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 A SAP Version 3.0: 21 July 2023

SAGE THERAPEUTICS INCORPORATED

Statistical Analysis Plan

Methods

Protocol Number 217-MDD-303

[SAP for Part A – De Novo Subjects 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: 3.0

Version Date of SAP: 21 July 2023

Sponsor: Sage Therapeutics, Inc.
215 First Street
Cambridge, Massachusetts 02142

Authorization Signature Page

Protocol Number: 217-MDD-303

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:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I am the author of this document
Signing Time: 21-Jul-2023 | 08:23 EDT
4CB4D7BF30974239AC1BC40A2362AF78

21-Jul-2023 | 08:23 EDT

Name: [redacted]
Syneos Health

Date

Approved by:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 21-Jul-2023 | 08:04 PDT
A9EFCEB136394EC48D3A1C13B23CD8DA

21-Jul-2023 | 08:04 PDT

[redacted]
Syneos Health

Date

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 21-Jul-2023 | 10:59 EDT
92E67E8BBDDC44E9BC56A6850815A6F4

21-Jul-2023 | 11:00 EDT

[redacted]
Sage Therapeutics, Inc.

Date

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 21-Jul-2023 | 10:47 EDT
FFC23379D63F4A4AB9ED9236C39354B6

21-Jul-2023 | 10:47 EDT

[redacted] Sage Therapeutics, Inc.

Date

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 21-Jul-2023 | 10:02 EDT
DDAF10A1376A455A9CFDCF2F69AA698C

21-Jul-2023 | 10:02 EDT

[redacted]
Sage Therapeutics, Inc.

Date

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 21-Jul-2023 | 09:26 EDT
89BBDD29A7B44DDA8896FB74228A3343

21-Jul-2023 | 09:26 EDT

[redacted]
Sage Therapeutics, Inc.

Date

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 21-Jul-2023 | 09:34 EDT
95A42B3B78C24820B3C963A26F4312B3

21-Jul-2023 | 09:35 EDT

[redacted] Sage Therapeutics, Inc.

Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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	Clinical 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
SOC	system organ class
SpO_2	pulse oximetry
TEAE	treatment-emergent adverse event

Abbreviation or specialist term	Explanation
WHO	World Health Organization

1. INTRODUCTION

Study 217-MDD-303 has two parts – Part A for de novo subjects, and Part B for subjects rolling over from 217-MDD-305 (a double-blind placebo-controlled study). This statistical analysis plan (SAP) is for the final analysis of Study 217-MDD-303 Part A, and is based on clinical study protocol, version 7.0, dated 10 May 2021. The SAP for Part B will be provided separately along with its own CSR.

The purpose of the SAP is to describe in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol for de novo subjects. The SAP will be approved and finalized before database lock.

2. STUDY OBJECTIVES

2.1. Primary Objective

To determine the safety and tolerability of initial treatment and/or re-treatment(s) with SAGE-217 in adults with Major Depressive Disorder (MDD) experiencing a major depressive episode (MDE) at study entry for de novo participants over a 1-year period.

2.2. Secondary Objective

The secondary objectives of Study 217-MDD-303A are:

- To assess the need for re-treatment with SAGE-217 following initial treatment in adults with MDD experiencing an MDE at study entry for de novo 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 study entry for de novo participants over a 1-year period

[redacted]

- [redacted]

3. STUDY ENDPOINTS

3.1. Primary Endpoints

- The safety and tolerability of the initial treatment with SAGE-217 and re-treatment with SAGE-217, as assessed by the incidence and severity of adverse events/serious adverse events; 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

- The need for re-treatment with SAGE-217 as assessed by:
  - Time to first re-treatment (Kaplan-Meier curves)
  - Number of subjects achieving the requirements for re-treatment
  - Number of re-treatment cycles for each subject
- 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]

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, long-term, longitudinal study in adult subjects with MDD currently experiencing an MDE. See Figure 1 for a schematic of the study design.

The Screening Period begins with the signature of the informed consent form (ICF); the ICF must be signed prior to beginning any screening activities.

The diagnosis of MDD must be made according to Structured Clinical Interview for DSM-5 Clinical Trial Version (SCID-5-CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the MADRS, HAM-D, and CGI-S.

Before Protocol Amendment 3 (dated 06 February 2020), all participants received SAGE-217 30 mg. After Protocol Amendment 3, all newly enrolled participants and all ongoing participants for subsequent treatment periods received SAGE-217 50 mg. Note: no participants were dosed under Amendment 3; the first participants who received 50 mg were enrolled under Protocol Amendment 4 (19 March 2020).

Subjects achieving response with SAGE-217 followed for 48 weeks

Beginning on Day 1, qualified subjects self-administer SAGE-217 30 mg or 50 mg (depending on the amendment the subject has consented to) orally once daily in the evening for 14 days. A follow-up visit will be conducted after the completion of the 14-day treatment period.

If a subject does not exhibit a response to SAGE-217 by Day 15 of the initial treatment, defined as a ≥50% reduction in HAM-D score from baseline, the subject will be terminated from the study upon completion of the 14-day follow-up period.

After the initial treatment period, the HAM-D responders will be followed naturalistically for 48 weeks. Subjects will return to the site every 8 weeks (Day 70 is the first 8-week visit – 56 days after the 14-day treatment period, irrespective of when the subject completed treatment period) during the 48-week observational period for clinical assessments.

SAGE-217 treatment cycles

Each 14-day treatment period of SAGE-217 and corresponding 14-day follow-up period is considered a cycle (Day 28). The initial treatment is Cycle 1 and re-treatments will be numbered sequentially. Each cycle will begin with Day 1 (eg, the first day of the first re-treatment period will be Day 1 of Cycle 2). A maximum of 5 treatment cycles is permitted; a new re-treatment cycle cannot start after Week 48.

The need for re-treatment will be assessed every 14 days via remote assessments during the 48-week observational period based on the results of the subject-reported PHQ-9; if the PHQ-9 score is ≥10, the subject will return to the site to be assessed by the clinician-administered HAM-D. New SAGE-217 cycles may be initiated for subjects with a HAM-D score ≥20 assessed approximately 1 week from the PHQ-9 score ≥10. In all subjects, the End of Study (EOS)/Week 52 Visit 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, i.e. first dose date of Cycle X – last dose date of Cycle (X-1) +1 >=56.

One time dose reduction is permitted within a treatment cycle at the discretion of the investigator if the safety of the subject is of concern; for subjects who start with 30mg this reduced dose is 20mg, while for subjects who start with 50mg this reduced dose is 40mg. If a subject was treated with 40mg in any treatment cycle, they may be assigned 50mg or 40mg at the start of a subsequent treatment cycle, according to the discretion of the investigator.

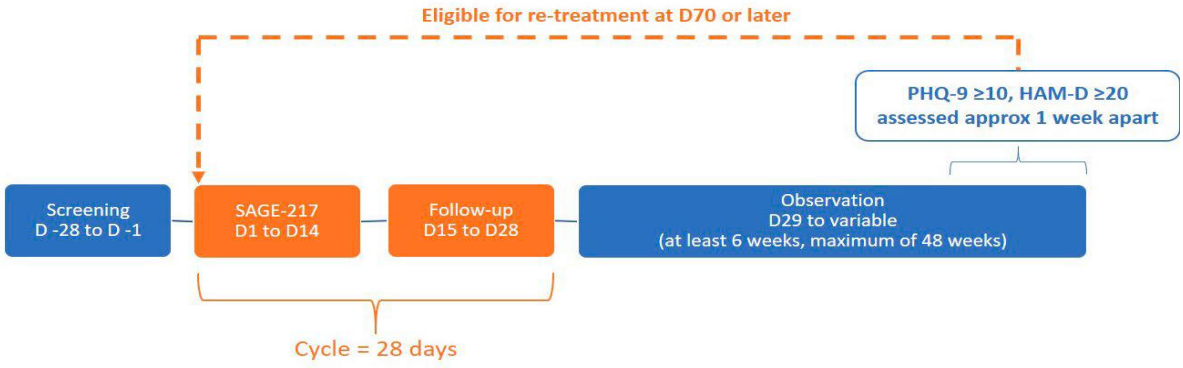
Details guiding the use of as-needed benzodiazepines and GABA-modulators for insomnia (eg, eszopiclone, zopiclone, zaleplon, and zolpidem), new ADT use, or increases in concomitant medication ADT dose are provided in protocol Section 9.2.1. The potential for withdrawal-related events, including seizure, is monitored following the guidelines outlined in protocol Section 8.5.1, which include study drug discontinuation or dose reduction. If a subject 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 Treatment and Follow-up Periods are summarized in Section 10.1, Appendix A; the assessments for the observational period and any unscheduled visits are summarized in Section 10.2, Appendix B.

SAGE-217 study periods

An observation period is defined as the time between end of one treatment cycle (marked by Day 28 visit date or Day 28 11:59 pm if Day 28 visit date is not available) and the beginning of the next treatment cycle (marked by the first dose date/time in the treatment cycle). A study period is defined as a treatment cycle, plus the observation period immediately following. Algorithms for study period derivations are discussed in Section 10.4, Appendix D.

Figure 1: Study Design Schematic



Note: The Observation period only applies to those subjects that exhibit a HAM-D response by Day 15 with the initial treatment, defined as a ≥50% reduction in HAM-D score from baseline. Subjects that do not exhibit a HAM-D response by Day 15 of Cycle 1 will be terminated from the study upon completion of the Day 28 follow-up visit. Subjects who exhibit a HAM-D response by Day 15 of Cycle 1 will be eligible for re-treatment at Day 70 or later.

4.2. Sample Size and Power

The sample size is not based on a formal sample size calculation. The sample size of 1200 de novo subjects was chosen in order to have at least 675 subjects complete 24 weeks of the study and at least 235 subjects complete through 56 weeks.

4.3. Randomization

Study 217-MDD-303 is an open-label design, hence randomization does not apply.

4.4. Blinding and Unblinding

All subjects who receive any study drug in this study will receive SAGE-217 in an open-label manner; hence blinding/unblinding does not apply.

5. MODIFICATIONS

5.1. Modifications to the Approved Clinical Study Protocol

There is no modification in the analysis of data compared to what has been written in the approved clinical study protocol.

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 subjects who signed the ICF and are not a screen failure.

6.2. Safety Set

The Safety Set is defined as all subjects who are administered study drug.

6.3. Period-specific Safety Set

The Period-specific Safety Set includes subjects in the Safety Set who are administered study drug in the corresponding treatment cycle.

6.4. Full Analysis Set

The Full Analysis Set (FAS) is defined as all subjects in the Safety Set who have HAM-D response at Day 15 in treatment cycle 1 and discontinuation from study date, if it exists, is after the end of treatment cycle 1.

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

6.5. Dose Switch Set

The Dose Switch Set is defined as all subjects in the safety set who received 30mg in Treatment Cycle 1, Day 1 and received 50mg on Day 1 in a subsequent re-treatment cycle.

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 subjects in the analysis set used unless specified otherwise.

