac{1}{K\text{-}1}\sum_{k=1}^{K}\left(\theta_k\text{-}\tilde{\theta}_{MI}\right)^2$ is the between-imputation variance.

It has been shown that the statistic

$$T = \frac{\tilde{\theta}_{MI} - \theta}{\sqrt{V_{MI}}}$$

has an approximate t distribution where $V = (K\text{-}1)\left(1 + \frac{W}{B}\right)^2$.

8.3.3.3.2. Tipping Point Analysis

The purpose of a tipping point analysis is to evaluate the sensitivity of results in missing data assumed missing at random (MAR) by finding out the size of the change assumed missing not a random (MNAR) that tips a statistically significant treatment effect on HAM-D to become not statistically significant. This analysis will use FAS.

In the tipping point analysis, missing HAM-D total score from each study visit will be imputed using multiple imputation in the following steps:

1. For treatment group (i.e., SAGE-217 + ADT) a positive constant shift from 0 will be added to the imputed HAM-D total score values at each study visit.

Assumed arbitrary missing pattern, a multiple imputation step with SAS MI FCS method will be used to impute the missing values of HAM-D total score with “mnar” procedure to make the shift. One hundred datasets will be generated for each study visit.

2. For each of the 100 complete datasets after imputation, the change from baseline will be calculated so that the MMRM model will be fitted to estimate treatment differences and corresponding p-values.

3. The 100 sets of MMRM results will be combined with SAS PROC MIANALYZE, which combines estimates as specified in step 2.

4. Steps 1 to 3 will be repeated with different values of the shift parameter until the tipping point will be reached at each study visit.

The tipping point will be provided by study visit along with the main estimates in change from baseline by study visit from MMRM in Section 8.3.3.1 . Sample SAS code for MI is provided in Section 11.2 Appendix B.

8.3.3.3.3. Weighted Generalized Estimating Equation

The standard GEE method in Section 8.3.3.2 is valid if the data are missing completely at random (MCAR), but it can lead to biased results if the data are missing at random (MAR). The weighted GEE implements the inverse probability-weighted method to account for dropouts under the MAR assumption. This analysis will be performed using the binary secondary endpoints - HAM-D response, HAM-D remission, CGI-I response, MADRS response and MADRS remission. This analysis will use FAS.

A weighted GEE method does not apply for the data with intermittent missing from any of the participants and the procedure does not converge in SAS. A SAS procedure with MI Markov Chain Monte Carlo (MCMC) with 100 imputations will be used to fill out intermittent missing values so that the data will have monotone missing pattern. Therefore, a weighted GEE on each binary endpoint will be run as a sensitivity analysis. Since the endpoints are a binary outcome, the imputation to fill out intermittent missing will be performed using the raw scores. The imputed values will be rounded and dichotomized to obtain each binary endpoint as defined in Section 8.3.1.1 and Section 8.3.1.2.

Therefore, a weighted GEE model including baseline HAM-D score, assigned ADT, assessment time point, and time point-by-treatment as explanatory variables will be used to estimate point estimates (i.e., odds ratios), 95% confidence intervals, and p-values. The results from the 100 imputed datasets will be combined using the SAS procedure MIANALYZE.

Sample SAS code for weighted GEE is provided in Section 11.2 Appendix B.

8.3.3.4. Analysis of Time to First HAM-D Response/Remission

Using the FAS, Kaplan-Meier (KM) method will be used to analyze time to first HAM-D response; the median time, first quartile (Q1), third quartile (Q3) , min and max to first response will be estimated. The number and percent of participants who had a response or was censored will be provided. A participant will be censored at the participant's last study day of HAM-D evaluation in the database if the participant did not have a response. Similar analysis will be done for first HAM-D remission.

8.3.3.5. Multiplicity Adjustment for Key Secondary Endpoint

Multiplicity adjustment to statistical testing of the hypothesis of the key secondary endpoint is conducted by using fixed sequence strategy (Dmitrienko et al 2013)[1]. Only if the primary endpoint is statistically significant at a two-sided 0.05 level, the key secondary endpoint will be tested at 5% level of significance.

All other secondary efficacy endpoints are not adjusted for multiplicity, and hence all p-values are considered as nominal.

