COVER PAGE

Official Title:	A Phase 3, Open-Label, 1-Year Study of the Safety, Tolerability, and Need for Re-Treatment with SAGE-217 in Adult Subjects with Major Depressive Disorder
NCT Number:	NCT03864614
Document Date:	Part B SAP Version 1.0: 23 January 2023

9. DOCUMENTATION OF STATISTICAL METHODS

The following statistical analysis plan is provided:

217-MDD-303B Statistical Analysis Plan v1.0_signed 20 January 2023

Statistical Analysis Plan

Methods

Protocol Number 217-MDD-303

[SAP for Part B – Rollover Participants Only]

STUDY TITLE: A PHASE 3, OPEN-LABEL, 1-YEAR STUDY OF THE SAFETY, TOLERABILITY, AND NEED FOR RE-TREATMENT WITH SAGE-217 IN ADULT SUBJECTS WITH MAJOR DEPRESSIVE DISORDER

Author of SAP: [redacted]

Version: Version 1.0

Version Date of SAP: 20 January 2023

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Authorization Signature Page

A Phase 3, Open-Label, 1-Year Study of the Safety, Tolerability, and Need for Re-Treatment with SAGE-217 in Adult Subjects with Major Depressive Disorder – Part B for Rollover Participants Only

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LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
ADT	antidepressant therapy
AE	adverse event
ATC	anatomical therapeutic chemical
BLQ	below the limit of quantitation
BMI	body mass index
CGI-I	Clinical Global Impression scale for improvement
CGI-S	Clinical Global Impression scale for severity
CS	Clinically significant
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ET	early termination
FSH	follicle stimulating hormone
GABA	γ-aminobutyric acid
HAM-D	Hamilton Depression Rating Scale
HIV	human immunodeficiency virus
ICF	informed consent form
[redacted]	[redacted]
LFT	liver function tests
LLOQ	lower limit of quantification
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Potentially clinically significant
PCSC	potentially clinically significant change
PHQ-9	Patient health Questionnaire
[redacted]	[redacted]
PT	preferred term
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SCID-5-CT	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for clinical trials
SD	standard deviation
[redacted]	[redacted]
SE	standard error
SI	International System of Units
SNRI	serotonin-norepinephrine reuptake inhibitor
SOC	system organ class

Abbreviation or specialist term	Explanation
SpO_2	pulse oximetry
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis of 217-MDD-303 study, Part B (hereafter referred to as 217-MDD-303B), and is based on the clinical study protocol, version 7.0, dated 10 May 2021. Study 217-MDD-303 has two parts – Part A for de novo participants, and Part B for participants rolling over from Study 217-MDD-305 (parent study). Study 217-MDD-305 is a completed Sage-sponsored randomized, double-blind, placebo-controlled study in which participants co-initiated an FDA-approved antidepressant therapy along with investigational product (SAGE-217 or placebo). This SAP is meant for 217-MDD-303 Part B participants only and describes the analyses to be summarized in the 217-MDD-303B CSR. It will be approved and finalized before database lock. The SAP for Part A will be provided separately, along with its own CSR.

2. STUDY OBJECTIVES (PART B ONLY)

2.1. Primary Objective

The primary objective of this study is to determine the safety and tolerability of initial treatment and/or re-treatment(s) with SAGE-217 in adults with MDD experiencing a major depressive episode (MDE) at entry in the parent study for rollover participants over a 1-year period.

2.2. Secondary Objective

The secondary objectives of this study are:

- To assess the need for re-treatment with SAGE-217 following initial treatment in adults with MDD experiencing an MDE at entry in the parent study for rollover participants over a 1-year period
- To assess the response of initial treatment and/or re-treatment(s) with SAGE-217 following an initial 2-week treatment period in adults with MDD experiencing an MDE at entry in the parent study for rollover participants over a 1-year period

[redacted]

- [redacted]

3. STUDY ENDPOINTS (PART B ONLY)

3.1. Primary Endpoints

The primary endpoint of this study is the safety and tolerability of the initial treatment with SAGE-217 and re-treatment with SAGE-217, as assessed by measures including the incidence and severity of adverse events (AEs)/ serious adverse events (SAEs); changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); and suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS).

3.2. Secondary Endpoints

Secondary endpoints of this study are:

- The need for re-treatment with SAGE-217 as assessed by:
  - Time to first re-treatment (Kaplan-Meier curves)
  - Number of participants achieving the requirements for re-treatment
  - Number of re-treatment cycles for each participant
- The response of initial treatment and/or re-treatment as assessed by:
  - Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at the end of each 14-day treatment (initial and/or re-treatment) period
  - HAM-D response at the end of each 14-day treatment (initial and/or re-treatment) period, defined as a ≥50% reduction in HAM-D score from baseline
  - HAM-D remission at the end of each 14-day treatment (initial and/or re-treatment) period, defined as HAM-D total score ≤7
  - Clinical Global Impression - Improvement (CGI-I) response, defined as "much improved" or "very much improved", at the end of each 14-day treatment (initial and/or re-treatment) period
  - Change from baseline in Clinical Global Impression - Severity (CGI-S) score at the end of each 14-day treatment (initial and/or re-treatment) period

[redacted]

- [redacted]
- [redacted]

- [redacted]
- [redacted]

4. STUDY DESIGN

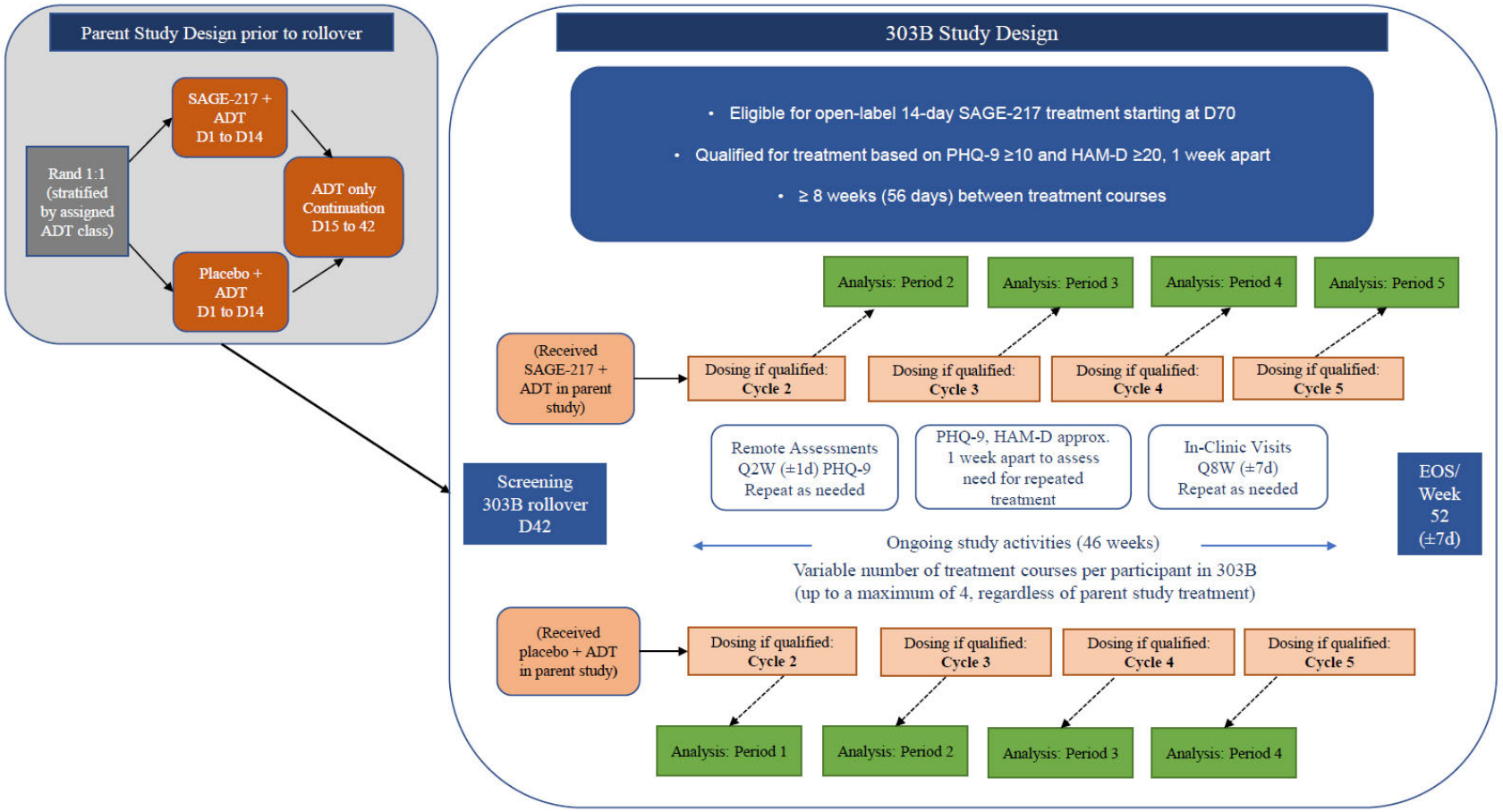
4.1. Overall Design

Adults with MDD who have completed Study 217-MDD-305 (the sole "parent study" and source of participants for the current study, 217-MDD-303B) will sign the ICF and be screened to determine eligibility to enter the study at the Day 42 visit of the parent study. Study 217-MDD-305 (parent study) utilized a double-blind treatment period of 14 days, wherein SAGE-217 or placebo was co-initiated with an investigator-selected and prespecified open-label ADT. Study 217-MDD-305 included a safety follow-up period of 28-days where the participants continued to receive open-label ADT (but not SAGE-217/placebo) with an end of study visit at Day 42.

The screening visit for 217-MDD-303B may occur on the same calendar day as the end-of-study visit in the parent study; in that case, no assessments conducted for the final, end-of-study visit in the parent study will need to be repeated. If participants do not enroll in the current study at the final, end-of-study visit in the parent study, but complete the screening visit for the current study within 5 calendar days, the drug and alcohol screen and pregnancy test (female participants only) should be repeated. Additional assessments may be conducted at the screening visit if necessary.

Participants are eligible to receive the first SAGE-217 treatment within this study only after 4 weeks into the study – 56 days since last blinded Investigational Product (IP) dose in the parent study. They could receive up to 4 treatment courses within this study separated by at least 56 days. This study is 46 weeks long, making the total follow up of a participant as long as 52 weeks from the first dose of blinded IP in 217-MDD-305. Participants are followed with remote assessment of PHQ-9 every two weeks and a score of >=10 would prompt them to return to the site within a week for HAM-D assessment. If HAM-D total score is >=20 and 56 days has elapsed since the last dose of study drug, the participant is qualified to receive SAGE-217 treatment course. Without any trigger by PHQ-9 score described above, a participant would return to the site every 8 weeks for clinical assessments. A Part B study schematic is shown in Figure 1.

Figure 1: Part B Study Design Schematic



ADT = antidepressant therapy; D = day; EOS = end of study; HAM-D = Hamilton Rating Scale for Depression; PHQ-9 = 9-item Patient Health Questionnaire; Q2W = once every 2 weeks; Q8W = once every 8 weeks
Note: Study Days are based on Day 1 dosing in the parent study.
Note: Assigned ADT from parent study may continue into Study 217-MDD-303B.

SAGE-217 treatment cycles

Each 14-day treatment period of SAGE-217 and corresponding 14-day follow-up period is considered a cycle (28 days). The observation period is defined as the end of treatment cycle until the beginning of next treatment cycle. The database reflects that first treatment and follow-up period (28 days) as Cycle 2, rather than Cycle 1 (i.e., these participants completed an initial double-blind treatment cycle in the parent study). For analyses purposes, the cycles are numbered differently based on the treatment the participants received in the parent study. Further information about the numbering of cycles is noted in Section 7.1. Unless otherwise specified, the data from the parent study were reported in the corresponding CSR and are out-of-scope for the analysis of data from this protocol.

The dose of SAGE-217 administered during each new treatment cycle is 50 mg or reduced dose of 40 mg, according to the criteria provided in the protocol. Each cycle begins with Day 1 (i.e., the first day of the first treatment period in this study is Day 1 of Cycle 2). A maximum of 4 treatment cycles within this study is permitted, so 5 overall (i.e., 4 cycles in the current study plus the initial double-blinded cycle in the parent study). A new re-treatment cycle cannot start after Week 48; participants starting a new SAGE-217 treatment cycle between Weeks 45 and 48 will be followed through the end of the treatment cycle (Day 28, end of Follow-up period of treatment cycle). If a participant does not tolerate the 50 mg dose, and has been reduced to 40 mg, the participant may initiate subsequent cycles at the reduced dose of 40 mg, as determined by the investigator.