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

All subject data, including those derived, to support tables and figures will be presented in the subject data listings. In general, the subject data listings will be sorted by dose cohort, subject number and assessment visit and date (and time, if applicable). The summary tables will be presented descriptively for the analysis population by dose cohort and/or by treatment cycle/study period. Displays on Dose Switch Set will be presented by first dose received in each cycle. A listing of dose cohort for each subject and first dose (mg) for each subject in each study period will be provided.

For the purpose of all safety and response analyses, unless specified otherwise, baseline is defined as the last non-missing measurement prior to the first dose of study drug. Period-specific baseline is defined as the last non-missing measurement before the first dose of study drug in each 14-day treatment cycle. If the time of an assessment is collected, baseline will be the latest assessment prior to first dose of study drug administration time; if the time of an assessment is not collected, the assessment on Day 1 is assumed to be prior to dosing if the protocol or study manual mentions that this assessment needs to be before dosing or it is collected as “pre-dose”.

Cohorts of this study are defined based on treatment received per dose dispensation as follows:

- High dose cohort is defined as subjects who received 50mg of SAGE-217 in Treatment Cycle 1, Day 1.
- Low dose cohort is defined as subjects who received 30mg of SAGE-217 in Treatment Cycle 1, Day 1 and received 30mg or 20mg of SAGE-217 as the last dose dispensed.
- Dose Switch cohort is defined as the subjects who received 30mg of SAGE-217 in Treatment Cycle 1, Day 1 and received 50mg of SAGE-217 in Treatment Cycle X, Day 1, where X>1. This is the same set of subjects who are in Dose Switch Set.

- 30mg cohort is defined as the subjects who received 30mg of SAGE-217 in Treatment Cycle 1, Day 1 and combines the Low Dose and Dose Switch cohorts.

Whenever possible, data will be presented for the 3 cohorts (high dose cohort, low dose cohort, dose switch cohort) separately, in addition to all groups together as SAGE-217 Overall cohort. In addition, when appropriate, data will also be presented for 30mg cohort, which refers to the first dose in first cycle, and thus combines the Low Dose and Dose Switch cohorts. For Dose Switch Set, the data will be presented by study period, by the Treatment Cycle X, Day 1 dose received per dose dispensation in the specific period as well as for SAGE-217 Overall (irrespective of dose received). All displays will be presented based on treatment received, with no consideration for planned treatment.

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

It is to be noted that the study drug is administered in the evening with food. The assessments at the clinic on Day 1 are hence before the first dose of study drug.

Study day will be defined as follows:

- The day of subject receiving the first dose of study drug is designated as Day 1.
- For visit days on or after Day 1, study day = visit date – Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date – Day 1 date. Thus, study days for screening visit are negative numbers. There is no “Day 0”.

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

7.1.2. Study Period Definition

- Treatment Period X starts with first dose of study drug date/time in Study Period X and ends with last dose of study drug 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, Day 28 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 vitals or HAM-D, 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 starts right after the end of Treatment Cycle X and ends right before the first dose of study drug in the Treatment Cycle X+1. Observation Period X end date/time: Right before the first dose of study drug in the Treatment Cycle X+1 if such treatment cycle exists, or study completion/discontinuation date if no X+1 cycle exists.
- Study period X starts with start of Treatment Period X and ends with end of Observation Period X.

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 start date is the same as treatment start date but time for either the evaluation or the treatment start is missing, consider this evaluation 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. Subject Completion Status

Subject completion status for the Safety Set is classified in the following manner:

Completer for the study:

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

Prematurely withdrew from study period X, where X=1,2,3,4,5:

- Study Conclusion CRF Page: indicates premature withdrawal from the study AND
- Subject dosing status: Subject 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, where X=1,2,3,4,5:

- 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, where X=1, 2, 3, 4, 5:

- Study Conclusion CRF Page: indicates premature withdrawal from the study AND
- Subject dosing status: Subject 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, where X=1, 2, 3, 4,5:

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

A subject is counted at the beginning of Observation Period X if the subject has completed the treatment cycle X.

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

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

A subject is eligible for re-treatment in treatment cycle X if (discontinuation/completion date - treatment end date in cycle X-1 >=56).

A subject is qualified for re-treatment in treatment cycle X if the subject is eligible for re-treatment in treatment cycle X AND there exists at least one HAM-D total score >=20 after treatment cycle X-1 end date (i.e., any time after 14 days from the treatment end date in cycle X-1) and must be before

- The first dose in treatment cycle X when treatment cycle X start date/time is non-missing OR
- last day in the study

Subjects reached threshold of re-treatment in Cycle X based on HAM-D>=20 on or after 56 days from the treatment end date in Cycle X-1:

A subject reached the threshold of re-treatment in Cycle X based on HAM-D>=20 in Cycle X-1 if the subject is eligible for re-treatment in 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 and this HAM-D evaluation must be before treatment start date/time in Cycle X if the subject received treatment in Cycle X. If the subject did not receive treatment in Cycle X, then the date of study discontinuation/completion will be used.

Subjects reached threshold PHQ-9>=10 after 14 days from the treatment end date in Cycle X:

A subject reached the threshold of re-treatment in Cycle X based on PHQ-9 >=10 in Cycle X if the subject is in FAS and continuing in observation period in Cycle X and there exists at least one PHQ-9 score >=10 after 14 days from the treatment end date in Cycle X (ie., in observation period X) and this PHQ-9 evaluation must be before treatment start date/time in Cycle X+1 if the

subject received treatment in Cycle X+1. If the subject did not receive treatment in Cycle X+1, then the date of study discontinuation/completion will be used.

7.1.4. Missing Data

All subjects 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

7.2.1. Subject Disposition

The analyses of subject disposition will use all subjects who provided written inform consent to the study.

The summaries of subject disposition will include the number of subjects who were screened, screen failed, enrolled, did not receive study drug, and who received any study drug, and the number and percentage of subjects who completed treatment cycle 1, who prematurely withdrew from the study during treatment cycle 1 and associated primary reason for discontinuation, who prematurely discontinued study treatment during treatment period 1 and associated primary reason for discontinuation, who completed the study, who prematurely withdrew from the study and primary reasons for not completing the study, and who switched the dose from 30 mg to 50 mg for the first time by study period. If a subject is rescreened because the subject had been a screen failure the first time, the status of the subject will be determined from the second screening. In the count of screened subjects, this subject will be counted only once.

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

The summaries of subject disposition by study period will include the number of subjects at the beginning of each observation period, the number and percentage of subjects dosed in the treatment cycle, who discontinued treatment during the 14-day treatment period, primary reason for discontinuing the treatment, and who completed the treatment in the study period. This will use Full Analysis Set.

The number and percentage of subjects by the length of study participation (through study completion/discontinuation date) since the time of first dose 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. This will use Safety Set. 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

The number and percentage of subjects initiating the latest re-treatment cycle X will be provided, along with the number and percentage of subjects who have not needed any re-treatment. This will use Safety Set.

A separate data listing will be provided for all subjects who prematurely discontinued treatment or prematurely withdrew from the study with reasons, number of days on study drug, etc. Separate data listings will be provided for subject participation by study period, and by treatment cycle.

A separate data listing will be provided for all subjects regarding screen failure status (Y/N), whether they meet all eligibility criteria (if not, which ones are not met) and reason for screen failure, if applicable.

A summary of subject progression, including information on how many subjects progressed from one cycle to another will be provided. A separate summary for subjects who discontinued treatment prematurely or withdrew from the study will be provided by study period to include the duration on the study and the latest HAM-D total score available.

A summary of the number and percentage of Safety Set subjects who discontinued the study in < 3 months , ≥3 months but less than 6 months, ≥6 months but less than 9 months, ≥9 months, with primary reason for discontinuation, will be summarized for the high dose and 30 mg dose cohorts; for those in the study for <3 months, the summarization will be further subset for those who discontinued from Day 1-15, Day 16-28, and after Day 28. The summary will also include the number and percentage of Safety Set subjects who completed the study overall and subset by the number of treatment cycles initiated.

A summary of the number and percentage of subjects who discontinued the study and with associated reason for discontinuation and the number and percentage of subjects who completed the study overall and subset by the number of treatment cycles initiated will be presented for Full Analysis Set subjects who were HAM-D responders at Day 15 in Treatment Cycle 1.

The latest available HAM-D (continuous and categories of none [<=7], mild [8-13], moderate [14-19], severe [20-25], and very severe [>=26]), latest available PHQ-9 (continuous and categories of minimal [0-4], mild [5-9], moderate [10-14], moderately severe [15-19], and severe [20-27]), and latest available CGI-S (continuous and categories of normal/borderline [1-2], mild [3], moderate [4], severe [5], and very severe [6]), and days since the start of the most recent treatment cycle to last day on study will be summarized for the high dose and 30 mg cohorts and overall for the Full Analysis Set. This summary will be presented for those who completed the study and those who prematurely discontinued the study.

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.

7.2.3. Demographics and Baseline Characteristics

The following analyses will be done for the Safety Set and the FAS separately.

Demographic data (age, race, sex, ethnicity, employment status, highest education level, marital/civil status) and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized. Highest education level will be categorized in the summary tables as follows:

- Less than or equal to12th grade, but no diploma
- 12th grade diploma or GED
- Some college but no degree
- Associate degree
- Bachelor's degree
- Master's degree
- Professional degree
- Doctoral degree

The severity of the depressive episode upon entry into the study will be evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS). The MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in subjects with mood disorders. MADRS is collected at Screening and at Day 1 (prior to dosing). 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 to calculate the MADRS total score. MADRS scores from Screening and Day 1 pre-dose will be summarized.

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, ≥65 years)
  - Elderly/Non-elderly: Age >=65 years, Age <65 years
- Baseline antidepressant use (Yes, No)
  [Antidepressant medications are identified by ATC3 level code of N06A]
- BMI (≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m2)
- Baseline HAM-D total score (<22, >=22)

- Baseline Anxious Depression Status (Yes, No)
  [Baseline HAM-D Anxiety Subscale standardized score >=39 (same as HAM-D Anxiety subscale raw score >=7)]

Diagnostic labs are part of screening; a data listing using Safety Set will be provided. The following diagnostic screening test results will be included in this listing.

Table 1: Diagnostic Screening Test Results

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

7.2.4. Medical/Surgical History

The following analyses will use the Safety Set and FAS.

The history related to MDD (date of initial diagnosis of MDD, antidepressant usage, information of depressive episodes, etc.) will be collected. Years since initial diagnosis of MDD, Antidepressant usage, 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 study drug – Date of interest. For imputation of incomplete dates in medical history, please see Section 10.3. When a subject reports the current episode to be the first one, the number of episodes will be imputed as 1 for summary purposes.

The following analyses will use the Safety Set.

Medical/surgical history collected at screening 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). A summary of medical/surgical history that are ongoing at the time of screening will be provided separately.

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

7.2.5. Prior and Concomitant Medications / Concomitant Procedures

The following analyses will use the Safety Set.