8.3.4. Characterization of Durability of SAGE-217 Treatment Effect

After completion of 14 days of treatment, the study participant is followed during the ADT continuation period, without any further treatment with blinded IP. During this period, clinic visits are scheduled for Days 18, 21, 28, 35 and 42.
Demonstration of SAGE-217 + ADT durable effect will be characterized via 2 complementary approaches:
1) clinically meaningful durable SAGE-217 + ADT treatment effect at Day 42 (see Section 8.3.4.1 below), and
2) statistically significant change from baseline at Day 42 in SAGE-217 + ADT versus placebo + ADT (for statistical demonstration of durable SAGE-217 treatment effect, see Section 8.3.4.2 below).

8.3.4.1. Durability of Clinically Meaningful Treatment Effect for SAGE-217

Durability of treatment effect is assessed over the post-treatment period in the SAGE-217 + ADT group, based on the efficacy observed at Day 15. The endpoint for clinically durable effect will be examined by the percent retention of the Day 15 reduction from baseline in HAM-D total score among SAGE-217 + ADT participants (referred to as "percent retention of D15 change from baseline (CFB)" going forward).

Percent retention of D15 CFB is defined as follows: Let X_b be the baseline HAM-D total score, X_{15} be Day 15 HAM-D total score, X_y be Day Y (Y>15) HAM-D total score. Then percent retention (%) for Day Y is defined as $\frac{X_y - X_b}{X_{15} - X_b} \times 100$. It will be calculated for the scheduled visits after Day 15, for the participants who had improvement in HAM-D total score at Day 15 since baseline (i.e . $X_{15} < X_b$). For example, for a participant with a baseline HAM-D of 27 (X_b) and a HAM-D score of 13 (X_{15}) at Day 15, percent retention at Day 42 with HAM-D of 16 (X_y) would be 79%. If D42 HAM-D score is 18, percent retention would be 64%.

A summary of percent retention of D15 CFB will be presented for participants who improved at Day 15 for post-Day 15 visits by treatment group, based on FAS. This will serve as the approach for assessing clinically durable effect for SAGE-217+ADT; mean percent retention of D15 CFB at Day 42 is considered clinically meaningful durability if it is >=65%. The mean (±SE) percent retention over time by treatment group will be presented in a line plot. In addition, the number, and percent of participants with at least 65% retention of D15 CFB at each of post-Day 15 scheduled visit will also be provided by treatment group.

This analysis will also be presented using the subgroup of assigned ADT use and the US COVID-19 status at time of enrollment.

Following analysis will be presented by treatment group for supportive purposes to assist with further understanding of clinical durability of effect of SAGE-217 + ADT. These analyses will be conducted using both FAS and using the subgroup of assigned ADT use and the US COVID-19 status at time of enrollment.

A. A summary of percent retention of D15 CFB will be presented for HAM-D responders at Day 15 for scheduled post-Day 15 visits. The mean (±SE) percent retention over time will be presented in a line plot. In addition, the number and percent of HAM-D responders at Day 15 with at least 65% retention of D15 CFB at each of post-Day 15 visit will also be provided.
B. The number and percent of HAM-D responders at scheduled post-Day 15 visits among HAM-D responders at Day 15 will be provided. A bar chart will be provided.
C. The number and percent of HAM-D remitters (HAM-D total score <=7) at post-Day 15 visits among HAM-D remitters at Day 15 will be provided. A bar chart will be provided.
D. Relapse: A relapse is defined for HAM-D responders at Day 15. A relapse is defined as having at least 2 consecutive HAM-D total score >=20 after Day 15, including the last value. The number and percent of participants with relapse will be provided.
E. Rebound: A rebound is defined for HAM-D responders at Day 15. A rebound is any HAM-D total score (after Day 15) >= Baseline HAM-D total score. The number and percent of participants with rebound will be provided.
F. The number and percent of CGI-I responders (CGI-IR) at post-Day 15 visits among CGI-I responders at Day 15 will be provided. A bar chart will be provided base.

A summary of percent retention of D15 CFB will be presented by treatment group for MADRS responders at Day 15 for scheduled post-Day 15 visits for FAS and the subgroup of assigned ADT use and the US COVID-19 status at time of enrollment. The mean (±SE) percent retention over time by treatment group will be presented in a line plot for FAS and the subgroup of assigned ADT use and US COVID-19 status at time of enrollment at time of enrollment.
Post Day 15 HAM-D and MADRS results supporting the above analyses will be listed separately.

8.3.4.2. Durability of Treatment Effect at Day 42 via Statistical Comparison of SAGE-217 Versus Placebo

These analyses have been discussed in Section 8.3.3.1 and Section 8.3.3.2 as part of the efficacy analyses with Day 42 using FAS.

A. MMRM analysis of change from baseline in HAM-D total score at Day 42 comparing SAGE-217+ADT versus placebo + ADT (LS mean, p-value and 95% CI) will be provided.