The need for re-treatment will be assessed every 14 days via remote assessments during the 48 week period from the first dose of parent study (i.e., 42 weeks from the ICF within this study) based on the results of the participant-reported PHQ-9; if the PHQ-9 score is ≥10, the participant will return to the site in approximately one week to be assessed by the clinician-administered HAM-D. New SAGE-217 cycles may be initiated for participants with a HAM-D score ≥20 as long as 56 days since last dose in last cycle have elapsed. In all participants, the End of Study/Week 52 Visit from the first dose of parent study (i.e., 46 weeks from the ICF within this study) is mandatory if another scheduled on site visit does not fall in the Week 52 window.

A minimum period of 8 weeks (56 days) is required between SAGE-217 treatment periods. This is based on a span of 8 weeks establishing ‘full remission’ of a depressive episode. Rollover participants, therefore, will not be eligible to begin their first SAGE-217 treatment period within this study until 56 days have elapsed from the date of last dose of blinded IP - SAGE-217 + ADT or Placebo + ADT - administered in the parent study.

If a participant exhibits suicidality at any time, they will return to the site as soon as possible for assessment by the Investigator.

The assessments for the Screening Period and Observational Period are summarized in Section 10.1, Appendix A; the assessments for the Treatment and Follow-up Periods are summarized in Section 10.2, Appendix B.

4.2. Sample Size and Power

The sample size depends on the number of participants rolling over from the parent study (217-MDD-305). Approximately 350 participants are expected to roll-over to this study from the parent study. No formal power calculations were performed. In total, 277 participants from the parent study had rolled over to this protocol - 133 from SAGE-217 + ADT and 144 from Placebo + ADT.

4.3. Randomization

Study 217-MDD-303B is an open-label rollover design, with participants who were previously randomized in the parent study 217-MDD-305 to Placebo + ADT or SAGE-217 + ADT, stratified by class of co-initiated ADT– selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). All participants in 217-MDD-303B will have the opportunity to receive open-label SAGE-217 if protocol-specified criteria are met.

4.4. Blinding and Unblinding

All participants in this study will receive SAGE-217 in an open-label manner as needed; hence blinding/unblinding does not apply. However, the blinding of the randomized treatment group in the parent study was maintained until the parent study was completed and treatment assignment unblinded.

5. MODIFICATIONS

5.1. Modifications to the Approved Clinical Study Protocol

The word "subject" has been updated to "participant" and the words "study drug" have been updated to "investigational product (IP)" according to the new convention.

Following FDA comments on the statistical section of the protocol, [redacted], anxiolytic, anti-insomnia medications [redacted].

Additional efficacy analyses have been incorporated – durability of response and time to relapse (Section 7.3.4 and 7.3.5, respectively).

The study conduct in the protocol calculated the study day based on the first dose of blinded IP in 217-MDD-305. In this analysis plan, sometimes we deviated from this by calculating the study day based on ICF date in this protocol. These are specified clearly in the respective section.

In the protocol, Safety Set was defined as all participants administered IP. In this analysis plan, the Safety Set definition has been updated to the subset of the Enrolled Set (i.e., all participants who signed the 217-MDD-303B ICF for rolling over to this study from the parent study) who were administered SAGE-217 – either in the parent study (i.e. 217-MDD-305) or within this protocol (217-MDD-303B). The Study-specific Safety Set is defined as all participants who are administered SAGE-217 within the protocol, 217-MDD-303B.

5.2. Modifications to the Approved Statistical Analysis Plan

This is the first version of the SAP for the final analysis.

5.3. Modifications to the Approved DMC Charter

Not applicable.

6. ANALYSIS SETS

6.1. Enrolled Set

The Enrolled Set is defined as all participants who signed the 217-MDD-303B ICF for rolling over to this study from the parent study.

6.2. Safety Set

The Safety Set is defined as the subset of the Enrolled Set who were administered SAGE-217 – either in the parent study (i.e., 217-MDD-305) or within this protocol (217-MDD-303B).

6.3. Study-specific Safety Set

The Study-specific Safety Set is defined as all participants who are administered SAGE-217 within the protocol 217-MDD-303B.

6.4. Period-specific Safety Set

The Period-specific Safety Set includes participants in the Safety Set who are administered SAGE-217 in the corresponding analysis period.

6.5. Full Analysis Set

The Full Analysis Set (FAS) is defined as all participants in the Study-specific Safety Set who have at least one HAM-D total score available after the first dose of SAGE-217 within this protocol. Period-specific efficacy analysis will be done on the subset of FAS who have been administered SAGE-217 in the corresponding analysis period.

Programming algorithms for Period-specific Safety Set and FAS derivations are discussed in Section 10.4, Appendix D.

7. STATISTICAL ANALYSIS

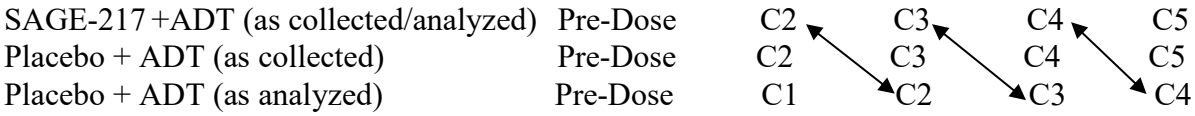
7.1. General Considerations

Unless otherwise specified, continuous endpoints will be summarized with n, mean standard deviation (SD), median, minimum (min) and maximum (max). The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (standard deviation) will be reported to 2 degrees of precision more than the observed data.

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.

The first cycle of treatment in the rollover participants is collected as Cycle 2. Cycle 1 refers to the treatment cycle experienced in the parent study which could be either SAGE-217 + ADT or Placebo + ADT. It is to be noted that for participants who received only Placebo + ADT in the parent study, Cycle 2, the first treatment cycle in this protocol, will be the first exposure to SAGE-217 for such participants. In order to present data from Placebo + ADT participants and SAGE-217 + ADT participants from parent study pooled together (referred to as All Participants in table outputs), yet to be able to interpret data based on the number of treatment cycles received, the treatment cycle and study periods need to be redefined for analysis purposes. The definitions of analysis treatment cycles and analysis study periods are described in Section 7.1.2. A graphical presentation of redefining cycles (Cx) is presented below, with arrows presenting how the SAGE-217 + ADT cycles align with Placebo + ADT cycles in analysis:



Relationship between analysis treatment cycles and analysis study periods is presented below:

	ICF	Dosed in C1	Obs period 1	Dosed in C2	Obs period 2	…..Periods 3, 4	Dosed in C5	Obs Period 5	EOS
Placebo + ADT	Obs Period 0	Analysis Study Period 1		Analysis Study Period 2		Similar to Analysis Study Period 2	Not Applicable		X
SAGE-217 + ADT	Obs Period 0 (Analysis Study Period 1 Not Applicable)			Analysis Study Period 2			Analysis Study Period 5		X

Note: Cycle refers to analysis cycle; pre-dose periods present events in Observation Period 0; for SAGE-217 + ADT group, Analysis Study Period 1 is not applicable; for Placebo + ADT group, Analysis Study Period 5 is not applicable.

All reference to cycle/period in this SAP hereafter refers to analysis cycles/periods.

All participant data, including those derived to support tables and figures will be presented in the participant data listings. Listings will contain data from participants who signed ICF for this protocol, unless specified otherwise. Events will be identified by study period. In general, the participant data listings will be sorted by participant number and assessment visit and date (and time, if applicable). The summary tables will be presented descriptively for the analysis population – for the entire study and/or by treatment cycle/study period.

For baseline subgroup definitions (refer to Section 7.2.3), baseline is defined as the last non-missing measurement prior to the first dose of blinded IP in the parent study.

Unless specified otherwise, period-specific baseline is defined as the last non-missing measurement before the first dose of SAGE-217 in each treatment cycle within this protocol. If the time of an assessment is collected, baseline will be the latest assessment prior to first dose administration time in this period; if the time of an assessment is not collected or missing, the assessment on Day 1 is assumed to be prior to dosing if the protocol or study manual mentions that this assessment needs to be before dosing or it is collected as "pre-dose". For determination of period-specific baseline for the first treatment cycle within this protocol, only the values collected within this study will be used; if it does not exist, the record will not be used for comparison with period-specific baseline (change or response).

For the pooled analysis across the treatment groups (Placebo + ADT and SAGE-217 + ADT as designated in the parent study), displays for cycles/periods 2, 3, and 4 will be presented by analysis cycle/period with pooled data from both groups. Cycle/Period 1 results of Placebo + ADT group and Cycle/Period 5 of SAGE-217 + ADT group will be presented separately.

All assessments, including unscheduled assessments or un-windowed assessments, are included in the derivation for last value on treatment, last value in the study period, and potentially clinically significant (PCS) values.

7.1.1. Study Day Definition

SAGE-217 is administered in the evening with food. The assessments at the clinic on Day 1 are hence before the first dose of SAGE-217 for a particular treatment period.

Study day from ICF of this study will be defined as follows, unless specified otherwise:

- The day of participant signing the ICF in this study is designated as Day 1.
- For visit days on or after Day 1, study day = visit date – Day 1 date + 1.
- For visits before ICF date, study day = visit date - Day 1 date

Study day from the first dose of SAGE-217 within specific study period will be calculated as: visit date – first dose date in the specific period +1.

7.1.2. Study Period Definition

Analysis study periods within this protocol are defined for participants who received Placebo + ADT and SAGE-217 + ADT as follows:

- For Placebo + ADT participants, the pre-dose Observation Period 0 starts from the signing of the ICF for this study protocol and ends either prior to first dose of SAGE-217 in this protocol, if any, or goes until the last day in the study (whichever occurs first). For study period X, where X =1, 2, 3, 4, the study period starts with the first dose in Cycle X and ends prior to the first dose in Cycle X+1 if it exists, or until the last day in the study (whichever occurs first). Note that Study Period 5 does not reside within this protocol for these participants.
- For SAGE-217 + ADT participants, the pre-dose Observation Period 0 starts from the signing of the ICF for this study protocol and ends either prior to first dose of SAGE-217 in this protocol, if any, or goes until the last day in the study (whichever occurs first). For study period X, where X = 2, 3, 4, 5, the study period starts with the first dose in Cycle X and ends prior to the first dose in Cycle X+1 if it exists, or until the last day in the study (whichever occurs first). Note that Study Period 1 does not reside within this protocol for these participants.

Each analysis study period (except pre-dose Observation Period 0) is divided into three exclusive analysis periods - treatment period, follow up period, and observation period; in addition, treatment period and follow up period together constitute of treatment cycle period.

The definition for different analysis periods (study periods 1, 2, 3, 4 for placebo+ADT participants and study periods 2, 3, 4, 5 for SAGE-217+ADT participants) are as follows:

- Treatment Period X starts with first dose of SAGE-217 date/time in Study Period X and ends with last dose of SAGE-217 in Study Period X (both with >0 capsules consumed) + 1 day.
- Follow-up Period X starts after the end of Treatment Period X, and ends on Day 28 visit date/time from vitals; or if vital signs are not assessed, HAM-D date/time is to be used. If none of these have a recorded time available, Day 28 vitals date will be used; if no vitals date, Day 28 HAM-D date will be used. If Day 28 does not exist in either HAM-D or vitals, then the earlier of (treatment period X start date/time + 28 days, study completion/discontinuation date) is to be used.
- Treatment Cycle Period X starts with start of Treatment Period X and ends with end of Follow-up Period X.
- Observation Period X (OBS <x>) starts right after the end of Treatment Cycle X and ends right before the first dose of SAGE-217 in Treatment Cycle X+1. Observation Period X end date/time: Right before the first dose of SAGE-217 in the Treatment Cycle X+1 if such treatment cycle exists, or study completion/discontinuation date if no Treatment Cycle X+1 exists.

The definitions for periods may be slightly different for different endpoints. For details of the algorithm used for defining the periods for concomitant medication, please refer to Section 7.2.5 and Section 10.4, Appendix D.

Except for AEs, which has been described separately in Section 7.4.1, if the evaluation date is the same as treatment start date but time for either the evaluation or the treatment start is

missing, this evaluation is considered according to the nominal visit designation (e.g. Cycle 1 or OBS1 will be assigned Study period 1); if the nominal visit designation is ambiguous, then assign in Study Period X-1, not in Study Period X.