All medications taken and procedures undergone during the study will be recorded; in addition, psychotropic medications taken within 6 months prior to screening, and non-psychotropic medications taken within 30 days prior to screening will also be collected. Psychotropic and non-psychotropic medications are collected on the same CRF page with prior or current psychotropic medication question answered "Yes" for psychotropic medication and "No" for non-psychotropic medication. All medications will be coded using World Health Organization-Drug dictionary (WHO-DD) March 2021.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken prior to the initiation of the start of study drug. Concomitant medications are defined as those with a start date on or after the first dose of study drug or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed concomitant. For imputation of missing concomitant medication dates, please refer to Section 10.3, Appendix C. Note that it is possible for a medication to be both 'prior' and 'concomitant'. Algorithms for concomitant medication period derivations are discussed in Section 10.4, Appendix D. Concomitant medications will also be defined by study period as follows: all medications with a start date on or after the first dose of study drug in the study period X but before the first dose of study drug in the study period X+1, or those with a start date before the first dose of study drug that were ongoing at the time of first dose of study drug in the study period X or with a stop date on or after the first dose of study drug 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 study drug in the study period X AND the start date on or before the last dose of study drug in the study period X or those with a start date before the first dose of study drug that were ongoing at the time of first dose of study drug 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 study drug in the study period X but before the first dose of study drug 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 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.

On-treatment and post-treatment concomitant medications by study period will be summarized – psychotropic and non-psychotropic medications separately.

Antidepressants that have been taken at the same dose for at least 60 days prior to the first dose of study drug are permitted if the subject intends to continue the stable dose through the initial treatment and follow-up period (through Day 28 of Cycle 1). Antidepressant medications are identified by ATC3 level code of N06A. 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.

Anxiolytic and anti-insomnia medication use at Baseline will be summarized. Anxiolytic medications are identified by ATC3 level code of N05B. Anti-insomnia medications are identified by ATC3 level code of N05C or standard medication name is in (TRAZODONE, MIRTAZAPINE) or ATC Level 4 = R06AA. 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. 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.

Baseline use of antidepressant, anxiolytic, or anti-insomnia medication in Study Period X are the medications specified above respectively with a start date before the first dose of study drug in the study period X AND they were ongoing or with a stop date on or after the first dose of study drug in the study period X.

Time to first anxiolytic, time to first anti-insomnia use, and [redacted]. Changes to dose of antidepressants taken at baseline vs. post-baseline, including dose increases, are not counted as new antidepressant. For the analyses of time to first anxiolytic and time to first anti-insomnia, only the medications started on or after the first dose date of study drug in the study are considered. A subject will be censored at the subject's last day in the study if the subject has not taken the specified medication after the first treatment. Programming algorithms for censoring are discussed in Section 10.4, Appendix D.

Concomitant procedures are recorded on a separate eCRF page; this will be presented in a listing by subject, 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. Study Drug Exposure

The following analyses will use the Safety Set.

Total drug exposure (in mg) is defined as the total study drug in mg for SAGE-217 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 drug exposure for the entire study is the sum of period-specific total drug exposure.

In the 50/40mg dose regimen, the daily dose is 2 capsules – 30+20 for 50mg, 20+20 for 40mg. The capsules are blinded 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.

Total exposure duration to study drug (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 exposure duration to study drug for the entire study is the sum of exposure duration over all study periods.

Percent of the planned exposure received is defined as the total drug exposure, divided by planned exposure, times 100. Planned exposure will be based on actual duration of treatment within the specific study period for the subject, based on whether there was a dose reduction in the 30mg or 50mg dosing days:

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

Planned 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 drug exposure, total exposure duration and percent of the planned exposure received for the entire study will be summarized descriptively.

Study drug exposure will also be summarized descriptively by study period.

7.2.7. Study Drug Adherence

The following analyses will use the Full Analysis Set.

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

The schedule of study drug is one capsule per day for 30/20mg dose regimen, and 2 capsules per day for 50/40mg regimen.

1. If the subject discontinues treatment within Day 2 and Day 14 (both inclusive), the planned number of capsules is the last dose day of study drug, times x, where x=1 for 30/20mg dose regimen, =2 for 50/40mg dose regimen.
2. If the subject does not discontinue treatment, the planned number of capsules is 14 for 30/20mg dose regimen, 28 for 50/40mg dose regimen.

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

Study drug adherence will be summarized descriptively by study period. Number and percentage of subjects with study drug adherence in categories - <75%, 75-100%, >100% - will be provided by study period.

Any dose reduction from 30mg to 20mg or 50mg to 40mg will be listed by treatment cycle.

7.3. Efficacy Analysis

Using the FAS, Kaplan-Meier (KM) survival curve by dose cohort will be provided for time to first re-treatment; median will be provided from KM estimates – for SAGE-217 Overall, High Dose, Low Dose and Dose Switch cohorts. A subject will be censored at the date of study discontinuation/completion if the subject did not re-treat; algorithms for censoring are discussed in Section 10.4, Appendix D. In addition to median, the first and third quartile will be provided. A similar plot will be provided for the High Dose cohort versus 30 mg cohort.

The number and percentage of subjects eligible for at least 1 re-treatment, qualified for at least 1 re-treatment, dosing in at least 1 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. Number of treatment cycles per subject will also be summarized. This summary will be repeated by antidepressant use at Study Period 1 Baseline. Box plots corresponding to the time to dosing in Treatment Cycle X+1 since the last dose in Treatment Cycle X (in days) by at least X re-treatments/exactly X re-treatments will be presented.

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

All efficacy analyses will be performed for the FAS unless otherwise specified. For Study Period 1 efficacy analyses may be performed on Safety 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 subjects 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 of individual ratings related to the following symptoms: depressed mood (sadness, hopeless, helpless, worthless), feelings of guilt, suicide, insomnia (early, middle, late), work and activities, retardation (slowness of thought and speech; impaired ability to concentrate; decreased motor activity), agitation, anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis, loss of weight, and insight. Each item is scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression. The score for each item will be summed to compute a total score, which ranges from 0 to 52, rounded to a whole number. 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. Following table describes the subscale score calculation:

Table 2: 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	Sum of the 6-item responses/22 x 100.

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

HAM-D response will be defined as having a 50% or greater reduction from baseline in HAM-D total score; only subjects who have non-missing total score of HAM-D at 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 subject's condition post-treatment. The Investigator will rate the subject'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 subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating as 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=extremely ill. CGI-S is collected at Screening, Days 1, 8, 15, 28 during each treatment cycle, and at Q8W visit during the observation periods.

[redacted]

[redacted]

7.3.1.5. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a 9-item subject-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]

[redacted]

[redacted]

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. Observation period (scheduled and unscheduled), unscheduled, end-of-treatment (EOT), and early termination (ET) visits will be mapped to a scheduled visit for analysis. In order to accommodate as much data as possible into analysis, these windows have been widened compared to protocol-specified operational window, to have no gap between them; these windows are used for analysis purposes only.

Once analysis visit windows are assigned, all visits, including scheduled visits, unscheduled visits, and EOT/ET visits will be eligible for being flagged as the "analyzed record" within the analysis window; a subject's individual analysis visit window could potentially contain more than 1 visit. In the event of multiple visits falling within an analysis window or in case of a tie, the following rules will be used in sequence to determine the "analyzed record" for the analysis visit window:

- If 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 subject. 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 3 displays windows for response analysis.

Table 3: Visit Windows for Efficacy Analysis (with respect to each treatment cycle)

Scheduled Visit	Target Study Day	Study Day Window for Visit
Baseline / Period-specific Baseline	Day 1	Latest available before the first dose in Treatment Cycle 1 / in Treatment Cycle X
Day 8 (±1 day)	Day 8	Day 2 – Day 11
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 63 – Day 77 Day 119 – Day 133

Scheduled Visit	Target Study Day	Study Day Window for Visit
	Day 182 Day 238 Day 294 Day 350	Day 175 – Day 189 Day 231 – Day 245 Day 287 – Day 301 Day 343 – Day 357

Notes: Parenthesized study day window are for Observation period visits (scheduled or unscheduled), unscheduled visits, EOT, and ET for subjects who have discontinued treatment prematurely and only when such visit date is more than 4 days from the last dose of study drug intake (visit date – last dose date +1 >4) within the same treatment cycle. If the date does not fall in the parenthesized window days, the visit will be matched against the Observation period visit only (Q8W) within the same study period. If the visit date is less than or equal to 4 days from the last dose date, or the visit comes from subjects who completed the treatment, parenthesized window days do not apply; the visit will be matched against the non-parenthesized window for treatment cycle as well as observation period visits, as appropriate, within the same study period.

End-of-Study (EOS) visit is a scheduled visit which is to be done for subjects who completed one year of follow up (target date from first cycle first dose date = Day 364). If the data from 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 first 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 cycle 1 first dose date) and in case of multiple visits the one closest to the target date of Day 364 (from cycle 1 first dose date) will be used in analysis. In summaries by study period, EOS visit will be presented within the last study period the subject had been treated with SAGE-217.

7.3.3. Analysis of Response Variable(s)

Response analyses for the first treatment cycle will be provided based on the Safety Set. The FAS will be used for all response summary tables by study period. Subjects who do not achieve HAM-D response at Day 15 (at least 50% reduction from baseline HAM-D total score or missing Day 15 HAM-D) will be discontinued from the study after the 14-day follow-up period with treatment cycle 1.

The following response endpoints will be summarized descriptively by scheduled assessment time point – for study period 1 and by each study period separately, for SAGE-217 Overall and by dose cohort:

- HAM-D total score – observed, change from baseline, percent change from baseline, change from period-specific baseline, percent change from period-specific baseline
- HAM-D subscale scores – observed, change from baseline, percent change from baseline, change from period-specific baseline, percent change from period-specific baseline
- HAM-D individual item score – observed, change from baseline, percent change from baseline, 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
- CGI-I response – missing response counted as No response
- CGI-S scores – observed and change from baseline, change from period-specific baseline
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Line plot of mean and standard deviation (SD) over time will be prepared for change from baseline in HAM-D total score, HAM-D subscale scores, and [redacted] separately for each study period, and HAM-D total score separately for different combination of each study period and anti-depressant use at baseline combination. 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, 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 score of HAM-D by study period.

To explore how the antidepressant use affects HAM-D results, the following summaries will be provided, and corresponding line plots for total score and bar charts for HAM-D response and remission will be provided:

- HAM-D total score for each study period, by use of antidepressant at period-specific baseline, using FAS subjects who were dosed in the specific study period
- HAM-D total score for Treatment Cycle 1, by use of antidepressant at baseline, using Safety set
- HAM-D Response for each study period, by use of antidepressant at period-specific baseline, using FAS subjects who were dosed in the specific study period
- HAM-D Response for Treatment Cycle 1, by use of antidepressant at baseline, using Safety set
- HAM-D Remission for each study period, by use of antidepressant at period-specific baseline, using FAS subjects who were dosed in the specific study period
- HAM-D Remission for Treatment Cycle 1, by use of antidepressant at baseline, using Safety set
- Summary of select efficacy endpoints – HAM-D total score, HAM-D response, HAM-D remission, CGI-S, CGI-I scores, CGI-I response, [redacted], [redacted] and [redacted] - by study periods will be presented for Dose Switch Set by the first dose of 30mg, 40mg or 50mg in the respective re-treatment 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, ≥65 years)
- BMI (≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m2)
- Anxious Depression status at Baseline (Yes, No)

In addition, for FAS who were dosed in study period X (X>1), the summary of HAM-D total score, HAM-D subscale scores, CGI-S score and [redacted] will be provided for Baseline, Day 8, Day 15, Day 28 and any scheduled visit in the current and previous study periods. Line plot of percent change from period-specific baseline will be provided for HAM-D total score and HAM-D subscale scores for FAS who were dosed in study period X for current and previous study periods on the same page.