B. GEE analysis of HAM-D response/remission rates comparing SAGE-217 + ADT versus placebo + ADT at Day 42 (Odds Ratio, p-value and 95% CI) will be provided.

8.4. Safety Analysis

A secondary objective of this study is to evaluate the safety and tolerability of SAGE-217 as assessed by the incidence and severity of adverse events. [redacted] Safety analyses will be conducted using the Safety Set, unless specified otherwise. The data will be presented by the actual treatment received rather than the treatment to which the participant was randomized; for definition of actual treatment assignment, see Section 7.1 .The safety endpoints evaluated at scheduled visits within the blinded treatment period are taken as done in nominal visit, without any windowing. If a value is available for a nominal scheduled visit within the blinded treatment period, that value will be used in summary by visit. If scheduled visit value is not available within the blinded treatment period and for all visits in ADT Continuation period, a value from the specific visit window will be included in summary, the choice of the record following the same rule as described in Section 8.3.2 .

"Any time during treatment" values are defined as any value on or after first blinded IP intake but on or before the last dose of blinded IP + 1 day. "Within 14 days after last dose" is defined as any value after last dose of blinded IP but on or before last dose of blinded IP + 14 days. "Last value on treatment" and "Last value on study" will be included in the summaries whenever indicated in the relevant sections below. "Last value on treatment" is defined as the last post-baseline value between first dose of blinded IP (exclusive) and up to last dose of blinded IP + 1 days (inclusive). "Last value on study" is defined as the last post-baseline value after the first dose of blinded IP.

The safety endpoints and variables considered in the summary tables for this study are summarized in Table 4 .

Table 4: Safety Endpoints and Variables in the Summary Tables

Safety Evaluation	Incidence	Observed Value	Change from Baseline	Abnormality (Out of Normal Range) / Clinical Significance (CS)	Potentially Clinically Significant (PCS)
AEs	X				
[redacted]					

Note: PCS criteria are outlined in sections 8.4.2-8.4.4
X = to be summarized in tables

Z = to be presented in listings only

8.4.1. Adverse Events

Adverse events (AEs) are collected starting at the time of informed consent and throughout the duration of participation in the study. A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset on or after the start of blinded IP. The TEAEs will be further categorized by the phase of occurrence as follows:

Adverse events are assigned an AE period based on the onset date/time. AE periods are defined as follows:

Pre-treatment AE: AE onset date before first blinded IP dosing date/time

TEAE: AE onset date/time on or after first blinded IP dose date/time (If an AE start date same as blinded IP first dose date, but no time either in AE start or treatment start, then consider this AE to be a TEAE.)

On-Treatment TEAE: AE onset date/time on or after first blinded IP dose date/time and on or before blinded IP last dose date + 1 day (Note that time does not matter for the end of this period.)

Post-Treatment TEAE: AE onset date after blinded IP last dose date +1 day (Typically, Day 16 through Day 42 – time does not matter)

If the date of an adverse event is incomplete and an unambiguous determination could not be made with respect to its onset time versus the first dose of blinded IP and/or last dose of blinded IP, the adverse event will be assumed to be a TEAE and a treatment period TEAE. For imputation of missing AE dates, please refer to Section 11.3 , Appendix C.

All adverse events will be coded using MedDRA version 23.0 or higher.

An overview summary table of TEAEs will present the number and percentage of participants as well as the number of events for the following:

- TEAE
  - On-Treatment TEAE
  - Post-Treatment TEAE
- TEAEs by maximum severity (severe>moderate>mild)
- TEAE leading to discontinuation of blinded IP
- TEAE leading to discontinuation of assigned ADT
- TEAE leading to dose reduction of blinded IP
- TEAE leading to withdrawal from the study
- Treatment-emergent Serious Adverse Event (TESAE)
- Death

- Incidence of TEAEs in the following categories will be provided by SOC and PT. A participant is counted only once under each SOC and PT in case of multiple occurrences of the same AE. In these tables, the display will be sorted by decreasing frequency of SOC in SAGE-217 + ADT group, then of SOC in the placebo + ADT group; if 2 or more SOCs have the same frequency, the order will be alphabetical. Within each SOC, preferred terms will be sorted by the same algorithm as in SOC. TEAE
  - On-Treatment TEAE
  - Post-Treatment TEAE
- TEAEs by maximum Severity
- TEAEs by relationship to blinded IP
- TEAEs by relationship to assigned ADT
- Serious TEAEs
- TEAEs leading to discontinuation of blinded IP
- On-treatment TEAEs leading to discontinuation of assigned ADT
- Post-treatment TEAEs leading to discontinuation of assigned ADT
- TEAE leading to dose reduction of blinded IP
- TEAEs leading to withdrawal from the study

Listing of AEs with onset prior to first dose of blinded IP will be provided. A separate listing of the TEAEs for participants who underwent dose reduction will be provided.