7.1.3. Participant Completion Status

Participants completion status for the Enrolled Set are classified in the following manner:

Prematurely withdrew from the study in pre-dose period:

- Study Conclusion CRF Page: indicates premature withdrawal from the study AND
- Participant dosing status: must not have been dosed with SAGE-217 within this protocol

Completed study in pre-dose period:

- Study Conclusion CRF Page: indicates completion of the study AND
- Participant dosing status: must not have been dosed with SAGE-217 within this protocol

Completer for the study:

- Study Conclusion CRF Page: indicates completion of the study AND
- Participant dosing status: must have been dosed with SAGE-217 within this protocol

Prematurely withdrawn from the study:

- Study Conclusion CRF Page: indicates premature withdrawal from the study AND
- Participant dosing status: must have been dosed with SAGE-217 within this protocol

Prematurely withdrew from study period X, X=1,2,3,4 for participants who received Placebo + ADT in the parent study, X=2,3,4,5 for participants who received SAGE-217 + ADT in the parent study:

- Study Conclusion CRF Page: indicates premature withdrawal from the study AND
- Participant dosing status: Participant is dosed in study period X and not dosed in study period X+1 if X+1 is viable in the study, and the study discontinuation date is on or after the first dose of study period X

For details of study discontinuation date derivation, refer to Section 10.4, Appendix D.

Completed study period X, X=1,2,3,4 for participants who received Placebo + ADT in the parent study, X=2,3,4,5 for participants who received SAGE-217 + ADT in the parent study:

- If the participant is dosed in Study period X+1 when X+1 is viable OR
- Study period X is the last period the participant is dosed and the participant did not prematurely withdraw in study period X per the previous definition

Discontinued treatment cycle X, X=1, 2, 3, 4 for participants who received Placebo + ADT in the parent study, X = 2, 3, 4, 5 for participants who received SAGE-217 + ADT in the parent study:

- Study Conclusion CRF Page: indicates premature withdrawal from the study AND
- Participant dosing status: Participant is dosed in cycle X and not dosed in cycle X+1 if X+1 is viable in the study, and the study discontinuation date is on or before the treatment cycle X end date

For details of study discontinuation date derivation, refer to Section 10.4, Appendix D.

Completed treatment cycle X, X=1, 2, 3, 4 for participants who received Placebo + ADT in the parent study, X = 2, 3, 4, 5 for participants who received SAGE-217 + ADT in the parent study:

- If the participant is dosed in cycle X+1 when X+1 is viable OR
- Cycle X is the last cycle the participant is dosed and the participant did not prematurely withdraw in treatment cycle X per the previous definition

7.1.3.1. Eligible/Qualified for Treatment/Re-treatment for Safety Set

Participants eligible/qualified for treatment/re-treatment for Safety Set are defined as follows:

A participant is eligible for treatment in treatment cycle X if (discontinuation/completion date – last dose date in cycle X-1 ≥56). For being eligible in the first cycle within this protocol, this means that at least 56 days have elapsed from the last dose of blinded IP in the parent study.

A participant is qualified for treatment in treatment cycle X if the participant is eligible for treatment in treatment cycle X AND there exists at least one HAM-D within this protocol where HAM-D total score ≥20 between end of treatment cycle X-1 and
- first dose in treatment cycle X when treatment cycle X start date/time is non-missing
OR
- last day in the study

Participants reached threshold of treatment based on HAM-D and PHQ-9 seperately:

A participant reached threshold of treatment based on HAM-D in treatment cycle X if the participant is eligible for treatment in treatment cycle X AND there exists at least one HAM-D total score ≥20 on or after 56 days from the treatment end date in cycle X-1 (for reaching the threshold in the first cycle of this protocol, the treatment end date is the last dose of blinded IP in the parent study) and this HAM-D evaluation must be before treatment cycle X start date/time if the treatment cycle X start date/time is non-missing. If the Treatment Cycle X start date/time is missing, then the date of study discontinuation/completion will be used.

A participant reached threshold of treatment based on PHQ-9 in treatment cycle X if the participant is eligible for treatment in treatment cycle X AND there exists at least one PHQ-9 score ≥10 on or after 56 days from the treatment end date in cycle X-1 (for reaching the threshold in the first cycle of this protocol, the treatment end date is the last dose of blinded IP in the parent study) and this PHQ-9 evaluation must be before treatment cycle X start

date/time if the treatment cycle X start date/time is non-missing. If the Treatment Cycle X start date/time is missing, then the date of study discontinuation/completion will be used.

Relationship between treatment in this study and re-treatment of SAGE-217

- for Placebo + ADT participants from the parent study, first re-treatment of SAGE-217 is the second treatment within this study
- for SAGE-217 + ADT participants from the parent study, first re-treatment of SAGE-217 is the first treatment within this protocol

For SAGE-217 + ADT participants from the parent study: re-treatment of SAGE-217 is consistent with the treatment within this protocol. Relationship between treatment in this study and re-treatment of SAGE-217 is presented below:

	Study Period 2	**Study Period 3**	**Study Period 4**	**Study Period 5**
Treatment in this study	First Treatment	Second Treatment	Third Treatment	Fourth Treatment
Re-treatment of SAGE-217	First Re-treatment	Second Re-treatment	Third Re-treatment	Fourth Re-treatment

For Placebo + ADT participants from the parent study: relationship between treatment in this study and re-treatment of SAGE-217 is presented below:

	Study Period 1	**Study Period 2**	**Study Period 3**	**Study Period 4**
Treatment in this study	First Treatment	Second Treatment	Third Treatment	Fourth Treatment
Re-treatment of SAGE-217		First Re-treatment	Second Re-treatment	Third Re-treatment

7.1.4. Missing Data

All participants will be used in the analyses, as per the analysis populations, using all non-missing data available; this may include windowing of unscheduled visits when scheduled visit data is missing. For windowing algorithm, please see Section 7.3.2. Imputation of missing data in scoring of questionnaires is discussed in respective sections below. Handling of missing or incomplete dates is discussed in Section 10.3, Appendix C.

7.2. Background Characteristics

Data will be presented using Placebo + ADT, SAGE-217 + ADT and All Participants column with Placebo + ADT and SAGE-217 + ADT referring to the treatment received in the parent study. In the parent study, all participants received the treatment (SAGE-217/Placebo) as planned. Data may be pooled across the Placebo + ADT and SAGE-217 + ADT groups in some summaries; this plan explicitly states how the summaries will be produced.

7.2.1. Participant Disposition

The analyses of participant disposition will use Enrolled set and will be presented by actual treatment group in the parent study in addition to the pooled group. The summary of participant disposition will include:

- the number of participants who signed ICF for this protocol (Enrolled Set),
- the number and percentage of participants who were dosed with SAGE-217 in either the parent study or this study (Safety Set),
- the number and percentage of participants who were never dosed with SAGE-217 in either the parent study or this study,
- the number and percentage of participants who were or were not dosed with SAGE-217 in this study (Study-specific Safety Set),
- the number and percentage of participants who completed this study,
- the number and percentage of participants who prematurely withdrew from this study and primary reasons for not completing the study, and
- the number and percentage of participants who discontinued investigational product in any treatment cycle in this study

A summary of participant disposition will be presented by study period using the period-specific Safety Set. This summary will include the number and percentage of participants dosed in the treatment cycle, who discontinued treatment during the 14-day treatment period, primary reason for discontinuing the treatment, who completed the treatment cycle, who completed the treatment period, who discontinued the study during the study period, and primary reason for study discontinuation. The denominator for percentages will be the period-specific Safety Set.

A separate data listing will be provided for all participants who prematurely discontinued treatment or prematurely withdrew from the study with reasons, number of days on SAGE-217, etc. Separate data listings will be provided for participant involvement by study period, and by treatment cycle.

The number and percentage of participants in each analysis set will be provided, using Enrolled Set as the denominator.

The number and percentage of participants by the length of study participation (through study completion/discontinuation date) since the time of ICF will be provided in category of months: < 3 months , ≥3 months but less than 6 months, ≥6 months but less than 9 months, ≥9 months.

Below is the definition of the cut off for the category, where start date varies based on the analysis:

- End of 3 month period: start date + 90 days
- End of 6 month period: start date + 181 days
- End of 9 month period: start date + 272 days

Refer to Section 10.4, Appendix D for the details of calculation of month.

In addition, the number and percentage of participants by the length of study participation since the time of first dose of SAGE-217 will be provided. For SAGE-217 + ADT participants from the parent study, the first dose of SAGE-217 is the first dose in the parent study; for Placebo + ADT participants from the parent study, the first dose of SAGE-217 is the first dose within this protocol. The number and percentage of participants completing 6 months follow up of SAGE-217, completing 6 months follow up of SAGE-217 without retreatment, complete 1 year follow up of SAGE-217, and complete 1 year follow up of SAGE-217 without retreatment since the first dose of SAGE-217 will be provided. The number and percentage of participants completing the latest re-treatment cycle X will be provided, along with the number and percentage of participants who have not needed any retreatment. This will use Safety Set.

The number and percentage of participants by the length of study participation (through study completion/discontinuation date) since the first dose in the parent study will also be provided in catgory of months: <3 months, ≥3 months but less than 6 months, ≥6 months but less than 9 months, ≥9 months. This will use the Safety Set, and will use blinded IP treatment group from the parent study. Study discontinuation reasons will be provided for each category. The number and percentage of participants completing the latest re-treatment cycle X will be provided, along with the number and percentage of participants who have not needed any retreatment.

The severity of depression, as measured by HAM-D, PHQ-9 and CGI-S, at the latest measurement within this protocol will be summarized, for the Enrolled Set and Full Analysis Set separately and by the completion status in the study. The level of severity will be categorized as follows:

- HAM-D Total Score categories:

  <=7-None, 8-13 – Mild, 14-19 – Moderate, 20-25 – Severe, ≥26 – Very Severe

- PHQ-9 Total Score categories:

  0-4 – Minimal, 5-9 – Mild, 10-14 – Moderate, 15-19 – Moderately severe, 20-27 – Severe

- CGI-S Total Score categories:

  1-2 = Normal/Borderline, 3 = Mild, 4 = Moderate, 5 = Severe, 6-7=Very severe

In addition, the following duration will be included:

- Days since start of most recent treatment cycle in this protocol to last day on study within this protocol (for participants enrolled and not received treatment in this protocol, this is missing)
- Days since start of treatment in parent study to last day on study within this protocol
- Days since start of most recent treatment cycle in parent study or this protocol to last day on study within this protocol (for participants enrolled and not dosed in this protocol, this is days since start of treatment in parent study to last day on study

within this protocol; for participants dosed in this protocol, this is days since start of most recent treatment cycle in this protocol to last day on study within this protocol)

A summary of participant progression will be prepared for the Enrolled Set, with summary statistics presented by actual treatment received in the parent study and overall. The number of participants enrolled, eligible for treatment, qualified for treatment, and dosed in this protocol will be provided; for participants treated with Placebo + ADT in the parent study, the count of participants not dosed in this study in total and by completion status will be provided along with the associated mean and median days since ICF in this study; for participants treated with SAGE-217 + ADT in the parent study, the count of participants with at least one dose of SAGE-217 in the parent or current study, at least one dose of SAGE-217 in the parent study (also subset to those eligible for retreatment in this protocol, qualified for retreatment in this protocol, and qualified and retreated in the next cycle in this protocol), and not dosed in the current study (also subset to those who withdrew, completed, completed before being eligible for retreatment, eligible and qualified for retreatment, qualified and were not retreated) will be provided, along with the associated mean and median days since first SAGE-217 dose in the parent study. For each treatment cycle in this study, the count of participants who discontinued the treatment cycle, completed the treatment cycle and entered observation, discontinued before eligibility for retreatment, eligible for retreatment, and qualified for retreatment (overall, not retreated, and retreated) will be provided.

The number and percentage of participants reaching the threshold of retreatment for a particular cycle of treatment based on HAM-D total score ≥20 or PHQ-9 total score ≥10 will be summarized for the FAS by actual treatment in the parent study and overall. For a given treatment cycle, participants who discontinued/completed the study at least 56 days since last dose of SAGE-217 in immediately prior treatment cycle are used as the denominator for percentages. For participants receiving placebo + ADT in the parent study, possible retreatment cycles include Treatment Cycles 2, 3, and 4; for participants receiving SAGE-217 + ADT in the parent study, possible retreatment cycles include Treatment Cycles 2, 3, 4, and 5.

7.2.2. Protocol Deviations

Protocol deviations identified during site monitoring will be captured on eCRF and categorized by the study team as major (efficacy, safety and GCP, separately) and minor deviations. The major deviations will be summarized by type, for the FAS and Enrolled Set separately.