For exploratory purposes, responders from Day 15 (>=50% decrease from period-specific baseline) in Treatment Cycle X will be followed to the end of the study through line plot of

HAM-D total score at scheduled visits, by dose group (only High and Low dose groups) and over subsequent cycles. To support the figure, summary tables will be provided.

A line plot of HAM-D total score for responders of cycle X who needed exactly X number of treatments will be provided by over time since the first dose in the latest treatment cycle, by dose group (only High and Low Dose groups). To support the figure, summary tables will be provided. Bar charts for percentage of responders and non-responders at Day 15 in each study period along with the percent of responders (separately for non-responders) at the previous cycle among each group will be presented.

7.3.4. Time to Relapse and Durability of Study Drug Effect

Time to relapse in each study period:

Time to relapse is defined as follows: Take only the HAM-D responders (HAM-D total score, change from period-specific baseline <= -50%) in study period X on D15 – safety set for study period 1, FAS for study periods 2-5. A relapse is defined as a subject having a HAM-D total score after D15 where HAM-D total score >=20 and there exists a PHQ-9 >=10 within 10 days prior to this HAM-D. Time to relapse is defined as the number of days from Day 15 in study period X to relapse for the first time within study period X. Responders in study period X who do not experience relapse within study period X will be censored at the latest HAM-D evaluation date before the first dose 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 subject. 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.

Durability of study drug effect in each study period:

Durability measured by HAM-D: Take only the HAM-D responders (HAM-D total score, change from period-specific baseline <= -50%) in study period X on D15 – safety set for study period 1, FAS for study periods 2-5. Durability of study drug effect measured by HAM-D criterion is defined as the number of days between Day 15 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 subject 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 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 subject. Durability measured by HAM-D 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.

Durability measured by PHQ-9: Take only the HAM-D responders (HAM-D total score, change from period-specific baseline <= -50%) in study period X on D15 safety set for study period 1, FAS for study periods 2-5. Durability of study drug effect measured by PHQ-9 criterion is defined as the number of days from Day 15 in study period X to the first PHQ-9 after Day 15 when PHQ-9 score >=10 within the study period X. A subject who does not have any PHQ-9 showing score >=10 post Day 15 within the study period X will be censored at the latest PHQ-9 evaluation date before the first dose 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 subject. [redacted]. [redacted]. In addition, for each study period, number of HAM-D evaluations post Day 15 per subject, percent of HAM-D evaluations post Day 15 per subject with >=50% reduction from period-specific baseline, number of PHQ-9 evaluations post Day 15 per subject and percent of PHQ-9 evaluations post Day 15 per subject with score <10 will be summarized by dose cohort.

7.4. Safety Analysis

The primary objective 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 for overall safety. Safety analyses will be provided based on the 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 3 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 post-baseline value between the first dose of study drug (exclusive) and up to last dose of study drug + 1 day (inclusive) within the study period. Last value on study within study period is defined as the last post-baseline value after the first dose of study drug within the study period.

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 4.

Table 4: 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
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 subject's participation in the study. All adverse events will be coded using MedDRA version 24.0.

A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset on or after the first dose of study drug. The TEAEs will be further categorized by study period of occurrence as follows:

A TEAE for study period X is defined as an adverse event with onset on or after the first dose of study drug in the treatment cycle X until prior to the first dose of study drug in the subsequent study period X+1.

- A treatment period TEAE in study period X is defined as an adverse event with onset on or after the first dose of study drug in the treatment cycle X but within 1 day since the last dose of study drug in the same treatment cycle.
- A follow up period TEAE in the study period X is defined as an adverse event with onset after 1 day from the last dose of study drug in the same treatment cycle but on or before 14 days after the last dose in the same study period (typically Day 28 visit day).
- A treatment cycle TEAE in the study period X includes treatment period TEAEs and follow-up period TEAEs within the study period X.
- An observation period TEAE in the study period X is defined as an adverse event with onset after 14 days after the last dose within study period X and before start of subsequent study period X+1.

If the date of an adverse event is incomplete and an unambiguous determination could not be made with respect to its onset time versus the first dose of study drug and/or last dose of

study drug, the adverse event will be assumed to be a TEAE and a treatment period AE in the cycle in which it started (or assigned to Cycle 1 if cycle of AE start could not be determined). For imputation of missing AE dates, please refer to 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 subjects as well as the number of events using Safety Set for the following:

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

An overview summary table of TEAE by study period will present the number and percentage of subjects as well as the number of events for the following, and this summary will be repeated by period-specific baseline use of antidepressant subgroups:

- 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 dose interruption
  - Treatment Cycle Period TEAE
- TEAE leading to Dose Reduction
  - Treatment Cycle Period TEAE

- TEAE leading to Dose Reduction or Dose Interruption
  - Treatment Cycle Period TEAE
- TEAE leading to discontinuation of study drug
  - Treatment Cycle Period TEAE
- 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 TEAE
    - Treatment Period TEAE
    - Follow-up Period TEAE
  - Observation Period TEAE
- Serious Adverse Event (SAE)
  - Treatment Cycle Period TEAE
    - Treatment Period TEAE
    - Follow-up Period TEAE
  - Observation Period TEAE

Incidence of TEAEs will be provided by SOC and PT. A subject is counted only once under each SOC and PT in case of multiple occurrences of the same AE. These summaries will be sorted by decreasing frequency of overall column, then by High Dose column, then alphabetically – for SOC first, then within SOC by PT.

For observation period TEAE summaries, the below rules will be used for the denominator in calculating the percentage:

- Study Period 1: number of subjects in the Safety Set at the beginning of the observation period in the study period 1 will be used as the denominator in calculating the percentage. (This is because the study terminates some subjects by design from follow up beyond treatment cycle 1)
- Study Period 2 to 5: number of subjects in the Safety Set for the specific study period will be used as the denominator in calculating the percentage.

Refer to SAP Section 7.1.3 regarding a subject counted at the beginning of Observation Period X.

Incidence of TEAEs in the following categories will be provided by SOC and PT for the entire study as well as for the specific period using Safety Set, unless specified otherwise:

- TEAE
  - Treatment Cycle Period TEAE
  - Treatment Period TEAE
  - Follow-up Period TEAE
  - Observation Period TEAE
- TEAEs by maximum severity (overall only)
  - Treatment Cycle Period TEAEs by maximum severity ("by study period" only)
  - Treatment Period TEAEs by maximum severity ("by study period" only)
  - Follow-up Period TEAEs by maximum severity ("by study period" only)
  - Observation Period TEAEs by maximum severity ("by study period" only)
- TEAEs by relationship (overall only)
  - Treatment Cycle Period TEAEs by relationship to study drug ("by study period" only)
  - Treatment Period TEAEs by relationship to study drug ("by study period" only)
  - Follow-up Period TEAEs by relationship to study drug ("by study period" only)
  - Observation Period TEAEs by relationship to study drug ("by study period" only)
- Serious TEAEs (overall only)
- Serious TEAEs by study period
- Serious TEAEs by relationship (overall and by study period)
- Treatment Cycle Period Serious TEAEs (overall and by study period)
- Treatment Period Serious TEAE (overall and by study period)
- Follow-up Period Serious TEAE (overall and by study period)
- Observation Period Serious TEAE (overall and by study period)
- TEAEs leading to discontinuation of study drug
- TEAEs leading to dose reduction of study drug (including a row for number of subjects who completed treatment in the study period with dose reduction)
- TEAEs leading to dose interruption of study drug

- TEAEs leading to dose reduction or interruption of study drug
- TEAEs leading to withdrawal from the study
  - Treatment Cycle Period TEAEs leading to withdrawal from the study ("by study period" only)
  - Treatment Period TEAEs leading to withdrawal from the study ("by study period" only)
  - Follow-up Period TEAEs leading to withdrawal from the study ("by study period" only)

Incidence of TEAEs in the following categories in each study period will be provided by dose cohort, SOC, and PT.

- Treatment Cycle Period TEAEs
- Treatment Period TEAEs
- Follow-up Period TEAEs
- Observation Period TEAEs
- Treatment Cycle Period TEAEs by maximum severity
- Treatment Cycle Period TEAEs by relationship to study drug
- TEAEs leading to discontinuation of study drug
- TEAEs leading to dose reduction of study drug
- Treatment Cycle Period Serious TEAEs
- Treatment Period Serious TEAEs
- Follow-up Period Serious TEAEs
- Observation Period Serious TEAEs
- Treatment Period most common TEAEs (PT only)

Listing of AEs with onset prior to first dose of study drug will be provided. All listings on TEAEs will provide the study period and period designation for each AE.

A summary of most common TEAE (defined as incidence more than 5%) by preferred term will be provided, overall and by study period, sorted by decreasing frequency using Safety Set. Similarly summary of most common treatment cycle period TEAE by preferred term, and summary of most common treatment period TEAE by preferred term will also be provided.

Using Dose Switch Set, a summary of TEAEs by SOC/PT and by study period (starting at Study period 2, because by definition, subjects in Dose Switch Set would have had 30mg starting dose in study period 1) will be provided by the first dose in the specific re-treatment study period (as well as for SAGE-217 Any Dose) for the following:

- Treatment Cycle Period TEAE

- Treatment Cycle Period Serious TEAE
- Treatment Cycle Period TEAEs by maximum severity
- Treatment Cycle Period TEAEs by relationship to study drug
- TEAEs leading to dose reduction of study drug
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from the study
- Most common (5% in any dose cohort) Treatment Period TEAE

For maximum severity, subjects 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 study drug, 'related' is defined as relationship being "possible" or "probable" or missing. A subject will be counted only once within each SOC and PT at the strongest relationship to study drug in the following order: related, not related.

In tables which present dose cohorts in columns, the incidences will be presented by descending frequency of SOC within SAGE-217 Overall, then by high dose cohort, then by dose switch cohort, then by low dose cohort; In tables which present study periods in columns, the incidence will be presented by descending frequency of SOC within Study Period 1, then by Study Period 2, etc. For tables using Dose Switch Set, the incidence will be presented by descending frequency of SOC within SAGE-217 Any Dose column, then by 50mg, then by 40mg, then by 30/20mg. Within an SOC, the incidence will be sorted by descending frequency, in the same order as done for SOC. In case of a tie in incidence, sorting will be in alphabetical order.

Adverse events with onset before the first dose of study drug will be provided in a separate listing. 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:

- Age group:18-24, 25-50, 51-64, ≥65 years
- Sex: Male, Female
- Race: White, Black or African American, Other
- Antidepressant use at Period-specific Baseline: Yes, No
- Anxious depression status at baseline: Yes, No

In addition, the following summaries will be provided by SOC/PT by study period for age group <65 years (non-elderly), and >=65 years (elderly):

- Treatment Cycle Period TEAE
- Treatment Period TEAEs
- Follow-up Period TEAEs

- Observation Period TEAEs
- Treatment Cycle Period TEAEs by maximum severity
- Treatment Cycle Period Serious TEAEs
- Treatment Period TEAEs leading to discontinuation of study drug
- Treatment Period TEAEs leading to dose reduction of study drug
- Treatment Period TEAEs leading to dose interruption of study drug
- Treatment Period TEAEs leading to dose reduction or dose interruption of study drug

7.4.2. Clinical Laboratory

The clinical laboratory tests to be performed for monitoring of safety are listed in Table 5. They are collected at Screening, Days 1, 8, 15 of each study period, and Q8W.