A summary of most common TEAEs by preferred term where the incidence is more than 2% in any treatment group will be provided, sorted by decreasing frequency of PT in SAGE-217 + ADT group, then of PT in the placebo + ADT group; if 2 or more PTs have the same frequency, the order will be alphabetical.

For maximum severity, participants will be counted only once within each SOC and PT at the maximum severity in the following order: severe> moderate> mild; an AE with missing severity will be omitted from severity presentation. A participant will be counted only once within each SOC and PT at the strongest relationship to blinded IP in the following order: related > not related. Adverse events with onset before the first dose of blinded IP will be provided in a separate listing. Separate data listing for deaths, SAEs, and participants who had AEs leading dose reduction will be provided.

In addition, TEAE summary by SOC/PT will also be presented by the following subgroups:

- Assigned Antidepressant Use: SSRI, SNRI
- Age group: 18-24, 25-50, 51-64 years
- Sex: Male, Female
- Race: White, Black or African American, Other

- BMI at baseline:≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m^2
- COVID-19 History: this will be summarized by worst case COVID-19 related preferred term(PT) coded by MedDRA in medical history data. For participants without COVID-19 related PT, the participants are categorized as 'Not Impacted'
- US COVID-19 status at time of enrollment: First informed consent sign date:

  <= 18Mar2021, > 18Mar2021

8.4.2. Clinical Laboratory

The clinical laboratory tests to be performed for monitoring of safety are listed in Table 5 . They are collected on Screening, days 1, 8, 15, 21, 28, and 42.

Table 5: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Coagulation
Red blood cell count Hemoglobin Hematocrit White blood cell count with differential Platelet count Red Blood Cell Indices (MCV, MCH, MCHC) Reflex to Red blood cell morphology if indices are abnormal	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase Gamma-glutamyl transferase Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphorus Triglycerides Thyroid stimulating hormone (TSH) Reflex to free T3/and freeT4 if TSH is abnormal	pH Specific gravity Protein Glucose Red blood cell Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial Thromboplastin time Prothrombin time International normalized ratio

All parameters will be converted to the International System of Units (SI) before analysis.

For laboratory results that are "≤ *x*", where *x* is a number as collected in the data, the numeric part of the result will be used in the calculation in the summary tables. The same is true if the result is presented as below limit of quantification (BLQ) and a lower limit of quantification (LLOQ) value is provided – LLOQ value will be used for calculation in the summary tables. The actual results as collected will be displayed in the listings.

Summary tables on lab parameters will include descriptive statistics for the observed values [redacted] by scheduled assessment timepoint in hematology, serum chemistry, coagulation, and quantitative urinalysis test results. [redacted]

If a normal range is provided for the parameter, out-of-range values will be flagged as low or high, where applicable, in the data listings. [redacted] Qualitative urinalysis parameters will be summarized descriptively.

The number and percentage of participants with PCS values will be provided in separate displays in hematology, serum chemistry, liver function tests and urinalysis tests provided for such occurrence at any time during treatment, last value on treatment, within 14 days after the last dose. Potentially clinically significant values will be identified for specific laboratory parameters as outlined in Table 6 .

Liver function tests will be monitored closely for PCS values, and will be summarized for occurrence for the following parameters for these PCS threshold (for condition involving more than one parameter, the results need to be from the same timepoint):

Alanine Aminotransferase: >3xULN, >5xULN, >10xULN
Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN
Alanine Aminotransferase or Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN
Alkaline Phosphatase: >1.5xULN, >2xULN
Total Bilirubin: >1.5xULN, >2xULN
Total Bilirubin > 2xULN **AND** (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN)
Total Bilirubin >2xULN **AND** Alkaline Phosphatase >2xULN **AND** (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN)

Total Bilirubin >2xULN **AND** Alkaline Phosphatase < 2xULN **AND** (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN)

Any lab results considered clinically significant by the investigator will be captured as adverse events, hence will be included in AE displays.

Pregnancy test results will be listed but not summarized.