7.2.3. Demographics and Baseline Characteristics

The following analyses will be done for the Safety Set, FAS, and Enrolled Set, separately. This data comes from the parent study database and will be presented by the actual treatment group from the parent study in addition to the pooled group.

The below demographic data and baseline characteristics will be summarized:

- age, race, sex, ethnicity

- baseline HAM-D total score in parent study
- latest HAM-D total score in parent study
- baseline HAM-A total score in parent study
- latest HAM-A total score in parent study
- Day 15 HAM-D responder in parent study (Yes, No)
- baseline height, weight and body mass index (BMI) in parent study

Subgroups of interest at baseline will be summarized for the following categories:

- Sex (Male, Female)
- Race (Black or African American, White, Other)
- Age (18-24, 25-50, 51-64 years)
- BMI in parent study (≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m2)
- Latest value of HAM-D total score in parent study (<20, ≥20)
- Assigned ADT in parent study (SSRI, SNRI) – if the participant received a different ADT in the parent study than that which was assigned in the parent study, then the ADT actually used in the parent study is used for summarization.
  - Still using same ADT at the time of ICF in this protocol
- Depression with Elevated Anxiety (Yes/No)
  - Defined as HAM-D Anxiety subscale standardized score ≥39 (same as HAM-D Anxiety subscale raw score ≥7) at baseline of the parent study
  - Defined as HAM-A total score ≥20 at baseline of the parent study

7.2.4. Medical/Surgical History

The following analyses will use the Safety Set and the actual treatment group in the parent study, in addition to the pooled group.

The history related to MDD (date of initial diagnosis of MDD, information of depressive episodes, etc.) are collected within the parent study database. Years since initial diagnosis of MDD and information of depressive episodes will be summarized. Years since initial diagnosis of MDD, days since start of current episode and days since start of first episode will be calculated using: First dose date of the blinded IP in the parent study – Date of interest. For imputation of incomplete dates in medical history, please see Section 10.3, Appendix C.

All medical/surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0. Medical/surgical history data will be summarized by system organ class (SOC) and preferred term (PT) – separately for what is collected at Screening in the parent study as well as what is collected for this protocol as interim medical history.

Participant history of psychiatric disorders and family psychiatric history from the parent study database will be summarized.

A listing of drug and alcohol screening from this protocol will be provided.

7.2.5. Prior and Concomitant Medications / Concomitant Procedures

The following analyses will use the Study-specific Safety Set.

All medications taken and procedures undergone during the study will be recorded; in addition, medications that are being taken at the time of entering this study (ICF) will be collected. All medications will be coded using World Health Organization-Drug dictionary (WHO-DD) March 2021.

Those medications that started prior to the first dose of SAGE-217 within this protocol are denoted as "prior". Those medications that started on or after the first dose of SAGE-217 within this protocol or are started before the first dose of SAGE-217 within this protocol yet continuing beyond the first dose of SAGE-217 will be denoted "Concomitant" (i.e., those with a start date on or after the first dose of SAGE-217, or those with a start date before the first dose of SAGE-217 that are ongoing or with a stop date on or after the first dose of SAGE-217). Note that a drug could be marked as both "prior" as well as "concomitant".

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

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

For study period = 1,2,3,4 for participants who received Placebo + ADT and study period = 2,3,4,5 for participants who received SAGE-217 + ADT in the parent study, concomitant medications will also be defined by study period as follows: all medications with a start date on or after the first dose of SAGE-217 in the study period X but before the first dose of SAGE-217 in the study period X+1, or those with a start date before the first dose of SAGE-217 that were ongoing at the time of first dose of SAGE-217 in the study period X or with a stop date on or after the first dose of SAGE-217 in the study period X. These will be further divided by study period as follows (if time is missing, the date will be used for this algorithm):

- On-treatment concomitant medications in study period X are all medications with a start date on or after the first dose of SAGE-217 in the study period X AND the start date on or before the last dose of SAGE-217 in the study period X or those with a start date before the first dose of SAGE-217 that were ongoing at the time of first dose of SAGE-217 in the study period X,
- Post-treatment concomitant medications in study period X are all medications with a start date after the last dose of SAGE-217 in the study period X but before the first dose of SAGE-217 in the study period X+1.

For further details on the programming algorithm of concomitant medication periods, please refer to Section 10.4, Appendix D.

Prior and concomitant non-psychotropic medication use will be summarized for Study-specific Safety Set for all participants in a pooled group by anatomical therapeutic chemical (ATC) level 1 and Standard Medication Name. Similar summary tables will be provided for psychotropic medications. The differentiation of non-psychotropic versus psychotropic medications are based on the answer to the prior or current psychotropic medication question on CRF page.

Concomitant medications overall, and on-treatment and post-treatment concomitant medications separately will be summarized for all participants in a pooled group by study period – psychotropic and non-psychotropic medications separately – using Period-specific Safety Set.

Antidepressant (ADT) medications are identified by ATC3 level code of N06A. Antidepressants other than the assigned ones in the parent study are not permitted within the parent study, but modification of ADT during this protocol is permitted within limits defined in the protocol. A summary of Antidepressant concomitant medication use at period-specific baseline and any change in these medications post-baseline (including the observation period) will be provided by study period, using Period-specific Safety Set and pooled group.

[redacted]

New ADT use is determined by a coded ADT term record that has a start date after the ICF date and is different from the ADT record that has been ongoing at the time of ICF. This analysis will use the Enrolled Set.

Anxiolytic medications are identified by ATC3 level code of N05B. A summary of anxiolytic concomitant medication use at period-specific baseline and any change in these medications post-baseline (including the observational period) will be provided by study period, using Period-specific Safety Set and pooled group. Time to first new anxiolytic use compared to the anxiolytic use at the time of ICF in this protocol will be analyzed with Kaplan-Meier plot by Pplacebo + ADT versus SAGE-217 + ADT group in the parent study, provided there is at least 20 participants in the pooled group. New anxiolytic use is determined by the similar algorithm as done for ADT, except ADT is replaced anxiolytic. This analysis will use the Enrolled Set.

Anti-insomnia medications are identified by ATC3 level code of N05C except when ATC level 4 = N05CF or standard medication name is in (TRAZODONE , MIRTAZAPINE)] or ATC Level 4 = R06AA. A summary of anti-insomnia concomitant medication use at period-specific baseline and any change in these medications post-baseline (including the observation period) will be provided by study period, using Period-specific Safety Set and pooled group. Time to first new anti-insomnia medication use compared to the anti-insomia use at the time of ICF in this protocol will be analyzed with Kaplan-Meier plot by Placebo + ADT versus SAGE-217 + ADT group in the parent study, provided there is at least 20 participants in the pooled group. New anti-insomnia drug use is determined by the similar

algorithm as done for ADT, except ADT is replaced with anti-insomnia drug. This analysis will use the Enrolled Set.

Concomitant procedures are recorded on a separate eCRF page; this will be presented in a listing by participant and will not be summarized. The study day for the end date of the procedure will be provided, when a complete end date is available.

7.2.6. Investigational Product Exposure

The following analyses will use the Period-specific Safety Set.

Total SAGE-217 exposure (in mg) is defined as the total SAGE-217 in mg that was taken during the study period. If the patient skips the dose on any of the days, the dose taken is 0 mg. Total SAGE-217 exposure for the entire study is the sum of period-specific total drug exposure.

The daily dose is 2 capsules – 30+20 for 50mg, 20+20 for 40mg. The capsules cannot be distinguished for the strength. If one capsule is taken within 50mg dosing in a day, 30mg exposure will be assumed for that day. If one capsule is taken within 40mg dosing in a day, 20mg exposure is unambiguous for that day. If more than 2 capsules are taken in a day, within 50mg dosing, additional capsules are assumed to be on strength 30mg; within 40mg dosing, additional capsules are assumed to be on strength 20mg.

Total SAGE-217 exposure duration (in days) for each study period is defined as: Date of last dose in the specific period – date of first dose in the specific period + 1. Note that this does not exclude days when the dose has been missed. Total SAGE-217 exposure duration for the entire study is the sum of SAGE-217 exposure duration over all study periods.

Percent of the planned SAGE-217 exposure received is defined as the total SAGE-217 exposure, divided by planned SAGE-217 exposure, times 100. Planned SAGE-217 exposure will be based on actual duration of treatment within the specific study period for the participant, further based on whether there was a dose reduction in the dosing days:

1. If the participant discontinues treatment within Day 2 and Day 14 (both inclusive) without a dose reduction, the planned exposure is: last dose day of SAGE-217 x initial dose in the cycle (50mg or 40mg)
2. If the participant discontinues treatment within Day 2 and Day 14 (both inclusive), but the participant has undergone a dose reduction on Day X, the planned exposure is: (X-1) x 50mg + (last dose day of SAGE-217 – X + 1) x 40mg.
3. If the participant does not discontinue treatment and does not have a dose reduction, the planned exposure is: 14 x initial dose in the cycle (50mg or 40mg)
4. If the participant does not discontinue treatment but has undergone a dose reduction on Day X, the planned exposure is: (X-1) x 50mg + (14 – X + 1) x 40mg.

Planned SAGE-217 exposure for the entire study is the sum of period-specific planned exposure and will be used as the denominator for the percent calculation for the entire study.

Total SAGE-217 exposure, total SAGE-217 exposure duration and percent of the planned SAGE-217 exposure received for the entire study will be summarized descriptively.

SAGE-217 exposure will also be summarized descriptively by study period.

7.2.7. Investigational Product Adherence

The following analyses will use the Full Analysis Set.

IP adherence (%) is defined as the number of capsules taken, divided by the number of capsules planned to be taken, times 100.

The schedule of SAGE-217 intake is 2 capsules per day.

1. If the participant discontinues treatment within Day 2 and Day 14 (both inclusive), the planned number of capsules is the last dose day of SAGE-217, times 2.
2. If the participant does not discontinue treatment, the planned number of capsules within a treatment cycle/study period is 28.

The planned number of capsules to be taken for the entire study is the sum of period-specific planned number of capsules to be taken and will be used as the denominator for the calculation of adherence for the entire study.

SAGE-217 adherence will be summarized descriptively by study period as well as for the entire study. Number and percentage of participants with IP adherence in categories - <75%, 75-100%, >100% - will be provided. [Since the dispensation of SAGE-217 had more capsules than required between consecutive visits, it is possible to have adherence to be more than 100%.]

7.3. Efficacy Analysis

Data will be presented by study period whenever appropriate. Unless otherwise specified, all efficacy analyses will use Full Analysis Set for the entire study and a subset to FAS for study period X who have been dosed in study period X.

For Placebo + ADT participants from the parent study: first treatment of SAGE-217 in this protocol is the treatment received on Analysis Cycle 1 Day 1 and the first re-treatment of SAGE-217 in this protocol is the treatment received on Analysis Cycle 2 Day 1.

For SAGE-217 + ADT participants from the parent study: first treatment/re-treatment of SAGE-217 in this protocol is the treatment received on Analysis Cycle 2 Day 1.

Summary of Retreatment of SAGE-217

Refer to Section 7.1.3 for the definition of eligible/qualified for re-treatment.

The number and percentage of participants eligible for at least 1 SAGE-217 re-treatment, qualified for at least 1 SAGE-217 re-treatment, dosing in at least 1 SAGE-217 re-treatment, and dosing in exactly X re-treatments, and the number of re-treatment cycles per participant and time between treatment cycles will be summarized for the FAS by blinded IP in the parent study.

Kaplan-Meier (KM) survival curves will be provided for time to first SAGE-217 re-treatment. Median and interquartile ranges will be provided from KM estimates which uses censored observations and will be presented in the figure. Time to first re-treatment in days is calculated as below:

- For Placebo + ADT participants from the parent study: time to first re-treatment in days = first dose date in Cycle 2 Day 1 - last dose of in Cycle 1 Day 1 + 1
- For SAGE-217 + ADT participants from the parent study: time to first re-treatment in days = first dose date in Cycle 2 Day 1 - last dose of blinded IP in parent study +1

The analysis will be provided separately for each group based on blinded IP received in the parent study. A participant will be censored at the last day in the study if the participant did not get any re-treatment. This analysis will be provided for the Study-specific Safety Set and the Safety Set. Algorithms for censoring are discussed in Section 10.4, Appendix D.

The number of participants not having a re-treatment, number of participants having at least one re-treatment, and summary statistics (mean, standard deviation, median, minimum, maximum) for time to first re-treatment for those having at least one re-treatment will be presented by blinded IP from the parent study for the Study-specific Safety Set.