Table 5: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Coagulation
Red blood cell count Hemoglobin Hematocrit White blood cell count with differential Platelet count Red blood cell 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 below the limit of quantification (BLQ) and a lower limit of quantification (LLOQ) value is provided – LLOQ value will be used for calculation in the summary tables. The actual results as collected will be displayed in the listings.

Summary tables on lab parameters will be done by study period, and will include descriptive statistics for the observed values, changes from baseline, and period-specific changes from 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 study period. The parameter values which are produced only if another parameter is abnormal will be included in data listings, but not summarized.

If a normal range is provided for the parameter, out-of-range values will be flagged as low or high, where applicable, in the subject 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). Qualitative urinalysis parameters will be summarized descriptively using number and percentage of subjects.

The number and percentage of subjects 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 the study drug, 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 6:Laboratory Parameters – Criteria for PCS 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.

Table 6: 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 (for condition involving more than one parameter, the results need to be from the same timepoint):

Alanine Aminotransferase: >3xULN, >5xULN, >10xULN
Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN
Alanine Aminotransferase or Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN
Alkaline Phosphatase: >1.5xULN, >2xULN
Total Bilirubin: >1.5xULN, >2xULN
Total Bilirubin > 2xULN **AND** (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN) [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), and standing diastolic blood pressure (mmHg) are collected at Screening, Days 1, 8, 15, 28 of each study period, and Q8W. Descriptive summaries of observed values, changes from baseline, and changes from baseline period-specific baseline will be provided for vital sign parameters – by scheduled assessment time point within each study period. 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.

Potentially clinically significant values will be identified for vital sign parameters as outlined in Table 7, Vital Signs – Criteria for PCS 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.

Table 7: 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 Screening, Days 1, 15 and Q8W. The following ECG parameters will be collected for each subject: 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 baseline ECG values. The observed value at each time point, change from baseline, and change from period-specific baseline at each post-baseline scheduled time point will be summarized. 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 subjects 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).

Potentially clinically significant values will be identified for ECG parameters as outlined in the following table. 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.

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

Table 8: 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

7.4.5. Physical Examination

Physical examination is scheduled at Screening, 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 is collected during the clinical visits at Screening, 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 subject's non-suicidal self-injurious behaviors is also assessed separately as part of C-SSRS. The "Baseline/Screening" C-SSRS form will be completed at Screening (lifetime history and past 24 months). The "Since Last Visit" C-SSRS form will be completed at all subsequent time points.

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.

Baseline for each question is defined as the worst of the assessments done before the first dose of study drug, excluding the lifetime version. This will typically include the 'past 24-month version' from screening and 'since last visit version' from Day 1, as well as any unscheduled visits done before the first dose of study drug; any Yes will make the baseline value as Yes.

Period-specific baseline is defined as the latest value on or before the first dose of the specific period but after the last study drug dose of the last study period, except for period 1 in which case Baseline defined above is same as Period 1 baseline.

The number and percentage of subjects with at least one response of 'Yes' to any C-SSRS suicidal ideation or suicidal behavior item, as well as for Subject'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.

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. 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 maximum rank score for any time post-baseline (period-specific) maximum rank score will be presented by study period. Maximum score 0 refers to all 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, ahead of the interim data cut) was undertaken at the time of NDA submission. Analyses from this snapshot of data was included in the original NDA submission.

9. REFERENCES

Clinical study protocol, version 5.0, 19 March 2020, 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. LIST OF APPENDICES

10.1. Appendix A: Schedule of Assessments (Screening, Treatment, and Follow-up Periods)

	Screening Period[a, b]	Cycle[c]			
		Open-label Treatment Period (Initial and Re-treatments)			Follow-up
Days	**D-28 to D-1**	**D1**	**D8 (+1d)**	**D15 (±1d)/ EOT[d]**	**D28 (±1d) and/or ET**
Study Procedure					
Informed Consent	X				
Duplicate Subject Check[e]	X				
Inclusion/Exclusion	X	X			
Demographics	X				
Medical/Family History	X				
SCID-5	X				
ICD-10	X				
MGH ATRQ	X				
Serum FSH test[f]	X				
Physical Examination[g]	X	X			
Body Weight/Height	X			X (wt only)	
Clinical Laboratory Assessments[h]	X	X	X	X	
Drug & Alcohol Screen[i]	X	X	X	X	
Pregnancy Test[j]	X	X		X[k]	
Hepatitis & HIV Screen	X				
[redacted]					
Vital Signs[n]	X	X	X	X	
12-Lead ECG[o]	X	X		X	
C-SSRS[p]	X	X	X	X	X
MADRS	X	X			
HAM-D[q, r]		X	X	X	X[s]
CGI-S	X	X	X	X	X
CGI-I			X	X	X
PHQ-9		X	X	X	X
[redacted]					

[redacted]					
Study Drug Dispensation		X	X		
Study Drug Administration		X (Day 1 through Day 14)			
Study Drug Accountability/Return			X	X	
[redacted]					
Adverse Events/SAEs[u]	X				
Prior/Concomitant Medications[v]	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; ICD-10 = International Statistical Classification of Diseases and Related Health Problems version 10; [redacted] MADRS = Montgomery-Åsberg Depression Rating Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; O = Optional; SCID-5 = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PHQ-9 = 9-item Patient Health Questionnaire; [redacted] SAE = serious adverse event; [redacted] wt = weight

[a] Screening procedures are to be conducted before initial (Cycle 1) treatment period only.

[redacted]

[c] Each cycle is 28 days (±1 day) and is comprised of a 14-day treatment period and a 14-day follow-up period. The initial treatment is considered Cycle 1 and re-treatments will be numbered sequentially. Each re-treatment cycle will begin with Day 1 (eg, the first day of the first re-treatment will be Day 1 of Cycle 2).

[d] Subjects 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 visits should occur 14 days after the last dose of treatment. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EOT and ET visits can be on the same day if a subject 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.

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

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

[g] A full physical examination will be conducted at Screening and abbreviated physical examinations will be conducted thereafter. A full physical examination includes assessment of body systems (eg, head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities).

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

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

[j] Serum pregnancy test at screening and urine pregnancy test thereafter.

[k] Female subjects who prematurely discontinue will have a pregnancy test performed at the ET visit.

[redacted]

[n] 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 subject has been resting for 5 minutes and then in the standing position. Vital signs may be repeated at the discretion of the Investigator as clinically indicated.

[o] Triplicate ECGs will be collected.

[p] The "Baseline/Screening" C-SSRS form will be completed at screening. The "Since Last Visit" C-SSRS form will be completed at any time of day at all subsequent time points.

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

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

[s] Subjects that do not exhibit a response to SAGE-217 by Day 15 of the initial treatment, defined as a ≥50% reduction in HAM-D score from baseline, will be terminated from the study upon completion of the 14-day follow-up period.

[redacted]

[u] Adverse events will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.
[v] Prior medications will be collected at Screening and concomitant medications will be collected at each subsequent visit.

10.2. Appendix B: Schedule of Events (Observational Period)

	Observational Period[a] (Day 29 through Week 52)			**EOS/Week 52 (±7 d)**
	Remote Assessment Q2W (±1 d)	**Visit Q8W/ET (± 3 d)**	**Unscheduled Visit (as needed)[b]**	
Study Procedure				
PHQ-9[c]	X[d]	X	X	X
Abbreviated Physical Examination		X		X
Body Weight		X		X
Clinical Laboratory Assessments		X		X
Drug & Alcohol Screen		X		X
Pregnancy Test		X		X
Vital Signs		X		X
12-Lead ECG		X		X
C-SSRS		X		X
HAM-D[e]		X	X	X
CGI-S		X		X
CGI-I		X		X
[redacted]				
Concomitant Medications[f]		X	X	X
[redacted]				
Adverse Events/SAEs[h]	X			

	Observational Period[a] (Day 29 through Week 52)			EOS/Week 52 (±7 d)
	Remote Assessment Q2W (±1 d)	**Visit Q8W/ET (± 3 d)**	**Unscheduled Visit (as needed)[b]**	
Study Procedure				

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] Within an Observational Period, the Q2W remote assessments will begin on Day 42 (±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.

[b] A subject 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.

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

[d] The subject will take the PHQ-9 every 14 days; if the PHQ-9 score is ≥10, then the subject 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 subject will take the PHQ-9 on a weekly basis: the subject 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 subject will take the PHQ-9 every 2 weeks thereafter.

[e] 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 treatment day of the previous SAGE-217 treatment cycle (ie, Day 70 or later), the subject will begin a 14-day re-treatment period with a 14-day follow-up visit (see Appendix A). If the HAM-D score is ≥20 but it has been less than 8 weeks since the last treatment day of the previous SAGE-217 treatment cycle (ie, Day 69 or earlier), see Section 9.2.1 for guidance on allowable interventions; the subject will take the PHQ-9 on a weekly basis until the 8-week period has lapsed, at which time the subject may begin a re-treatment period with SAGE-217 (see Appendix A), or until the PHQ-9 score is <10.

[f] Concomitant medications will be collected at each in-clinic visit.

[redacted]

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

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 initiation of the treatment, then the month and day will be set to December 31st .
  - If the year of AE onset > the year of initiation of treatment, then the month and day will be set to January 1st.
- 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 conmed 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 / Dose Cohorts

Safety Set for Period X: Subjects who had Treatment Period X start date non-missing

Full Analysis Set: Subjects who had HAM-D total score at Day 15 less than 50% of HAM-D total score at baseline in Treatment Cycle 1, and the discontinuation from study date/time, if the subject discontinued from the study prematurely, from study conclusion page is not equal to or before Treatment Cycle 1 end date/time. (This is the set who enters Obs Period 1 and is subject to re-treatment.)

High Dose Cohort: Subjects who received 50mg of SAGE-217 in Treatment Cycle 1, Day 1.

Low Dose Cohort: Subjects who received 30mg of SAGE-217 in Treatment Cycle 1, Day 1 and received 30mg or 20mg of SAGE-217 as the last dose received.

Dose Switch cohort: Subjects who received 30mg of SAGE-217 in Treatment Cycle 1, Day 1 and received 50mg of SAGE-217 in Treatment Cycle X, Day 1, where X>1.

30 mg cohort: Combination of Low Dose and Dose Switch cohorts.

Adverse Event Periods

Pre-treatment AE: AE onset date before Treatment Cycle 1 start date/time

TEAE: AE onset date on or after Treatment Cycle 1 start date/time

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 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: Conmeds with start date before Treatment Cycle 1 start date/time

On-treatment in Study Period X: Conmed 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

Baseline use of antidepressant, anxiolytic, or anti-insomnia medication in Study Period X are the medications with a start date before the first dose of study drug in the study period X AND they were ongoing or with a stop date on or after the first dose of study drug in the study period X.