Table 6: Potentially Clinically Significant Values for Specific Laboratory Parameters

Laboratory Parameter	**Units**	**Criteria for PCS Values (Observed values)**	
		High	Low
Hematology			
Hemoglobin -male	g/L	>185	<115
Hemoglobin -female	g/L	>170	<100
Hematocrit-male	Fraction of 1	>0.55	<0.385
Hematocrit-female	Fraction of 1	>0.49	<0.345
Platelet count	10^9/L	>600	<125
White blood cell	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
Serum Chemistry			
Albumin	g/L	>70	<28
Blood urea nitrogen	mmol/L	>10.71	NA
Calcium	mmol/L	>2.75	<2.0
Chloride	mmol/L	>120	<90
Creatinine	mmol/L	>3xULN or >3x Baseline	
Gamma Glutamyl Transferase		>3xULN	
Glucose	mmol/L	>13.9	<2.8
Sodium	mmol/L	>150	<132
Potassium	mmol/L	>5.4	<3.3
Protein	g/L		<45
Bicarbonate	mmol/L	>34	<18
Chloride	mmol/L	>120	<90
Phosphorus	mmol/L	>1.94	<0.61

Laboratory Parameter	Units	Criteria for PCS Values (Observed values)	
Liver Function Tests (LFT)			
Bilirubin	µmol/L	>2xULN	NA
Aspartate Aminotransferase	U/L	>3xULN	NA
Alanine Aminotransferase	U/L	>3xULN	NA
Alkaline Phosphatase	U/L	>1.5xULN	NA

8.4.3. Vital Signs

Vitals for the following parameters – respiratory rate (breaths/minute), oral temperature (degrees C), supine heart rate (beats/minute), supine systolic blood pressure (mmHg), supine diastolic blood pressure (mmHg), standing heart rate (beats/minute), standing systolic blood pressure (mmHg), standing diastolic blood pressure (mmHg), – are collected at screening, days 1, 3, 8, 12, 15, 18, 28, and 42. Descriptive summaries of observed values [redacted] will be provided for vital sign parameters – by scheduled assessment time point. It will also include the summary of last values on treatment and on study assessments.

Additionally, [redacted] will be summarized for such occurrence any time during treatment, last value on treatment, within 14 days after the last dose. Potentially clinically significant values will be identified for vital sign parameters as outlined in Table 7 .

[redacted]

[redacted]

[redacted]

[redacted]

8.4.4. Electrocardiogram

Supine 12-lead ECGs will be performed in triplicate, and are collected on screening, days 1, 15, and 42. The following ECG parameters will be listed for each participant: heart rate (beats per minute), PR (msec), RR (bmp), QRS (msec), QT (msec), and QTcF (msec).

The average of the triplicate values will be used in the summary, including baseline ECG values. The observed value at each time point [redacted] This summary will also include the last values on treatment and on study.

[redacted] will be summarized for such occurrence any time during treatment, last value on treatment, and within 14 days after the last dose. Potentially clinically significant values will be identified for ECG parameters as outlined in Table 8 . This analysis includes triplicate values individually and is not based on average value. In addition, the maximum value of QTcF if within any of the PCS criteria will be summarized.

[redacted]

8.4.5. Physical Examination

Physical examination is scheduled on screening, day 1 and 42 (and EOT if applicable). Only clinically significant abnormalities are captured in the database – for post-baseline observations, these will be reported as adverse events, hence these will be included in AE displays; for pre-baseline observations, these will be reported as medical history, hence these will be included in Medical History displays. The dates of physical examination will be listed to confirm that the examination was done.

[redacted]

[redacted]

[redacted]

[redacted]

9. SUMMARY OF INTERIM AND DMC ANALYSES

Not applicable

10. REFERENCES

1. Dmitrienko A., D'Agostino, Sr. R.B., and Huque, M.F (2013). Key multiplicity issues in clinical drug development. Statistics in Medicine. 32(7); 1079-1111

11. LIST OF APPENDICES

11.1. Appendix A: Schedule of Assessments

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

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

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

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

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

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

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

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

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

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

11.2. Appendix B: Details of Statistical Methodology

Sample SAS code for Mixed Effects Model for Repeated Measures (MMRM):