Summary of Treatment

The number and percentage of participants needing at least one SAGE-217 treatment (i.e., meeting the criteria for treatment, but not necessarily treated) and exactly X treatments within this protocol will be provided. The number of treatment cycles per participant and time between treatment cycles will be summarized for the FAS by blinded IP in the parent study.

A listing of PHQ-9 and HAM-D scores leading to SAGE-217 treatment will be provided. A listing of treatment cycles, including treatment cycle number, dates of each treatment start and end (including first treatment), duration of treatment, date of 28-day follow-up visit, and last day on study (only populated on last retreatment) will be provided.

Kaplan-Meier (KM) survival curves will be provided for time to first SAGE-217 treatment within this protocol since ICF date by blinded IP in the parent study. Median and interquartile ranges will be provided from KM estimates which uses censored observations and will be presented in the figure. Time to first treatment in days is counted as below:

- For Placebo + ADT participants from the parent study: time to first treatment in days = first dose date in Cycle 1 Day 1 – ICF date + 1
- For SAGE-217 + ADT participants from parent study: time to first treatment in days = first dose date in Cycle 2 Day 1 – ICF date + 1

The analysis will be provided for the Enrolled Set by blinded IP received in the parent study. A participant will be censored at the last day in the study if the participant did not get any treatment. Algorithms for censoring are discussed in Section 10.4, Appendix D.

The number of participants not having a treatment, number of participants having at least one treatment, and summary statistics (mean, standard deviation, median, minimum, maximum) for time to first treatment for those having at least one treatment will be presented by blinded IP from the parent study for the Enrolled Set.

For exploratory purposes the time to first treatment within this protocol since the last dose of blinded IP in parent study will be analyzed to compare Placebo + ADT versus SAGE-217 + ADT group from the parent study. This analysis will use Enrolled Set and KM survival curve will be provided. Time to first treatment in days is counted as below:

- For Placebo + ADT participants from the parent study: time to first treatment in days = first dose date in Cycle 1 Day 1 – last dose of blinded IP in parent study + 1
- For SAGE-217 + ADT participants from parent study: time to first treatment in days = first dose date in Cycle 2 Day 1 – last dose of blinded IP in parent study + 1

If a participant does not have any treatment within this protocol, the participant will be censored at the last day in the study. Algorithms for censoring are discussed in Section 10.4, Appendix D.

The number of participants not having a treatment, number of participants having at least one treatment, and summary statistics (mean, standard deviation, median, minimum, maximum) for time to first treatment calculated using last dose of parent study for those having at least one treatment will be presented by blinded IP from the parent study for the Safety Set.

Kaplan-Meier (KM) survival curve will be provided for time to first SAGE-217 treatment within this protocol by assigned ADT class (SSRI or SNRI) at the baseline of parent study – separately for SAGE-217 + ADT and Placebo + ADT group from the parent study. The days are counted from the last dose of blinded IP in the parent study to the first dose of SAGE-217 in this protocol. A participant will be censored at the last day in the study if the participant did not get any treatment in this protocol. Algorithms for censoring are discussed in Section 10.4, Appendix D. This analysis will be done on the Enrolled Set.

7.3.1. Definition of Response Variables

The efficacy variables are defined below.

7.3.1.1. 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 Days 1, 8, 15, 28 during each treatment cycle, and then once every 8 weeks (Q8W) during the observation periods. The 17-item HAM-D comprises individual ratings related to the following symptoms: depressed mood (sadness, hopeless, helpless, worthless), feelings of guilt, suicide, insomnia (early, middle, late), work and activities, retardation (slowness of thought and speech; impaired ability to concentrate; decreased motor activity), agitation, anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms,

hypochondriasis, loss of weight, and insight. Each item is scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression. 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. The following table describes the subscale score calculation:

Table 1: HAM-D Subscale Score Calculations

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 Anxiety psychic Somatic symptoms general	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 calculate HAM-D total score to calculate the subscale.
Maier	Depressed mood Feeling of guilt Work and activities Retardation	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

HAM-D Subscales	Items	Calculation
	Agitation Anxiety psychic	calculate HAM-D total score to calculate the subscale.

HAM-D response will be defined as having a 50% or greater reduction from period-specific baseline in HAM-D total score; only participants who have non-missing total score of HAM-D at period-specific baseline as well as the visit will be considered in HAM-D response evaluation. HAM-D remission will be defined as having a HAM-D total score of ≤7; if HAM-D total score is missing at the visit, 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").

7.3.1.2. 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: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse. The CGI-I is rated at post-treatment assessments on Days 8, 15, 28 during each treatment cycle, and Q8W visit during the observation periods. By definition, all CGI-I assessments are evaluated against baseline conditions. CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved." Missing CGI-I at the visit will not be evaluated for response. For a sensitivity analysis the worst-case scenario imputation will be used, i.e. missing values for CGI-I response will be considered as "No response".

7.3.1.3. 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 on Days 1, 8, 15, 28 during each treatment cycle, and at Q8W visit during the observation periods.

7.3.1.4. 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, 8, 15, 28 during each treatment cycle, at Q2W (remote), and at Q8W visit during the observation periods. 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.

[redacted]

[redacted]

7.3.1.7. 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 in the parent study and during the clinic visit on Day 1 of each study period.

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, or the maximum possible values for the missing responses, whichever is smaller, to calculate the MADRS total score.

7.3.2. Visit Windows

The scheduled visits within a treatment cycle will not be windowed and will be used at nominal visit value for analysis purposes. Visits are scheduled in the observation period every eight weeks, but they are collected in the database without reference to the exact day; therefore the data from these visits need to be mapped to the observational visit scheduled, Days 70, 126, 182, 238, 294, 350 for each observational period. In addition, the unscheduled, end-of-treatment (EOT) and early termination (ET) visit will be mapped to a scheduled visit for analysis. The visits before the first dose of SAGE-217 within this protocol do not need to be windowed but will be used for determination of period-specific baseline or end-of-study values. Note that according to the protocol, the schedule of visits starts fresh once the participant is dosed in a cycle, and no longer follows the schedule of every 8 weeks from the previous period.

In order to accommodate as much data as possible into analysis, these windows have been widened compared to protocol-specified operational window; these windows are used for analysis purposes only. Once analysis visit windows are assigned, all visits, including scheduled visits, unscheduled visits, and EOT/ET 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 is available, except for observational visits, then the scheduled visit data will be used.
- If there is no data from the scheduled visit available, the data closest to the scheduled study day for that window will be used.
  - If there is a tie between the data in the number of days before and after the scheduled day, the later data will be used.
  - If there is a tie on the target day, the record with later time 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 (e.g. in case one is available after Week 52) will remain in the database and will be included in the listings.

Table 2 displays windows for response analysis.

Table 2: Visit Windows for Efficacy Analysis (with respect to each treatment cycle)

Scheduled Visit	Target Study Day	Study Day Window for Visit
Period-specific Baseline (Periods 2,3,4,5 for SAGE-217, Periods 1,2,3,4 for Placebo)	Day 1	Latest available before the first dose in Treatment Cycle X but data collected within this protocol
Day 8 (+1 day)	Day 8	Day 2 – Day 11

Scheduled Visit	Target Study Day	Study Day Window for Visit
Day 15 (±1 day)	Day 15	Day 12 – Day 18
Day 28 (±3 day)	Day 28 (last dose date + 14 days)	Day 19 – Day 37 (last dose date + 5 days, +23 days)
Q8W (±3 days)*	Day 70 Day 126 Day 182 Day 238 Day 294 Day 350	Day 63 – Day 77 Day 119 – Day 133 Day 175 – Day 189 Day 231 – Day 245 Day 287 – Day 301 Day 343 – Day 357

*To be used for all observational period visit – scheduled or unscheduled.
Note: Parenthesized study day and study day window are for unscheduled visits, EOT, and ET for participants who have discontinued treatment prematurely and such visit date is more than 4 days from the last dose of SAGE-217 intake (visit date – last dose date +1 >4) within the cycle

End-of-Study (EOS) visit is a scheduled visit which is to be done for participants who completed the study (target date from the first dose date in parent study = Day 364). If the data from the EOS visit is available, then scheduled visit data will be used. If EOS scheduled visit is not available, and there are visits (observational period visit, unscheduled visit, EOT, or ET) that cannot be windowed to a cycle-specific day, they will then be evaluated for EOS window for the completers (per study conclusion CRF page) (≥Day 358 counting from the first dose in the parent study) and in case of multiple visits the one closest to the target date of Day 364 (from first dose date in parent study) will be used in analysis. In summaries by study period, EOS visit will be presented within the last study period the participant had been treated with SAGE-217.

7.3.3. Analysis of Response Variable(s)

The following endpoints will be summarized descriptively by scheduled assessment time point – by each study period separately:

- HAM-D total score – observed, change from period-specific baseline, percent change from period-specific baseline
- HAM-D subscale scores – observed, change from period-specific baseline, percent change from period-specific baseline
- HAM-D individual item score – observed, change from period-specific baseline, percent change from period-specific baseline
- HAM-D response – missing response not accounted (bar chart will also be provided)
- HAM-D response – missing response counted as No response (bar chart will also be provided)
- HAM-D remission – missing remission not accounted (bar chart will also be provided)

- HAM-D remission – missing remission counted as No remission (bar chart will also be provided)
- CGI-I score -observed
- CGI-I response – missing response not accounted (bar chart will also be provided)
- CGI-I response ¬ missing response counted as No response (bar chart will also be provided)
- CGI-S scores – observed and change from period-specific baseline

[redacted]

Line plot of mean and standard deviation (SD) over time will be prepared for change and percent change from baseline in HAM-D total score and HAM-D subscale scores, separately for each study period. For line plots of these efficacy endpoints and bar charts of HAM-D response and remission by study period, for each time point on X axis, the number of participants withdrawing from the study between last time point and this time point will be provided in a row below the X-axis. For time points beyond Day 70, another row of numbers indicating how many participants got retreated (and thus are no longer continuing within this study period) between the last time point and this time point will be provided; this number should be 'not applicable' (NA) at time points before Day 70 within each period. In line plots, a vertical line at Day 70 will be provided to indicate in footnote that this is when a participant becomes eligible for re-treatment; for bar charts, Day 70 will be starred and footnoted in a similar way.

Forest plot for change from period-specific baseline in HAM-D scores at Day 15 –means, 95% confidence interval – will be provided for total score by subgroup and by study period. Similar plot will be provided for change from period-specific baseline in subscale scores of HAM-D by study period.

Following subgroup summaries by study period will be provided for HAM-D total score:

- Sex (Male, Female)
- Race (Black or African American, White, Other)
- Age (18-24, 25-50, 51-64 years)
- Depression with Elevated Anxiety, measured by HAM-D Anxiety Subscale Score (Yes, No)
- Depression with Elevated Anxiety, measured by HAM-A Total Score (Yes, No)
- BMI in parent study (≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m2)

A listing of MADRS collected at baseline of each study period including the screening value from the parent study will be provided.

7.3.4. Durability of Response

Durability measured by HAM-D is defined as follows: Take only the HAM-D responders in study period X on D15. Durability of response by HAM-D criterion is defined as the number of days between Day 15 HAM-D assessment in study period X to the first period-specific study day when the reduction in the HAM-D total score from the period-specific baseline within the study period X is less than 50%. A participant who does not have any HAM-D showing less than 50% reduction in HAM-D total score from the period-specific baseline after Day 15 in the study period X will be censored at the latest HAM-D evaluation date before the first dose date in study period X+1 if it exists or the last HAM-D evaluation in the study if there is no further treatment cycle for the participant. Durability measured by HAM-D will be calculated only for the subset of D15 HAM-D responders in Study Period X who have at least one HAM-D after Day 15 HAM-D date.

Durability measured by PHQ-9: Take only the HAM-D responders in study period X on D15. Durability of response by PHQ-9 criterion is defined as the number of days from Day 15 PHQ-9 assessment in study period X to the first PHQ-9 after Day 15 when PHQ-9 score ≥10 within the study period X. A participant who does not have any PHQ-9 showing score ≥10 within the study period X will be censored at the latest PHQ-9 evaluation date before the first dose date in study period X+1 if it exists or the last PHQ-9 evaluation in the study if there is no further treatment cycle for the participant. [redacted].

For each study period, number of HAM-D evaluations post Day 15 per participant, percent of HAM-D evaluations post Day 15 per participant ≥50% reduction from period-specific baseline, number of PHQ-9 evaluations post Day 15 per participant and percent of PHQ-9 evaluations post Day 15 per participant with score <10 will be summarized.