The below rules apply to antidepressant, anxiolytic, or anti-insomnia medication during observation period derivation. 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 the current period.

For antidepressant, anxiolytic, or anti-insomnia medication records, any switch from period-specific baseline is determined by the period: Treatment period, Follow Up period and Observation period, where follow-up period is same as Treatment Cycle. For definitions of periods, please refer to Section 7.1.2.

Censoring for Time-To Event Analysis

For any time-to analysis, define time to event/censor and a censor variable = 1/0

For any time-to analysis, each subject 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.

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

Time to first re-treatment: 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 subject has Study Conclusion page filled in and Treatment Cycle 2 dosing did not occur (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 subject 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 subject (CENSOR = 1)

Durability of study drug 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 subjects 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 subject (CENSOR = 1)

[redacted]

[redacted]

Time to first anxiolytic med use: Ref Date – Date of first dose in Treatment Cycle 1 +1, where Ref Date is

= Start Date of first anxiolytic med use on or after the first dose date of SAGE-217 (CENSOR=0) if there exists one in the database, OR

= Date of Study Discontinuation or Completion if the subject has Study Conclusion page filled in and there is no evidence of anxiolytic medication use in the database (CENSOR=1) if the reason for discontinuation is not lost-to-follow-up

= Date of last contact from the Study Conclusion page if the reason for discontinuation is lost-to-follow up

Anxiolytic med is determined by ATC Level 3 = N05B.

Time to first anti-insomnia med use: Ref Date – Date of first dose in Treatment Cycle 1 +1, where Ref Date is

= Start Date of first anti-insomnia med use on or after the first dose date of SAGE-217 (CENSOR=0), OR

= Date of Study Discontinuation or Completion if the subject has Study Conclusion page filled in and there is no evidence of anti-insomnia medication use in the database (CENSOR=1) if the reason for discontinuation is not lost-to-follow-up

= Date of last contact from the Study Conclusion page if the reason for discontinuation is lost-to-follow up

Anti-insomnia med is determined by: [ATC Level 3 = N05C or standard medication name is in (TRAZODONE, MIRTAZAPINE)] or ATC Level 4 = R06AA

Time to end of follow-up: Ref Date – Date of first dose in Treatment Cycle 1 + 1, where

Ref Date = Study discontinuation/completion date, defined from the study conclusion CRF page from the same variable, except when the subject 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 (CENSOR = 0)

Time to first HAM-D total score >=20 after Cycle 1 Day 15 Response: (Ref Date – Date of Cycle 1 Day 15 visit) + 1, where Ref Date = Date of first HAM-D total score >=20 after Cycle 1 Day 15 (CENSOR = 0), OR

=Date of the last HAM-D evaluation before the first dose in Cycle 2 if it exists (CENSOR = 1)

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

Time to first HAM-D total score >=20 after Cycle 1 Day 15 response will be computed only for those subjects who are HAM-D responders at Day 15 in Cycle 1 and who have at least one HAM-D after Day 15 date.

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.

Calculation 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.

10.5. Appendix E: List of Displays

Following is a list of table numbering not used for the study:

14.2.1.1
14.2.2.11.2
14.2.2.11.5
14.2.2.11.8
14.2.2.11.11
14.2.2.11.14

Index of Tables

Table 14.1.7.5	Summary of On-Treatment Concomitant Non-Psychotropic Medications by Study Period	Safety Set
Table 14.1.7.6	Summary of Post-Treatment Concomitant Non-Psychotropic Medications by Study Period	Safety Set
Table 14.1.7.7	Summary of On-Treatment Concomitant Psychotropic Medications by Study Period	Safety Set
Table 14.1.7.8	Summary of Post-Treatment Concomitant Psychotropic Medications by Study Period	Safety Set
Table 14.1.7.9	Summary of Use of Concomitant Antidepressant Medications by Study Period	Safety Set
Table 14.1.7.10	Summary of Use of Concomitant Anxiolytic Medications by Study Period	Safety Set
Table 14.1.7.11	Summary of Use of Concomitant Anti-insomnia Medications by Study Period	Safety Set
Table 14.1.8.1	Summary of Study Drug Exposure by Study Period	Safety Set
Table 14.1.8.2	Summary of Study Drug Adherence by Study Period	Full Analysis Set
Table 14.2.1.2	Summary of Re-treatments	Full Analysis Set
Table 14.2.1.3	Summary of Re-treatment for Subjects With Exactly X Treatments	Full Analysis Set
Table 14.2.1.4	Summary of Re-treatments by Antidepressant Use at Study Period 1 Baseline	Full Analysis Set
Table 14.2.2.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score – Study Period 1	Safety Set
Table 14.2.2.2.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Study Period	Full Analysis Set
Table 14.2.2.3	Summary of Hamilton Rating Scale for Depression (HAM-D) Subscale Scores – Study Period 1	Safety Set
Table 14.2.2.4	Summary of Hamilton Rating Scale for Depression (HAM-D) Subscale Score by Study Period	Full Analysis Set
Table 14.2.2.5	Summary of Hamilton Rating Scale for Depression (HAM-D) Individual Item Score – Study Period 1	Safety Set
Table 14.2.2.6	Summary of Hamilton Rating Scale for Depression (HAM-D) Individual Item Score by Study Period	Full Analysis Set
Table 14.2.2.7.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Response – Study Period 1	Safety Set
Table 14.2.2.7.2	Sensitivity Analysis: Summary of Hamilton Rating Scale for Depression (HAM-D) Response – Study Period 1	Safety Set
Table 14.2.2.8.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Response by Study Period	Full Analysis Set
Table 14.2.2.8.2	Sensitivity Analysis: Summary of Hamilton Rating Scale for Depression (HAM-D) Response by Study Period	Full Analysis Set
Table 14.2.2.8.2.1	Sensitivity Analysis: Summary of Hamilton Rating Scale for Depression (HAM-D) Response by Study Period and Antidepressant Use at Period-specific Baseline	Full Analysis Set
Table 14.2.2.9.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Remission – Study Period 1	Safety Set

Table 14.2.2.9.2	Sensitivity Analysis: Summary of Hamilton Rating Scale for Depression (HAM-D) Remission – Study Period 1	Safety Set
Table 14.2.2.9.2.1	Sensitivity Analysis: Summary of Hamilton Rating Scale for Depression (HAM-D) Remission, by Antidepressant Use at Baseline - Study Period 1	Safety Set
Table 14.2.2.10.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Remission by Study Period	Full Analysis Set
Table 14.2.2.10.2	Sensitivity Analysis: Summary of Hamilton Rating Scale for Depression (HAM-D) Remission by Study Period	Full Analysis Set
Table 14.2.2.10.2.1	Sensitivity Analysis: Summary of Hamilton Rating Scale for Depression (HAM-D) Remission by Study Period and Antidepressant Use at Period-specific Baseline	Full Analysis Set
Table 14.2.2.11.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Study Period and Antidepressant Use at Period-specific Baseline	Full Analysis Set
Table 14.2.2.11.3	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Antidepressant Use at Baseline – Study Period 1	Safety Set
Table 14.2.2.11.4	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Study Period and Age	Full Analysis Set
Table 14.2.2.11.6	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Age – Study Period 1	Safety Set
Table 14.2.2.11.7	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Study Period and Sex	Full Analysis Set
Table 14.2.2.11.9	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Sex – Study Period 1	Safety Set
Table 14.2.2.11.10	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Study Period and Race	Full Analysis Set
Table 14.2.2.11.12	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Race – Study Period 1	Safety Set
Table 14.2.2.11.13	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Study Period and BMI	Full Analysis Set
Table 14.2.2.11.15	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by BMI – Study Period 1	Safety Set
Table 14.2.2.11.16	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Study Period and Anxious Depression Status at Baseline	Full Analysis Set
Table 14.2.2.11.17	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Anxious Depression Status at Baseline – Study Period 1	Safety Set

Table 14.2.2.12.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by the First Dose in the Study Period	Dose Switch Set
Table 14.2.2.12.2	Summary of Hamilton Rating Scale for Depression (HAM-D) Response by First Dose in the Study Period	Dose Switch Set
Table 14.2.2.12.3	Summary of Hamilton Rating Scale for Depression (HAM-D) Remission by First Dose in the Study Period	Dose Switch Set
Table 14.2.2.13.1A	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score for Current and Past Study Periods using Subjects Dosed in Study Period 2	Full Analysis Set
Table 14.2.2.13.1B	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score for Current and Past Study Periods using Subjects Dosed in Study Period 3	Full Analysis Set
Table 14.2.2.13.1C	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score for Current and Past Study Periods using Subjects Dosed in Study Period 4	Full Analysis Set
Table 14.2.2.13.1D	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score for Current and Past Study Periods using Subjects Dosed in Study Period 5	Full Analysis Set
Table 14.2.2.13.2A1	Summary of Hamilton Rating Scale for Depression (HAM-D) Core Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 2	Full Analysis Set
Table 14.2.2.13.2A2	Summary of Hamilton Rating Scale for Depression (HAM-D) Core Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 3	Full Analysis Set
Table 14.2.2.13.2A3	Summary of Hamilton Rating Scale for Depression (HAM-D) Core Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 4	Full Analysis Set
Table 14.2.2.13.2A4	Summary of Hamilton Rating Scale for Depression (HAM-D) Core Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 5	Full Analysis Set
Table 14.2.2.13.2B1	Summary of Hamilton Rating Scale for Depression (HAM-D) Anxiety Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 2	Full Analysis Set
Table 14.2.2.13.2B2	Summary of Hamilton Rating Scale for Depression (HAM-D) Anxiety Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 3	Full Analysis Set
Table 14.2.2.13.2B3	Summary of Hamilton Rating Scale for Depression (HAM-D) Anxiety Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 4	Full Analysis Set
Table 14.2.2.13.2B4	Summary of Hamilton Rating Scale for Depression (HAM-D) Anxiety Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 5	Full Analysis Set
Table 14.2.2.13.2C1	Summary of Hamilton Rating Scale for Depression (HAM-D) Bech-6 Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 2	Full Analysis Set
Table 14.2.2.13.2C2	Summary of Hamilton Rating Scale for Depression (HAM-D) Bech-6 Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 3	Full Analysis Set