- If type=un:

```
ods output lsmeans=estimates diffs=diffs;
proc mixed data=&data;
class trtpn avisitn usubjid antidep;
model chg=base trtpn avisitn trtpn*avisitn antidep / ddfm=kr s;
repeated avisitn / subject=usubjid type=un;
lsmeans trtpn*avisitn /diff=all cl alpha=0.05 OM;
** assuming trtpn=1 for the placebo, trtpn=2 for SAGE-217
lsmestimate trtpn*avisitn ' Placebo Over Treatment Period (Equal Weights)' 1 1 1 1 0 0
                                                0 0 0  0 0 0 0 0 0 0 0 0 / divisor=4 OM;
lsmestimate trtpn*avisitn ' Sage Over Treatment Period (Equal Weights)' 0 0 0 0 0 0
                                                0 0 0 1 1 1 1 0 0 0 0 0/ divisor=4 OM;
lsmestimate trtpn*avisitn 'Sage vs Placebo Over Treatment Period (Equal Weights)'
                                        -1  -1 -1  -1 0 0 0 0 0 0 1 1 1 1 0 0 0 0 0 / divisor=4 OM;

lsmestimate trtpn*avisitn 'Placebo Over Day 12, Day 15, and Day 18 (Equal Weights)' 0 0 1
                                                1 1 0 0 0 0  0 0 0 0 0 0 0 0 0 0 / divisor=3 OM;

lsmestimate trtpn*avisitn 'Sage Over Day 12, Day 15, and Day 18 (Equal Weights)' 0 0 0 0 0
                                                0  0 0 0 0 0 0 1 1 1 0 0 0 0/ divisor=3 OM;

lsmestimate trtpn*avisitn 'Sage vs Placebo Over Day 12, Day 15, and Day 18 (Equal
Weights)'  0  0  -1  -1 -1 0 0 0 0 0 0 0 1 1 1 0 0 0 0 / divisor=3 OM;
run;
```

Sample SAS code for Generalized Estimating Equation (GEE):

```
proc genmod data=&data;
class usubjid trtpn antidep avisitn;
model aval=base trtpn avisitn trtpn*avisitn antidep /dist=bin link=logit;
repeated participant=usubjid / type=un; * if convergence not met, use type=exch;
lsmeans trtpn*avisitn / diff exp cl;
run;
```

Sample SAS code for Multiple Imputation (MI):

```
** Missing category 1, trtp=A represent the PLACEBO group
```

```
proc mi data=in seed=xxxx nimpute=100 round=. . . . 1 1 1 1 1 1 1 1 1 1 1 1 1 out=
fcs_reg1;

class trtp ADT;

FCS reg;

mnar model (base day3 day8 day12 day15 day18 day21 day28 day35 day42/ modelobs=
(trtp='A'));

var strata base day3 day8 day12 day15 day18 day21 day28 day35 day42;

run;

** Missing category 2

proc mi data=&data seed=xxxx nimpute=100 round=. . . . 1 1 1 1 1 1 1 1 1 1 1 1 1
1out=fcs_reg2;

class trtp ADT;

fcs nbiter=20 reg (base day3 day8 day12 day15 day18 day21 day28 day35 day42/details);

var trtp ADT base day3 day8 day12 day15 day18 day21 day28 day35 day42;

run;
```

Sample SAS code for Tipping Point Analysis:

```
proc mi data=&data out=temp seed=xxxxxx nimpute=100;
class trtpn adt;
var trtpn adt base day3 day8 day12 day15 day18  day21 day28 day35 day42 ;
fcs reg;
mnar adjust(day_xx/shift=xx adjustobs=(trtpn='2'))
    adjust(day_xx/shift=xx adjustobs=(trtpn='2'))
    adjust(day_xx/shift=xx adjustobs=(trtpn='2'))
    adjust(day_xx/shift=xx adjustobs=(trtpn='2'))
    adjust(day_xx/shift=xx adjustobs=(trtpn='2'))
    adjust(day_xx/shift=xx adjustobs=(trtpn='2')) ;
run;
```

Sample SAS code for Weighted GEE analysis:

- Change the missing pattern from arbitrary to monotone;

```
proc mi data=&data out==&data1 seed= xxxxxx nimpute=100;
mcmc chain=multiple impute= monotone ;
var base adt day3 day8 day12 day15 day18 day21 day28 day35 day42 ;
run;

proc gee data==&data ;
by _imputation_;
```

```
class usubjid trtpn adttype avisitn ;
missmodel base trtpn avisitn trtpn*avisitn adttype / type=obslevel;
model dep = base trtpn avisitn trtpn*avisitn adttype  /dist=bin link=logit ;
repeated subject=usubjid / type=un ; * if convergence not met, use type=exch;
lsmeans trtpn*avisitn / diff exp cl;
run;
```

11.3. Appendix C: Handling of Missing Dates

Dates missing the day, or both the day and month of the year will adhere to the following conventions in order to classify TEAEs and to classify prior and concomitant medications.