7.3.5. Time to Relapse

A relapse is defined within each study period separately and is restricted to HAM-D responders at Day 15 in the specific period. Time to relapse is the number of days between Day 15 HAM-D and the first time after Day 15 in the specific period when the participant has HAM-D total score ≥20 preceded by PHQ-9 score ≥10 within 10 days. If the participant does not have a relapse within Study Period X, the participant will be censored at the latest HAM-D evaluation date before the first dose date of next study period if it exists, or the latest HAM-D evaluation date in the study if there is no further treatment cycle for the participant. Time to relapse will be calculated only for the subset of D15 HAM-D responders in Cycle X who have at least one HAM-D after Day 15 HAM-D date. KM survival curve will be

provided by study period, using Safety Set for each period (restricted to Day 15 HAM-D responders only). The number of participants not having a relapse within the study period (i.e. censored), number of participants having a relapse within the study period, and summary statistics (mean, standard deviation, median, minimum, maximum) for time to relapse for those having relapse within the study period will be summarized.

7.4. Safety Analysis

The primary objective of this study is to evaluate the safety and tolerability of SAGE-217 as assessed by the incidence and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; and suicidal ideation and behavior using the C-SSRS. Safety analyses will use the Safety Set and/or Study-specific Safety Set for overall safety. Safety analyses will be provided based on the Period-Specific Safety Set for each study period when appropriate.

The safety endpoints evaluated at scheduled visits are taken as done in nominal visit, without any windowing. If a value is available for a nominal scheduled visit, that value will be used in summary by visit. Unscheduled visits, EOT and ET visits will be windowed using the same window days outlined in Table 2 for efficacy endpoints. If scheduled visit value is not available, 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 7.3.2.

Last value on treatment and Last value in the study period will be included in the summaries whenever indicated in the relevant sections below. Last value on treatment is defined as the last value between the first dose of SAGE-217 (exclusive) and up to last dose of SAGE-217 + 1 day (inclusive) within the specific study period. Last value on study is defined as the last value after the first dose of SAGE-217 within the entire study.

Potentially clinically significant (PCS) values for parameters in lab, vital signs and ECG have been identified by the medical personnel in the team ahead of the analysis. These are listed in the respective sections below.

The safety endpoints and variables considered in the summary tables for this study are summarized in Table 3.

Table 3: Safety endpoints and variables in the summary tables

Safety Evaluation	Incidence	Observed Value	Change/ Period-specific change from Baseline	Abnormality/Clinical Significance (CS)	Potentially Clinical Significance (PCS)
AEs	X				
Labs		X	X	Z	X
ECGs		X	X	Z	X
Vital Signs		X	X		X

Safety Evaluation	Incidence	Observed Value	Change/ Period-specific change from Baseline	Abnormality/Clinical Significance (CS)	Potentially Clinical Significance (PCS)
C-SSRS	X	X	X		

Note: PCS criteria are outlined in Sections 7.4.2-7.4.4
X = to be summarized in tables
Z = to be presented in listings only

7.4.1. Adverse Events

Adverse events (AEs) are collected starting at the time of informed consent and throughout the duration of the participant's participation in the study. All AEs will be coded using MedDRA version 24.0. AEs collected in parent study are not included in AE summary in this study.

A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset on or after the first dose of SAGE-217 – either in the parent study or within this protocol and on or after the ICF sign off date. For more clarification, a TEAE is defined as below:

- For Placebo + ADT participants from parent study: TEAE is defined as an AE with onset on or after the first dose of SAGE-217 in this protocol.
- For SAGE-217 + ADT participants from the parent study: TEAE is defined as an AE with onset on or after the ICF sign off in this protocol.

Adverse events recorded in the database of this protocol with onset on or after the ICF sign date in this protocol and before the first dose of SAGE-217 within this protocol if it exists or before the last day of study within this protocol if the participant was never treated with SAGE-217 within this protocol are considered as Observation Period 0 AE. Obervation Period 0 AE are divided into 2 groups:

- for SAGE-217 + ADT participants from the parent study - these are part of TEAEs for this study
- for Placebo + ADT participants from the parent study - these are not part of TEAEs for this study, but are flagged as pre-treatment adverse events for listing purposes.

The TEAEs will be further categorized by study period of occurrence as follows (X=1 through 5 defined within this protocol):

A TEAE for study period X is defined as an AE with onset on or after the first dose of SAGE-217 in the treatment cycle X until prior to the first dose of SAGE-217 in the subsequent study period X+1. Each analysis study period is divided into three exclusive analysis periods - treatment period, follow up period, and observation period; in addition, treatment period and follow up period together constitute of treatment cycle period. For

details of the algorithm used for defining the periods for AEs, please refer to Section 10.4, Appendix D.

If the date of an AE is incomplete and an unambiguous determination could not be made with respect to its onset time versus the first dose of SAGE-217 and/or last dose of SAGE-217, the AE will be assumed to be a TEAE and a treatment period TEAE in the cycle it started (or assigned to Cycle 1 for Placebo + ADT or Cycle 2 for SAGE-217 + ADT if cycle of AE start could not be determined). For imputation of missing AE dates, please refer Section 10.3, Appendix C. For further details on the programming algorithm of AE periods, please refer to Section 10.4, Appendix D.

An overview summary table of TEAEs will present the number and percentage of participants as well as the number of events using Safety Set as well as Study-specific Safety Set for the following:

- TEAE
- TEAEs by maximum severity (severe>moderate>mild)
- TEAE leading to discontinuation of SAGE-217
- TEAE leading to dose reduction
- TEAE leading to withdrawal from the study
- Death
- Serious Adverse Event (SAE)

An overview summary table of TEAE by study period (including Observation Period 0 TEAEs) will present the number and percentage of participants as well as the number of events using Safety Set for the following:

- TEAE
  - Treatment Cycle Period TEAE
    - Treatment Period TEAE
    - Follow-up Period TEAE
  - Observation Period TEAE
- TEAEs by maximum severity (severe>moderate>mild)
  - Treatment Cycle Period TEAE
    - Treatment Period TEAE
    - Follow-up Period TEAE
  - Observation Period TEAE
- TEAE leading to discontinuation of SAGE-217
- TEAE leading to Dose Reduction

- TEAE leading to withdrawal from the study
  - Treatment Cycle Period TEAE
    - Treatment Period TEAE
    - Follow-up Period TEAE
  - Observation Period TEAE
- Death
  - Treatment Cycle Period
    - Treatment Period
    - Follow-up Period
  - Observation Period
- Serious Adverse Event (SAE)
  - Treatment Cycle Period Serious TEAE
    - Treatment Period Serious TEAE
    - Follow-up Period Serious TEAE
  - Observation Period Serious TEAE

Incidence of TEAEs in 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. All AE summaries described below will use the analysis data set mentioned with respective display. The study level summaries will be sorted by decreasing frequency of SOC first, then by PT within the SOC, then alphabetical within the PT. The by-period summaries will be sorted by decreasing frequency (percent) of Study Period 1 column, by Study Period 2, 3, 4, 5 respectively, then alphabetically – for SOC first, then by PT within SOC, then alphabetical within PT. For subperiod (treatment period/follow up period/treatment cycle period/observation period) TEAE summaries, participants in Period-specific Safety Set in the study period X will be used as the denominator in calculating the percentage.

- TEAE (Safety as well as Study-specific Safety Set at study level, Period-specific Safety Set for by-period (including Observation Period 0 TEAEs))
- Treatment Cycle Period TEAE (Study-specific Safety set at Study level, Period-specific Safety Set for by-period summaries)
- Treatment Period TEAE (Study-specific Safety set at Study level, Period-specific Safety Set for by-period summaries)
- Follow-up Period TEAE (Study-specific Safety set at Study level, Period-specific Safety Set for by-period summaries)

- Observation Period TEAE (Study-specific Safety set at Study level, Period-specific Safety Set for by-period summaries)
- TEAEs by maximum severity (Safety and Study-specific Safety set at Study level)
  - Treatment Period TEAEs by maximum severity ("by study period" only – Period-specific Safety Set)
  - Follow-up Period TEAEs by maximum severity ("by study period" only – Period-specific Safety Set)
  - Treatment Cycle Period TEAEs by maximum severity ("by study period" only – Period-specific Safety Set)
  - Observation Period TEAEs by maximum severity ("by study period" only – Period-specific Safety Set)
- TEAEs by relationship to SAGE-217 (Study-specific Safety Set at study level)
  - Treatment Period TEAEs by relationship to SAGE-217 ("by study period" only – Period-specific Safety Set)
  - Follow-up Period TEAEs by relationship to SAGE-217 ("by study period" only – Period-specific Safety Set)
  - Treatment Cycle Period TEAEs by relationship to SAGE-217 ("by study period" only – Period-specific Safety Set)
  - Observation Period TEAEs by relationship to SAGE-217 ("by study period" only – Period-specific Safety Set)
- Serious TEAEs (Safety as well as Study-specific Safety Set at study level, Safety Set for by-period (including Observation Period 0 TEAEs))
- Treatment Cycle Period Serious TEAEs (Study-specific Safety set at Study level, Period-specific Safety Set for by-period summaries)
- Treatment Period Serious TEAE (Study-specific Safety set at Study level, Period-specific Safety Set for by-period summaries)
- Follow-up Period Serious TEAE (Study-specific Safety set at Study level, Period-specific Safety Set for by-period summaries)
- Observation Period Serious TEAE (Study-specific Safety set at Study level, Period-specific Safety Set for by-period summaries)
- Serious TEAEs by relationship to SAGE-217 (Study-specific Safety Set at study level, Period-specific Safety Set for by-period summaries)
- Treatment Period TEAEs leading to discontinuation of SAGE-217 (Study-specific Safety set at Study level, Period-specific Safety Set for by-period summaries)

- Treatment Period TEAEs leading to dose reduction in SAGE-217 (Study-specific Safety set at Study level, Period-specific Safety Set for by-period summaries), (including a row for number of participants who completed treatment in the study period with dose reduction)
- TEAEs leading to withdrawal from the study (Study-specific Safety set at Study level, Safety Set for by-period summaries)
  - Treatment Cycle Period TEAEs leading to withdrawal from the study ("by study period" only – Period-specific Safety Set)
  - Treatment Period TEAEs leading to withdrawal from the study ("by study period" only – Period-specific Safety Set)
  - Follow-up Period TEAEs leading to withdrawal from the study ("by study period" only – Period-specific Safety Set)

Listing of Observation Period 0 AEs with onset prior to first dose of SAGE-217 but after the ICF sign off date in this protocol will be provided from participants who received Placebo + ADT in the parent study. All listings on TEAEs will provide the study period of AE onset and AE period designation for each AE.

A summary of most common TEAE (defined as incidence more than 2%) by preferred term will be provided, sorted by decreasing frequency using Safety as well as Study-specific Safety Set. A separate summary of most common treatment cycle period TEAE by preferred term will also be provided using Study-specific Safety Set. Further, these summaries will be provided by the study period using the Safety Set and Period-specific Safety Set, respectively.

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. For relationship to SAGE-217, 'related' is defined as relationship being "possible" or "probable" or missing. A participant will be counted only once within each SOC and PT at the strongest relationship to SAGE-217 in the following order: related, not related.

Separate data listing for deaths and non-fatal SAEs will be provided.

In addition, Treatment Cycle Period TEAE summary by SOC/PT by study period will also be presented by the following subgroups using Period-specific Safety Set:

- Age group:18-24, 25-50, 51-64 years
- Sex: Male, Female
- Race: White, Black or African American, Other
- Depression with Elevated Anxiety, measured by HAM-D Anxiety Subscale Score (Yes, No)
- Depression with Elevated Anxiety, measured by HAM-A Total Score (Yes, No)

- BMI in parent study (≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m^2)

7.4.2. Clinical Laboratory

The clinical laboratory tests to be performed for monitoring of safety are listed in Table 4. They are collected at Days 1, 8, 15, and Q8W.

Table 4: 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 morphology	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	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 consistent units according to the International System of Units (SI) before presentation.

For the laboratory results that are "< or = x", where x is a number as collected in the data, the numeric part of the result will be used in calculation in the summary tables. Same is true if the result is presented as BLQ and a 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 be done by study period using Period-specific Safety Set, and will include descriptive statistics for the observed values and changes from period-specific baseline by scheduled assessment timepoint in hematology, serum chemistry, coagulation and quantitative urinalysis test results. It will also include the summary of last post-baseline values on treatment and on study within each study period. The parameter values which are produced only if another parameter is abnormal will be included in data listings, but not summarized.