Table 14.2.2.13.2C3	Summary of Hamilton Rating Scale for Depression (HAM-D) Bech-6 Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 4	Full Analysis Set
Table 14.2.2.13.2C4	Summary of Hamilton Rating Scale for Depression (HAM-D) Bech-6 Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 5	Full Analysis Set
Table 14.2.2.13.2D1	Summary of Hamilton Rating Scale for Depression (HAM-D) Maier Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 2	Full Analysis Set
Table 14.2.2.13.2D2	Summary of Hamilton Rating Scale for Depression (HAM-D) Maier Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 3	Full Analysis Set
Table 14.2.2.13.2D3	Summary of Hamilton Rating Scale for Depression (HAM-D) Maier Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 4	Full Analysis Set
Table 14.2.2.13.2D4	Summary of Hamilton Rating Scale for Depression (HAM-D) Maier Subscale Score for Current and Past Study Periods using Subjects Dosed in Study Period 5	Full Analysis Set
Table 14.2.2.14.1A	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score for Current and Subsequent Study Periods for Responders at Day 15 in Treatment Cycle 2	Full Analysis Set
Table 14.2.2.14.1B	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score for Current and Subsequent Study Periods for Responders at Day 15 in Treatment Cycle 3	Full Analysis Set
Table 14.2.2.14.1C	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score for Current and Subsequent Study Periods for Responders at Day 15 in Treatment Cycle 4	Full Analysis Set
Table 14.2.2.14.1D	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score for Current and Subsequent Study Periods for Responders at Day 15 in Treatment Cycle 5	Full Analysis Set
Table 14.2.2.14.2A	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score over Time for Responders at Day 15 at Treatment Cycle 1 for Subjects who Had Been Dosed in Exactly 1 Treatment Cycle	Full Analysis Set
Table 14.2.2.14.2B	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score over Time for Responders at Day 15 at Treatment Cycle 2 for Subjects who Had Been Dosed in Exactly 2 Treatment Cycles	Full Analysis Set
Table 14.2.2.14.2C	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score over Time for Responders at Day 15 at Treatment Cycle 3 for Subjects who Had Been Dosed in Exactly 3 Treatment Cycles	Full Analysis Set
Table 14.2.2.14.2D	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score over Time for Responders at Day 15 at Treatment Cycle 4 for Subjects who Had Been Dosed in Exactly 4 Treatment Cycles	Full Analysis Set

Table 14.2.2.14.2E	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score over Time for Responders at Day 15 at Treatment Cycle 5 for Subjects who Had Been Dosed in Exactly 5 Treatment Cycles	Full Analysis Set
Table 14.2.2.15.1	Summary of Relapse – Study Period 1	Safety Set – HAM-D Responders at Day 15 in Cycle 1
Table 14.2.2.15.2	Summary of Relapse by Study Period	Full Analysis Set – HAM-D Responders at Day 15 in Cycle X
Table 14.2.2.16.1	Summary of Durability of Study Drug Effect, Measured by HAM-D – Study Period 1	Safety Set – HAM-D Responders at Day 15 in Cycle 1
Table 14.2.2.16.2	Summary of Durability of Study Drug Effect, Measured by HAM-D, by Study Period	Full Analysis Set – HAM-D Responders at Day 15 in Cycle X
[redacted]		
Table 14.2.2.18.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Response by Antidepressant Use at Baseline – Study Period 1	Safety Set
Table 14.2.2.18.1.2	Sensitivity Analysis: Summary of Hamilton Rating Scale for Depression (HAM-D) Response, by Antidepressant Use at Baseline – Study Period 1	Safety Set
Table 14.2.2.18.2	Summary of Hamilton Rating Scale for Depression (HAM-D) Response by Antidepressant Use at Period-Specific Baseline, by Study Period	Full Analysis Set
Table 14.2.2.18.3	Summary of Hamilton Rating Scale for Depression (HAM-D) Remission by Antidepressant Use at Baseline – Study Period 1	Safety Set
Table 14.2.2.18.4	Summary of Hamilton Rating Scale for Depression (HAM-D) Remission by Antidepressant Use at Period-Specific Baseline, by Study Period	Full Analysis Set

Table 14.2.3.1	Summary of Clinical Global Impression – Improvement (CGI-I) – Study Period 1	Safety Set
Table 14.2.3.2	Summary of Clinical Global Impression – Improvement (CGI-I) – by Study Period	Full Analysis Set
Table 14.2.3.3	Summary of Clinical Global Impression – Improvement (CGI-I) – by the First Dose in the Study Period	Dose Switch Set
Table 14.2.3.4	Summary of Clinical Global Impression – Improvement (CGI-I) Response – Study Period 1	Safety Set
Table 14.2.3.4.1	Sensitivity Analysis: Summary of Clinical Global Impression – Improvement (CGI-I) Response – Study Period 1	Safety Set
Table 14.2.3.5	Summary of Clinical Global Impression – Improvement (CGI-I) Response by Study Period	Full Analysis Set
Table 14.2.3.5.1	Sensitivity Analysis: Summary of Clinical Global Impression – Improvement (CGI-I) Response by Study Period	Full Analysis Set
Table 14.2.3.6	Summary of Clinical Global Impression – Improvement (CGI-I) Response by the First Dose in the Study Period	Dose Switch Set
Table 14.2.3.6.1	Sensitivity Analysis: Summary of Clinical Global Impression – Improvement (CGI-I) Response by the First Dose in the Study Period	Dose Switch Set
Table 14.2.4.1	Summary of Clinical Global Impression – Severity (CGI-S) – Study Period 1	Safety Set
Table 14.2.4.2	Summary of Clinical Global Impression – Severity (CGI-S) by Study Period	Full Analysis Set
Table 14.2.4.3	Summary of Clinical Global Impression – Severity (CGI-S) by the First Dose in the Study Period	Dose Switch Set
Table 14.2.4.4A	Summary of Clinical Global Impression – Severity (CGI-S) Score for Current and Past Study Periods using Subjects Dosed in Study Period 2	Full Analysis Set
Table 14.2.4.4B	Summary of Clinical Global Impression – Severity (CGI-S) Score for Current and Past Study Periods using Subjects Dosed in Study Period 3	Full Analysis Set
Table 14.2.4.4C	Summary of Clinical Global Impression – Severity (CGI-S) Score for Current and Past Study Periods using Subjects Dosed in Study Period 4	Full Analysis Set
Table 14.2.4.4D	Summary of Clinical Global Impression – Severity (CGI-S) Score for Current and Past Study Periods using Subjects Dosed in Study Period 5	Full Analysis Set
[redacted]		

[redacted]

Table 14.3.1.1	Overview of Treatment-Emergent Adverse Events	Safety Set
Table 14.3.1.2	Overview of Treatment-Emergent Adverse Events by Study Period	Safety Set
Table 14.3.1.3	Overview of Treatment-Emergent Adverse Events by Study Period by Period-Specific Baseline Use of Antidepressant	Safety Set
Table 14.3.2.1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.2.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.2.3	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.2.3.1	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Dose Cohort	Safety Set
Table 14.3.2.3.2	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term by the First Dose in the Study Period	Dose Switch Set
Table 14.3.2.3.3	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.2.4	Summary of Treatment Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Study Period	Safety Set

Table 14.3.2.4.1	Summary of Treatment Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Dose Cohort	Safety Set
Table 14.3.2.4.2	Summary of Treatment Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.2.5	Summary of Follow-up Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.2.5.1	Summary of Follow-up Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Dose Cohort	Safety Set
Table 14.3.2.5.2	Summary of Follow-up Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.2.6	Summary of Observation Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.2.6.1	Summary of Observation Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Dose Cohort	Safety Set
Table 14.3.2.6.2	Summary of Observation Period Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.3.1	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Set
Table 14.3.3.2	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity by Study Period	Safety Set
Table 14.3.3.2.1	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity by Dose Cohort	Safety Set
Table 14.3.3.2.2	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity by the First Dose in the Study Period	Dose Switch Set
Table 14.3.3.3	Summary of Treatment Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity by Study Period	Safety Set
Table 14.3.3.4	Summary of Follow-up Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity by Study Period	Safety Set
Table 14.3.3.5	Summary of Observation Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity by Study Period	Safety Set
Table 14.3.4.1	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug	Safety Set
Table 14.3.4.2	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug by Study Period	Safety Set

Table 14.3.4.2.1	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug by Dose Cohort	Safety Set
Table 14.3.4.2.2	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to Study Drug by the First Dose in the Study Period	Dose Switch Set
Table 14.3.4.3	Summary of Treatment Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug by Study Period	Safety Set
Table 14.3.4.4	Summary of Follow-up Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug by Study Period	Safety Set
Table 14.3.4.5	Summary of Observation Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug by Study Period	Safety Set
Table 14.3.5.1	Summary of Treatment Emergent Adverse Events leading to Discontinuation of Study Drug by System Organ Class and Preferred Term	Safety Set
Table 14.3.5.2	Summary of Treatment Emergent Adverse Events leading to Discontinuation of Study Drug by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.5.2.1	Summary of Treatment Emergent Adverse Events leading to Discontinuation of Study Drug by System Organ Class and Preferred Term by Dose Cohort	Safety Set
Table 14.3.5.2.2	Summary of Treatment Emergent Adverse Events leading to Discontinuation of Study Drug by System Organ Class and Preferred Term by the First Dose in the Study Period	Dose Switch Set
Table 14.3.5.3	Summary of Treatment Emergent Adverse Events leading to Dose Reduction of Study Drug by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.5.3.1	Summary of Treatment Emergent Adverse Events leading to Dose Reduction of Study Drug by System Organ Class and Preferred Term by Dose Cohort	Safety Set
Table 14.3.5.3.2	Summary of Treatment Emergent Adverse Events leading to Dose Reduction of Study Drug by System Organ Class and Preferred Term by the First Dose in the Study Period	Dose Switch Set
Table 14.3.5.4	Summary of Treatment Emergent Adverse Events leading to Dose Reduction of Study Drug in Any Study Period by System Organ Class and Preferred Term	Safety Set
Table 14.3.5.5	Summary of Treatment Emergent Adverse Events leading to Dose Interruption of Study Drug by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.5.5.1	Summary of Treatment Emergent Adverse Events leading to Dose Interruption of Study Drug by System Organ Class and Preferred Term by Dose Cohort	Safety Set
Table 14.3.5.5.2	Summary of Treatment Emergent Adverse Events leading to Dose Interruption of Study Drug by System Organ Class and Preferred Term by the First Dose in the Study Period	Dose Switch Set
Table 14.3.5.6	Summary of Treatment Emergent Adverse Events leading to Dose Interruption of Study Drug in Any Study Period by System Organ Class and Preferred Term	Safety Set

Table 14.3.5.7	Summary of Treatment Emergent Adverse Events leading to Dose Reduction or Dose Interruption of Study Drug by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.5.7.1	Summary of Treatment Emergent Adverse Events leading to Dose Reduction or Dose Interruption of Study Drug by System Organ Class and Preferred Term by Dose Cohort	Safety Set
Table 14.3.5.7.2	Summary of Treatment Emergent Adverse Events leading to Dose Reduction or Dose Interruption of Study Drug by System Organ Class and Preferred Term by the First Dose in the Study Period	Dose Switch Set
Table 14.3.5.8	Summary of Treatment Emergent Adverse Events leading to Dose Reduction or Dose Interruption of Study Drug in Any Study Period by System Organ Class and Preferred Term	Safety Set
Table 14.3.6.1	Summary of Treatment Emergent Adverse Events leading to Withdrawal from the Study by System Organ Class and Preferred Term	Safety Set
Table 14.3.6.2	Summary of Treatment Emergent Adverse Events leading to Withdrawal from the Study by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.6.2.1	Summary of Treatment Emergent Adverse Events leading to Withdrawal from the Study by System Organ Class and Preferred Term by the First Dose in the Study Period	Dose Switch Set
Table 14.3.6.2.2	Summary of Treatment Cycle Period Treatment Emergent Adverse Events leading to Withdrawal from the Study by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.6.2.3	Summary of Treatment Period Treatment Emergent Adverse Events leading to Withdrawal from the Study by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.6.2.4	Summary of Follow-up Period Treatment Emergent Adverse Events leading to Withdrawal from the Study by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.7.1	Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.7.1.1	Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term and Relationship to Study Drug	Safety Set
Table 14.3.7.1.2	Summary of Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Relationship to SAGE-217 by Study Period	Safety Set
Table 14.3.7.1.3	Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.7.2	Summary of Treatment Cycle Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.7.2.1	Summary of Treatment Cycle Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by Dose Cohort	Safety Set