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in derivation. In instances where imputed values will be presented, imputed values will be flagged.

Adverse Events

If the AE start date is completely missing, do not impute a date but consider it as TEAE, unless the AE end date is before the initiation of treatment, in which case the AE will be considered prior.

For partial AE start dates:

a. When the year is known, but the month and day is unknown, then:
   - If the year matches the year of first dose date and the end date (if present) is after first dose date, or AE is ongoing, then impute as the month and day of min (first dose date + 1 day, last dose date).
   - If the year of AE onset < year of initiation of the treatment, then the month and day will be set to December 31st.
   - If the year of AE onset > the year of initiation of treatment, then the month and day will be set to January 1st.

b. If the year and month are known, but the day is unknown, then:
   - If the year of AE onset = the year of initiation of the treatment and:
     - the month of AE onset = the month of initiation of the treatment, then the day will be set to the day of initiation of the treatment.
     - the month of AE onset < the month of initiation of the treatment, then the day will be set to the last day of month of the particular year.
     - if the month of AE onset > the month of initiation of the treatment, then the day will be set to the 1st day of month.
   - If the year of AE onset < the year of initiation of the treatment, then the day will be set to the last day of month of the particular year.

- If the year of AE onset > the year of initiation of the treatment, then the day will be set to the 1st day of month.

If the imputed AE onset date is after the AE stop date, then the onset date will be set to the stop date. When the year and day are present and the month is missing, treat it as if the day is missing, and only year is present. Follow the imputation rules for "year is known, but the month and day is unknown".

c. When the year is missing, but the month and/or day is known, treat this date as missing; do not impute.

Dates in Disease History (Dates of diagnosis, current episode, first episode)

If the year is present and the month and day are missing, then the month and day will be set to January 1.

If the year and day are present and the month is missing, then the month will be set to January.

If the year and month are present and the day is missing, then the day will be set to the 1st day of month

Prior and Concomitant Medications

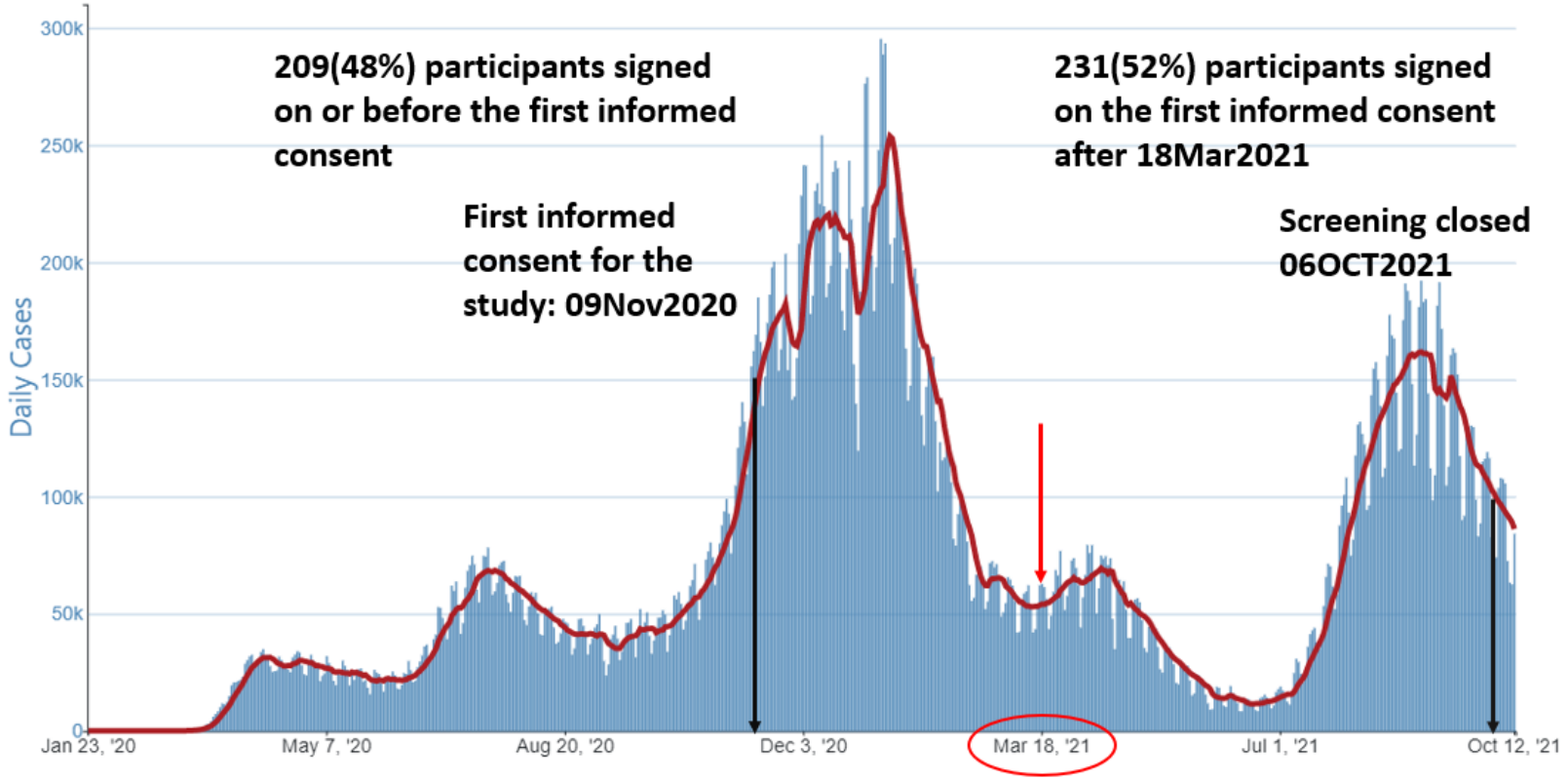
For the partial start date of medication:

a. If the year is present and the month and day are missing, then the month and day will be set to January 1.
b. If the year and day are present and the month is missing, then the month will be set to January.
c. If the year and month are present and the day is missing, then the day will be set to the 1st day of month.
d. If the imputed start date of medication is after the end date (imputed date if applicable) of medication, then the start date will be set to the end date of medication.

For the partial end date of medication:

a. If the year is present and the month and day are missing, then the month and day will be set to min (December 31, date of death).
b. If the year and day are present and the month is missing, then the month will be set to min (December, month of death). If the year and month are present and the day is missing, then the day will be set to min (last day of the month, month of death).
c. If the year and day are present and the month is missing, then treat it as if the day is also missing. Set the month and day to be min (December 31, date of death).

11.4. Appendix D: Daily Trends in Number of COVID-19 Cases in The United States Reported to Centers for Disease Control and Prevention (CDC)



The date of 18March2021 has been determined as the cutoff pre and during peak vs. post-peak.

SOURCE: CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailycases.

As the context of COVID-19 has substantially increased the numbers of individuals experiencing MDD, it is reasonable to examine if enrollment during different periods of the US pandemic had an impact on treatment outcomes.

Rather than assessing the impact of COVID on the treatment outcome, the analyses ask if it is possible that the experience of prolonged quarantine influenced treatment outcomes, particularly during the wave of COVID in the US over the 2020-2021 winter period.
As such, the sponsor has chosen a timepoint which allows for a balanced sample but helps elucidate any potential effects on the placebo response during this period, which may influence the study outcome.

11.5. Appendix E: List of Displays

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Table Number	Title	Analysis Set
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Table Number	Title	Analysis Set
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Table Number	Title	Analysis Set
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Table 14.2.5.4.5	Weighted GEE Model-Based Results on Montgomery-Asberg Depression Rating Scale (MADRS) Remission by Study Visit	Full Analysis Set
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Table Number	Title	Analysis Set
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Table 14.2.6.1.3	Model-based Results on Change from Baseline in Patient Health Questionnaire (PHQ-9) Total Score by Study Visit	Full Analysis Set
Table 14.2.6.1.4	Summary of Patient Health Questionnaire (PHQ-9) Total Score by Study Visit and Assigned Antidepressant Use	Full Analysis Set
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Table 14.2.7.2	Summary of Hamilton Rating Scale for Depression (HAM-D) Percent Retention (%) of Day 15 Change from Baseline at Post-D15 Visits, for HAM-D Responders at Day 15	Full Analysis Set – HAM-D Responders at Day 15
Table 14.2.7.3	Summary of Hamilton Rating Scale for Depression (HAM-D) Response at Post-Day 15 Visits, for HAM-D Responders at Day 15	Full Analysis Set – HAM-D Responders at Day 15
Table 14.2.7.4	Summary of Hamilton Rating Scale for Depression (HAM-D) Remission at Post-Day 15 Visits, for HAM-D Remitters at Day 15	Full Analysis Set – HAM-D Remitters at Day 15

Table Number	Title	Analysis Set
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Listing Number	Title	Analysis Set
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