A listing of clinical lab data for all enrolled participants will be included in the data listing, identifying participants in Placebo + ADT and SAGE-217 + ADT group from the parent study. The data listing will include study period number and visit for records. Any assessments with start date on or after the ICF sign date in this protocol and before the first dose of SAGE-217 within this protocol if it exists or before the last day of study within this protocol if the participant was never treated with SAGE-217 within this protocol will be assigned Observation Period 0.

If a normal range is provided for the parameter, out-of-range values will be flagged as low or high, where applicable, in the participant data listings. A shift table for these parameters will include the out-of-range values for the period-specific baseline, then the shift from normal at period-specific baseline to high or low at any time during treatment (on or after first dose and on or before last dose + 1 day) and any time post-baseline during the study period (on or after first dose in the respective period but before the first dose of next study period). This will be provided using Period-specific Safety Set. Qualitative urinalysis parameters will be summarized descriptively using number and percentage of participants.

The number and percentage of participants with PCS values will be provided in separate displays in hematology, serum chemistry, and liver function tests for such occurrence any time post-baseline (i.e. after first dose of SAGE-217, irrespective of whether it happens in scheduled or unscheduled assessments) during the entire study. Potentially clinically significant values will be identified for specific laboratory parameters as outlined in Table 5. For each study period, an occurrence of PCS values any time in the treatment period, the last value during the treatment period, any time in the treatment cycle, the last value during the treatment cycle and any time during the study period will be summarized, using Period-specific Safety Set.

Table 5: Laboratory Parameters – Criteria for PCS Values

Laboratory Parameter	Sex	Units	Criteria for PCS Values (Observed values)	
			High	Low
Hematology				
Hemoglobin	Male	g/L	>185	<115
	Female	g/L	>170	<100
Hematocrit	Male	Fraction of 1	>0.55	<0.385
	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
Liver Function Tests (LFT)				
Total Bilirubin		µmol/L	>2xULN	NA
Aspartate Aminotransferase		U/L	>3xULN	NA
Alanine Aminotransferase		U/L	>3xULN	NA
Alkaline Phosphatase		U/L	>1.5xULN	NA

Liver function tests will be monitored more closely than above for potentially clinically significant values, and will be summarized by each study period for an occurrence of PCS values any time in the treatment period, the last value during the treatment period, any time in the treatment cycle, the last value during the treatment cycle and any time during the study period, for the following parameters for these PCS threshold:

- 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) **[any time post-baseline, does not need to be measured at the same time point of assessment]**

- [(Total Bilirubin >2xULN) **AND** Alkaline Phosphatase <2xULN (any time post-baseline, measured at the same time point of assessment)] **AND** [(ALT or AST >3xULN) **AND** Alkaline Phosphatase <2xULN, any time post-baseline, measured at the same time point of assessment], refer to algorithm in Section 10.4, Appendix D.

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

Pregnancy test results will be listed but not summarized.

7.4.3. Vital Signs

Vital signs 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 Days 1, 8, 15, 28, and Q8W. Descriptive summaries of observed values and changes from period-specific baseline will be provided for vital sign parameters – by scheduled assessment time point within each study period, using Period-specific Safety Set. It will also include the last values on treatment and on study within study period assessments. The orthostatic vital sign – the change from supine to standing (Supine – Standing) – heart rate, systolic and diastolic blood pressure – will also be summarized by study period and scheduled assessment timepoint.

A listing of vital signs data collected will be included in the data listing, identifying participants in Placebo + ADT and SAGE-217 + ADT group from the parent study. The data listing will include study period number and visit for records. Any assessments with start date on or after the ICF sign date in this protocol and before the first dose of SAGE-217 within this protocol if it exists or before the last day of study within this protocol if the participant was never treated with SAGE-217 within this protocol will be assigned Observation Period 0.

Potentially clinically significant values will be identified for vital sign parameters as outlined in the Table 6. For each study period, an occurrence of PCS values any time in the treatment period, the last value during the treatment period, any time in the treatment cycle, the last value during the treatment cycle and any time during the study period will be summarized, using Period-specific Safety Set.

Table 6: Vital Signs – Criteria for PCS Values

		Criteria for PCS Values			
Vital Sign	**Units**	**Observed values**		**Change from Baseline values**	
		High	Low	Increase	Decrease
Heart rate (supine and standing)	Beats/min	>120	<40	NA	NA
Systolic Blood Pressure (supine and standing)	mmHg	>180	<90	≥30	≥30
Diastolic Blood pressure (supine and standing)	mmHg	>110	<50	≥20	≥20
Supine – Standing Systolic Blood Pressure	mmHg	≥20			
Supine – Standing Diastolic Blood Pressure	mmHg	≥10			
Possible Orthostatic hypotension: supine – standing SBP and DBP	mmHg	SBP ≥ 20 and DBP ≥ 10			
	mmHg	SBP ≥ 20 or DBP ≥ 10			

Any vital signs results considered clinically significant by the investigator will be captured as adverse events, hence will show up in AE displays.

7.4.4. Electrocardiogram

Supine 12-lead ECGs will be performed in triplicate, and are collected at Days 1, 15 and Q8W. The following ECG parameters will be collected for each participant: heart rate (beats per minute), PR (msec), QRS (msec), QT (msec), and QTcF (msec).

The average of the triplicate values will be used in the summary, including period-specific baseline ECG values. The observed value at each time point and change from period-specific baseline at each post-baseline scheduled time point will be summarized for the Period-specific Safety Set. This summary will also include the last values on treatment and on study within study period. Each ECG is evaluated as 'normal', 'abnormal, not clinically significant' and 'abnormal, clinically significant'; the number and percentage of participants with at least one of the triplicate values in the categories of 'abnormal, clinically significant' and 'abnormal, not clinically significant' will be provided by period-specific baseline and each post-baseline scheduled assessment time point (plus the end of treatment and EOS assessments, if any) for the Period-specific Safety Set.

Potentially clinically significant values will be identified for ECG parameters as outlined in Table 7. This analysis includes triplicate values individually and is not based on the average value (note: for the PCS values derived from change from Baseline: Baseline is the average of the triplicate values). For each study period, an occurrence of PCS values any time in the treatment period, the last value during the treatment period, any time in the treatment cycle, the last value during the treatment cycle and any time during the study period will be summarized, using Period-specific Safety Set.

The maximum value of QTcF if within any of the PCS criteria will also be summarized by study period.

Table 7: ECG Parameters – Criteria for PCS and PCSC Values

		Criteria for PCS Values			
ECG	**Units**	**Observed values**		**Change from Baseline**	
		High	Low	Increase	Decrease
QTcF Interval	msec	>450 but <=480, >480 but <=500, >500	NA	≥30 to 60 >60	NA

A listing of ECG data collected this study will be included in the data listing, identifying participants in Placebo + ADT and SAGE-217 + ADT group from the parent study. The data listing will include study period number and visit for records. Any assessments with start date on or after the ICF sign date in this protocol and before the first dose of SAGE-217 within this protocol if it exists or before the last day of study within this protocol if the participant was never treated with SAGE-217 within this protocol will be assigned Observation Period 0.

7.4.5. Physical Examination

Physical examination is scheduled at Day 1 and Q8W. 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.

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

Suicidality data collected on the C-SSRS "Since Last Visit" form is collected during the clinical visits at Days 1, 8, 15, 28, and Q8W. The C-SSRS includes 'yes' or 'no' responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

The participant's non-suicidal self-injurious behavior is also assessed separately as part of C-SSRS.

The assessments for suicidal ideation are ranked as follows with 5 being the worst:

1. Wish to be dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods
4. Active suicidal ideation with some intent
5. Active suicidal ideation with specific plan

The assessments for suicidal behavior are ranked as follows with 5 being the worst:

1. Preparatory acts or behavior
2. Aborted attempt
3. Interrupted attempt
4. Actual attempt (non-fatal)
5. Completed suicide

Suicidal behavior is considered worse than suicidal ideation.

Period-specific baseline for each question is defined as the response in the latest assessment before the first dose of SAGE-217 in the specific period.

The number and percentage of participants with at least one response of 'Yes' to any C-SSRS suicidal ideation or suicidal behavior item, as well as for participant's non-suicidal self-injurious behavior, will be summarized for period-specific baseline and any time post-baseline (period-specific) separately within each study period, using Period-specific Safety Set.

Summary of shift from period-specific baseline in C-SSRS suicidal ideation and suicidal behavior will be presented for the following categories (no suicidal ideation/behavior, suicidal ideation, suicidal behavior) for each scheduled assessment time point within each study period, using Period-specific Safety Set. If the answer to all available assessments in suicidal ideation and all available assessments in suicidal behavior is 'No' then the category for the table is considered as 'No suicidal ideation/behavior'. If any of the assessments in suicidal behavior is Yes, the category is considered as 'Suicidal behavior'. If any of the assessments in suicidal ideation is Yes but all available assessments in suicidal behavior is No, the category is considered as 'Suicidal ideation'.

In addition, a summary of shift in suicidal ideation from period-specific baseline to the maximum rank score for any time post- period-specific baseline will be presented by study period, using Period-specific Safety Set. Maximum score 0 refers to No for all assessments in the desired period for all 5 questions on suicidal ideation.

8. SUMMARY OF INTERIM AND DMC ANALYSES

This is an open-label study. An interim data cut with data cleaned to a pre-specified level (in data management documentation, as agreed by the study team) up to data entered at the pre-specified date has been undertaken at the time of NDA submission. Analyses from this snapshot of data have been included in the original NDA submission in separate section of Integrtaed Summary of Safety.

9. REFERENCES

Clinical study protocol, version 7.0, 10 May 2021, Company: Sage Therapeutics Inc.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th edition, DSM-5). Arlington, VA: American Psychiatric Publishing. 2013.

10. APPENDICES

10.1. Appendix A: Schedule of Events (Screening and Observational Period)

	Screening[a] (within 5 days of completing the final, end-of-study visit in the parent study)	Observational Period[b] (Day 56 through Week 52)			EOS/Week 52 (±7 d)
		Remote Assessment Q2W (±1 d)	Visit Q8W/ ET (±3 d)	Unscheduled Visit (as needed)[c]	
Study Procedure					
Informed Consent	X				
Interim Medical History [d]	X				
[redacted]					
PHQ-9 [e]		X[f]	X	X	X
Inclusion/Exclusion	X				
Abbreviated Physical Examination			X		X
Body Weight			X		X
Clinical Laboratory Assessments			X		X
Drug & Alcohol Screen	X [g]		X		X
Pregnancy Test (urine)	X [g]		X		X
Vital Signs			X		X
12-Lead ECG			X		X
C-SSRS			X		X
HAM-D [h]			X	X	X
CGI-S			X		X
CGI-I			X		X
[redacted]					
Prior/Concomitant Medications[i]	X		X	X	X
Adverse Events/SAEs[j]	X				

ECG = electrocardiogram; ET = early termination; d = days; EOS = end of study; HAM-D = Hamilton Rating Scale for Depression, 17-item; [redacted] O = optional; PHQ-9 = 9-item Patient Health Questionnaire; Q2W = once every 2 weeks; Q8W = once every 8 weeks; [redacted] SAE = serious adverse event

[a] Rollover participants will enter the study for screening at the Day 42 visit during the Observational Period. This visit may occur on the same day as the final, end-of-study visit in the parent study. If conducted on the same day, the assessments listed at this visit do not need to be repeated; in this case, the informed consent and inclusion/exclusion criteria only will be documented. If the Screening Visit is not conducted on the same day as the final, end-of-study visit in the parent study, the pregnancy test and drug and alcohol screen are to be conducted. Additional assessments may be conducted if necessary.

[b] Within an Observational Period, the Q2W remote assessments will begin on Day 56 (±1 day) and occur every 2 weeks (14 days) thereafter. The Q8W visits will begin on Day 70 (±3 days) and occur every 8 weeks (56 days) thereafter.

[c] A participant will return to the site outside of the Q8W visit schedule if the PHQ-9 score is ≥10 and/or upon any suicidal thoughts or behaviors.

[d] Any new medical conditions or procedures with onset/start date after completion of the parent study and prior to signing informed consent in the current study will be recorded as interim medical history.

[e] All PHQ-9 assessments will be performed [redacted].

[f] The participant will take the PHQ-9 every 14 days; if the PHQ-9 score is ≥10, then the participant will return to the site to be assessed by the clinician-administered HAM-D in approximately one week. If the HAM-D score is <20, the participant will take the PHQ-9 on a weekly basis: the participant will return to the site to be assessed by the HAM-D each week that the PHQ-9 score remains ≥10; if the PHQ-9 score is <10, the participant will take the PHQ-9 every 2 weeks thereafter.

[g] To be assessed if the visit is not conducted on the same calendar day as the final (end-of-study) visit in the parent study.

[h] If the HAM-D score is ≥20 (assessed approximately one week from having a PHQ-9 score ≥10) and it has been at least 8 weeks since the last dose of double-blind treatment in the parent study (ie, Day 70 or later), the participant will begin a 14-day SAGE-217 treatment period with a 14-day follow-up visit. If the HAM-D score is ≥20 but it has been less than 8 weeks since the last dose of double-blind treatment in the parent study (ie, Day 69 or earlier), see Section 9.2.1 of the protocol for guidance on allowable interventions; the participant will take the PHQ-9 on a weekly basis until the 8-week period has lapsed, at which time the participant may begin a treatment period with SAGE-217, or until the PHQ-9 score is <10.

[i] Concomitant medications ongoing at Screening and at subsequent visits will be collected.

[j] Adverse events will be collected starting at the time of informed consent and throughout the duration of the participant's participation in the study. Ongoing adverse events from the parent study will be recorded at the Screening Visit.

10.2. Appendix B: Schedule of Events (Treatment and Follow-Up Periods)

	Cycle[a]			
	Open-label Treatment Period (Re-treatments)			Follow-up
Days	**D1**	**D8 (+1d)**	**D15 (±1d)/ EOT[b]**	**D28 (±1d)**
Study Procedure				
Abbreviated Physical Examination	X			
Body Weight			X	
Clinical Laboratory Assessments[c]	X	X	X	
Drug & Alcohol Screen[d]	X	X	X	
Pregnancy Test[e]	X		X	
[redacted]				
Vital Signs[g]	X	X	X	X
12-Lead ECG[h]	X		X	
C-SSRS[i]	X	X	X	X
MADRS	X			
HAM-D [j,k]	X	X	X	X
CGI-S	X	X	X	X
CGI-I		X	X	X
PHQ-9	X	X	X	X
[redacted]				
Investigational Product Dispensation	X	X		
Investigational Product Administration	X (Day 1 through Day 14)			
Investigational Product Accountability/Return		X	X	
Adverse Events/SAEs[l]	X			
Prior/Concomitant Medications[m]	X			

CGI-I = Clinical Global Impression – Improvement; CGI-S – Clinical Global Impression – Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ET = early termination; ECG = electrocardiogram; EOT =

end of treatment; FSH = follicle stimulating hormone; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; MADRS = Montgomery-Åsberg Depression Rating Scale; O = Optional; PHQ-9 = 9-item Patient Health Questionnaire; [redacted] SAE = serious adverse event; [redacted] wt = weight

[a] Each cycle is 28 days (±1 day) and is comprised of a 14-day treatment period and a 14-day follow-up period. Rollover participants may be eligible for re-treatment beginning on Day 1 of Cycle 2; any subsequent re-treatments will be numbered sequentially.

[b] Participants who discontinue treatment early should return to the site for an end of treatment (EOT) visit as soon as possible, preferably the day after treatment is discontinued. The follow-up visit should occur 14 days after the last dose of treatment. Participants who discontinue treatment due to tolerability should be followed without any further administration of study drug in any subsequent cycle. If at any time after the EOT visit, a participant decides to terminate the study, the participant should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a participant discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for the EOT visit will be conducted.

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

[d] Urine toxicology for selected drugs of abuse (as per the laboratory manual) and breath test for alcohol.

[e] Urine pregnancy test.

[redacted]

[g] 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. When vital signs are scheduled at the same time as blood draws, vital signs should be obtained first.

[h] Triplicate ECGs will be collected. When ECG and blood draws are scheduled at the same time, ECG should be performed before blood draws.

[i] The "Since Last Visit" C-SSRS form will be completed at any time of day.

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

[k] The assessment timeframe for the HAM-D scale will refer to the past 7 days (1 week).

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

[m] Concomitant medications will be collected during in-clinic visits.

10.3. 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:

- 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 the month as the month of the first dose date, and day as the day of the first dose date + 1 day.
  - If the year of AE onset < year of the first dose of treatment within this protocol, 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.
- 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 first dose day + 1 day.
    - the month of AE onset < the month of initiation of the treatment, then the day will be set to the last day of month.
    - 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.
  - 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”.

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

Prior and Concomitant Medications

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

For the partial start date of medication:

- 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 treat it as if the day is also missing. Set the month and day to be January 1.
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month.
- If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the end date of medication.

For the partial end date of medication:

- If the year is present and the month and day are missing, then the month and day will be set to December 31.
- 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 December 31.
- If the year and month are present and the day is missing, then the day will be set to the last day of the month.

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 treat it as if the day is also missing. Set the month and day to be January 1.
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month.

10.4. Appendix D: Algorithms

Defining Analysis Datasets

Period-specific Safety Set: Participants who had Treatment Period X start date non-missing

Full Analysis Set for Period X: Participants who are in the Safety Set for period X and have at least one post-baseline HAM-D total score available for study period X

Adverse Event Periods

Refer to Section 7.4.1 for the definition of TEAE and observation Period 0 AE derivation.

Treatment Period AE in Study Period X: AE onset date/time on or after Treatment Cycle X start date/time and on or before last dose date + 1 day in Treatment Cycle X (Note that time does not matter for the end of this period.)

Follow-up Period AE in Study Period X: AE onset date after last dose date +1 day and on or before last dose date + 14 days in Treatment Cycle X (Typically, Day 16 through Day 28 – time does not matter)

Observation Period AE in Study Period X: AE onset date after last dose date + 14 days in Study Period X and before Study Period X+1 start date/time

Treatment Cycle period AE in Study Period X: All AEs that are flagged as either Treatment Period or Follow-up Period AE in Study Period X

If an AE start date is the same as start of Treatment Cycle X, but time is missing in AE start or treatment start, then AE is considered in Cycle X.

Concomitant Medication Periods

Prior: Medications with start date before first treatment cycle start date/time within this protocol

On-treatment in Study Period X: Medication start date on or after Treatment Cycle X start date and on or before the last dose date in Treatment Cycle X, OR Conmed start date before Treatment Cycle X start date and conmed end date either missing or on or after the Treatment Cycle X start date

Post-treatment in Study Period X: Conmed start date after last dose date in Treatment Cycle X and before the Treatment Cycle X+1 start date

Concomitant in Study Period X: All Conmeds that are flagged as either on-treatment or post-treatment in Study Period X

[Note this is determined for period-specific baseline Antidepressant, Anxiolytic and Anti-insomnia medications for each period.]

If the end date of a period is the same as the start date of the next period, and

a. the medication start date falls on this date, then consider the medication as occurring in the next period.

b. the medication end date falls on this date, then consider the medication concomitant in the next period in addition to being concomitant in the current period.

Censoring for Time-To-Event Analysis

For any time-to-event analysis, define time to event and include a flag (1/0) to identify censored observations

For any time-to-event analysis with any snap shot of database – interim or final, each participant must have a non-missing time to event and a non-missing censor value. Time is calculated in days with no respect to time component. Censoring rules are provided below for each specific time-to-event analysis.

If a participant has no assessment after the date of last dose in Treatment Cycle 1, the participant will be included and censored at Day 1.

These general rules will apply in all cases, except for time to relapse and durability of investigational product effect in each study period. Time to relapse and durability of investigational product effect for Study Period X will be computed and summarized only for those participants who are HAM-D responders at Day 15 in Study Period X and who have at least one HAM-D (for time to relapse and durability of investigational product effect by HAM-D) or at least one PHQ-9 ([redacted]) after the Day 15 date.

Time to first retreatment: Ref Date – Date of last dose date in Treatment Cycle 1 +1, where

Ref Date = Date of first dose in Treatment Cycle 2 (CENSOR = 0), OR

= Date of Study Discontinuation or Completion if the participant has Study Conclusion page filled in and Treatment Cycle 2 dosing did not occur (CENSOR=1)

Note: For SAGE-217 + ADT participants from the parent study, Date of last dose date in Treatment Cycle 1 is the last dose of in parent study.

Time to first treatment within this protocol: Ref Date – Date of last dose of blinded IP in the parent study (or Date of ICF – see Section 7.3 for relevant analysis) + 1, where

Ref Date = Date of first dose within this protocol (CENSOR = 0), OR

= Date of Study Discontinuation or Completion if the participant has Study Conclusion page filled in and SAGE-217 dosing within this protocol did not occur (CENSOR=1)

[redacted]

Time to first new anxiolytic use within this protocol: Ref Date – Date of ICF in this protocol + 1, where

Ref Date = Date of first new anxiolytic start within this protocol (CENSOR = 0) [new is determined by a different code of anxiolytic with start date after the ICF date which was not being used at the date of ICF], OR

= Date of Study Discontinuation or Completion if the participant has Study Conclusion page filled in and new ADT has not been started after ICF date (CENSOR=1)

Time to first new anti-insomnia use within this protocol: Ref Date – Date of ICF in this protocol + 1, where

Ref Date = Date of first new anti-insomnia start within this protocol (CENSOR = 0) [new is determined by a different code of anti-insomnia with start date after the ICF date which was not being used at the date of ICF], OR

= Date of Study Discontinuation or Completion if the participant has Study Conclusion page filled in and new ADT has not been started after ICF date (CENSOR=1)

Time to relapse in Study Period X: (Ref Date – Date of Day 15 visit in Study Period X) + 1, where Ref Date

= Date of first relapse in Study Period X where relapse is defined as a participant having a HAM-D total score after Day 15 where HAM-D total score ≥20 and there exists a PHQ-9 ≥10 within 10 days prior to this HAM-D (CENSOR = 0)

= Date of the latest HAM-D evaluation before the first dose in Study Period X+1 if it exists (CENSOR = 1)

= Date of the last HAM-D evaluation in the study if there is no further treatment cycle for the participant (CENSOR = 1)

Durability of investigational product effect by HAM-D in Study Period X: (Ref Date – Date of Day 15 visit in Study Period X) + 1, where Ref Date

= First date after Day 15 within Study Period X when the reduction in HAM-D total score from the period-specific baseline is less than 50% (CENSOR = 0)

or, for participants without any HAM-D showing less than 50% reduction in HAM-D total score from the period-specific baseline after Day 15 in the Study Period X

= Date of the latest HAM-D evaluation after Day 15 within Study Period X and before the first dose in Study Period X+1 if it exists (CENSOR = 1)

= Date of the last HAM-D evaluation after Day 15 within Study Period X and in the study if there is no further treatment cycle for the participant (CENSOR = 1)

[redacted]

Study discontinuation/completion date:

Study discontinuation/completion date is defined from the study conclusion page from the same variable, except when the participant is discontinued for the reason of Lost-to-follow-up, in which case the date of discontinuation is defined as the date of last contact from the study conclusion page.

Calcultion of Month:

- a year is counted as 365.2425 days
- a month is counted as 365.2425/12 = 30.436875 days

  "<3 months" = "Study Day 91 or less"
  ">=3 months and <6 months" = "Study Day >=92 and , <=182"
  ">=6 months and <9 months" = "Study Day >=183, <=273"
  ">= 9 months" = "Study Day >=274"
  where Start Day is calculated as: End Date-Start Date +1

Derivation of PCS for liver function test based on combination results of Total Bilirubin, Alkaline Phosphatase, Alanine Aminotransferase or Aspartate Aminotransferase:

- [(Total Bilirubin >2xULN) **AND** Alkaline Phosphatase <2xULN (any time post-baseline, measured at the same time point of assessment)] **AND** [(ALT or AST >3xULN) **AND** Alkaline Phosphatase <2xULN, any time post-baseline, measured at the same time point of assessment]

In order to derive the records which met the above criteria, the participants should meet both of the following 2 criteria:

1. Total Bilirubin >2xULN AND Alkaline Phosphatase <2xULN (any time post-baseline, measured at the same time point of assessment)
2. (ALT or AST >3xULN) AND Alkaline Phosphatase <2xULN (any time post-baseline, measured at the same time point of assessment)

Time point of assessments in Criterion 1 and Criterion 2 do not have to be the same. However, in order to summarize by the time frame (for example, any time in the treatment period, the last value during the treatment period, etc.), the time point in both criteria should fall into the same time frame. Note that the above PCS criterion cannot be evaluated for last value on treatment unless both condition happens to be satisfied on the last assessment.

Appendix E: List of Displays

Index of Tables

Table Number	Title	Analysis Set
Table 14.1.1.1	Summary of Participant Disposition	Enrolled Set
Table 14.1.1.2	Summary of Analysis Sets	Enrolled Set
Table 14.1.1.3	Summary of Participant Disposition by Study Period	Period-Specific Safety Set
Table 14.1.1.4	Summary of Study Participation	Safety Set
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