Table 14.3.7.2.2	Summary of Treatment Cycle Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by the First Dose in the Study Period	Dose Switch Set
Table 14.3.7.2.3	Summary of Treatment Cycle Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.7.3	Summary of Treatment Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.7.3.1	Summary of Treatment Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by Dose Cohort	Safety Set
Table 14.3.7.3.2	Summary of Treatment Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.7.4	Summary of Follow-up Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.7.4.1	Summary of Follow-up Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by Dose Cohort	Safety Set
Table 14.3.7.4.2	Summary of Follow-up Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.7.5	Summary of Observation Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by Study Period	Safety Set
Table 14.3.7.5.1	Summary of Observation Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by Dose Cohort	Safety Set
Table 14.3.7.5.2	Summary of Observation Period Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.8.1	Summary of Treatment Period Most Common (>5% in Any Cohort) Treatment Emergent Adverse Events by Preferred Term	Safety Set
Table 14.3.8.2	Summary of Treatment Period Most Common (>5% in Any Cohort) Treatment Emergent Adverse Events by Preferred Term by Study Period	Safety Set
Table 14.3.8.2.1	Summary of Treatment Period Most Common (>5% in Any Dose Cohort and Study Period) Treatment Emergent Adverse Events by Preferred Term by Dose Cohort	Safety Set
Table 14.3.8.2.2	Summary of Treatment Period Most Common (> 5% in Any Study Period and First Dose Level) Treatment Emergent Adverse Events by Preferred Term by the First Dose in the Study Period	Dose Switch Set
Table 14.3.8.3.1	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Age Group by Study Period	Safety Set

Table 14.3.8.3.2	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Sex by Study Period	Safety Set
Table 14.3.8.3.3	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Race Group by Study Period	Safety Set
Table 14.3.8.3.4	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term and ADT use at Period-Specific Baseline, by Study Period	Safety Set
Table 14.3.8.3.5	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Anxious Depression Status at Baseline, by Study Period	Safety Set
Table 14.3.8.4.1	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Elderly Group by Study Period	Safety Set
Table 14.3.8.4.2	Summary of Treatment Cycle Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term, Maximum Severity and Elderly Group by Study Period	Safety Set
Table 14.3.8.4.3	Summary of Treatment Cycle Period Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Elderly Group by Study Period	Safety Set
Table 14.3.8.4.4	Summary of Treatment Period Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug, by System Organ Class, Preferred Term, and Elderly Group by Study Period	Safety Set
Table 14.3.8.4.5	Summary of Treatment Period Treatment Emergent Adverse Events Leading to Dose Reduction of Study Drug, by System Organ Class, Preferred Term, and Elderly Group by Study Period	Safety Set
Table 14.3.8.4.6	Summary of Treatment Period Treatment Emergent Adverse Events Leading to Dose Interruption of Study Drug, by System Organ Class, Preferred Term, and Elderly Group by Study Period	Safety Set
Table 14.3.8.4.7	Summary of Treatment Period Treatment Emergent Adverse Events Leading to Dose Reduction or Dose Interruption of Study Drug, by System Organ Class, Preferred Term, and Elderly Group by Study Period	Safety Set
Table 14.3.8.4.8	Summary of Treatment Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Elderly Group by Study Period	Safety Set
Table 14.3.8.4.9	Summary of Follow-up Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Elderly Group by Study Period	Safety Set
Table 14.3.8.4.10	Summary of Observation Period Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Elderly Group by Study Period	Safety Set
Table 14.3.8.5.1	Summary of Most Common (>5% in any dose cohort) Treatment Emergent Adverse Events by Preferred Term	Safety Set

Table 14.3.8.5.2	Summary of Most Common (>5% in any dose cohort) Treatment Emergent Adverse Events by Preferred Term by Study Period	Safety Set
Table 14.3.8.5.3	Summary of Most Common (>5% in any dose cohort) Treatment Cycle Period Treatment Emergent Adverse Events by Preferred Term	Safety Set
Table 14.3.8.5.4	Summary of Most Common (>5% in any dose cohort) Treatment Cycle Period Treatment Emergent Adverse Events by Preferred Term by Study Period	Safety Set
Table 14.3.9.1	Summary of Serum Chemistry Results by Study Period and Study Visit	Safety Set
Table 14.3.9.2	Summary of Shift from Normal Baseline in Serum Chemistry Results during the Study by Study Period and Study Visit	Safety Set
Table 14.3.9.3	Summary of Potentially Clinically Significant Liver Function Tests by Study Period	Safety Set
Table 14.3.9.4	Summary of Potentially Clinically Significant Serum Chemistry (excluding LFT) Results by Study Period	Safety Set
Table 14.3.10.1	Summary of Hematology Results by Study Period and Study Visit	Safety Set
Table 14.3.10.2	Summary of Shift from Normal Baseline in Hematology Results during the Study by Study Period and Study Visit	Safety Set
Table 14.3.10.3	Summary of Potentially Clinically Significant Hematology Results by Study Period	Safety Set
Table 14.3.11.1	Summary of Urinalysis Results by Study Period and Study Visit – Quantitative Results	Safety Set
Table 14.3.11.2	Summary of Urinalysis by Study Period and Study Visit – Qualitative Results	Safety Set
Table 14.3.12.1	Summary of Coagulation Results by Study Period and Study Visit	Safety Set
Table 14.3.13.1	Summary of Vital Signs by Study Period and Study Visit	Safety Set
Table 14.3.13.2	Summary of Potentially Clinically Significant Vital Signs by Study Period	Safety Set
Table 14.3.13.3	Difference in Supine to Standing Vital Signs (Supine minus Standing) by Study Period and Study Visit	Safety Set
Table 14.3.14.1	Summary of ECG data by Study Period and Study Visit	Safety Set
Table 14.3.14.2	Summary of Abnormal ECG by Study Period and Study Visit	Safety Set
Table 14.3.14.3	Summary of Potentially Clinically Significant QTcF in ECG Data by Study Period	Safety Set
Table 14.3.15.1	Summary of Shift from Period-specific Baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation and Suicidal Behavior Data by Study Period and Study Visit	Safety Set
Table 14.3.15.2	Summary of Columbia-Suicide Severity Rating Scale (C-SSRS) on Suicidal Ideation and Suicidal Behavior Data by Study Period	Safety Set
Table 14.3.15.3	Summary of Shift from Baseline in C-SSRS Maximum Severity Score in Suicidal Ideation at Any Time Post-Baseline by Study Period	Safety Set

Index of Listings

Number	Title	Analysis Set
Listing 16.1.7	Subject Dosing Groups	Safety Set
Listing 16.2.1.1	Subject Disposition	All Subjects
Listing 16.2.1.2	Premature Withdrawal from Study or Premature Discontinuation from Study Drug	Safety Set
Listing 16.2.1.3	Subject Participation by Study Period	Safety Set
Listing 16.2.1.4	Subject Participation by Treatment Cycle	Full Analysis Set
Listing 16.2.2.1	Protocol Deviations	All Subjects
Listing 16.2.3.1	Inclusion/Exclusion Criteria	All Subjects
Listing 16.2.4.1	Demographics	Safety Set
Listing 16.2.4.2	Baseline Characteristics	Safety Set
Listing 16.2.4.3	Montgomery-Asberg Depression Rating Scale (MADRS)	Full Analysis Set
Listing 16.2.5.1	Medical and Surgical History	Safety Set
Listing 16.2.5.2	Disease History	Safety Set
Listing 16.2.5.3	Subject History of Psychiatric Disorder	Safety Set
Listing 16.2.5.4	Family History of Psychiatric Disorder	Safety Set
Listing 16.2.6.1	Prior and Concomitant Psychotropic Medications	Safety Set
Listing 16.2.6.2	Prior and Concomitant Non-Psychotropic Medications	Safety Set
Listing 16.2.6.3	Use of Antidepressant during the Study	Safety Set
Listing 16.2.6.4	Use of Anxiolytics during the Study	Safety Set
Listing 16.2.6.5	Use of Anti-insomnia during the Study	Safety Set
Listing 16.2.6.6	Concomitant Procedures	Safety Set
Listing 16.2.7.1	Study Drug Administration	Safety Set
Listing 16.2.7.2	Study Drug Exposure	Safety Set
Listing 16.2.7.3	Study Drug Adherence	Safety Set
Listing 16.2.7.4	Study Drug Dose Reduction	Safety Set
Listing 16.2.8.1	Hamilton Rating Scale for Depression (HAM-D)	Safety Set
Listing 16.2.9.1	Clinical Global Impression (CGI) – Improvement	Safety Set
Listing 16.2.10.1	Clinical Global Impression (CGI) – Severity	Safety Set

Listing 16.2.16.1	Patient Health Questionnaire (PHQ-9) and Hamilton Rating Scale for Depression (HAM-D) Leading to Re-treatment	Full Analysis Set
Listing 16.2.17.1	Adverse Events	Safety Set
Listing 16.2.17.2	Non – fatal Serious Adverse Events	Safety Set
Listing 16.2.17.3	Adverse Events Leading to Death	Safety Set
Listing 16.2.17.4	Adverse Events with Onset Prior to First Dose of Study Drug	Safety Set
Listing 16.2.17.5	Adverse Events Leading to Premature Discontinuation of Study Drug	Safety Set
Listing 16.2.17.6	Adverse Events Leading to Premature Withdrawal from the Study	Safety Set
Listing 16.2.17.7	Adverse Events for Subjects who Experienced Dose Reduction	Safety Set
Listing 16.2.18.1.1	Serum Chemistry Data (Excluding Liver Function Tests)	Safety Set
Listing 16.2.18.1.2	Serum Chemistry Data (Excluding Liver Function Tests) that are Potentially Clinically Significant	Safety Set
Listing 16.2.18.1.3	Serum Chemistry Data, Liver Function Tests	Safety Set
Listing 16.2.18.1.4	Potentially Clinically Significant Values of Liver Function Tests	Safety Set
Listing 16.2.18.2.1	Hematology Data	Safety Set
Listing 16.2.18.2.2	Hematology Data that are of Potential Clinical Concern	Safety Set
Listing 16.2.18.3	Urinalysis Data	Safety Set
Listing 16.2.18.4	Coagulation Data	Safety Set
Listing 16.2.18.5	Pregnancy Test	Safety Set
Listing 16.2.18.6	Diagnostic Screening Laboratory Tests	Safety Set
Listing 16.2.19.1.1	Vital Signs	Safety Set
Listing 16.2.19.1.2	Vital Signs that are of Potential Clinical Concern	Safety Set
Listing 16.2.20.1.1	Electrocardiogram (ECG) data	Safety Set
Listing 16.2.20.1.2	Electrocardiogram (ECG) data that are of Potential Clinical Concern	Safety Set
Listing 16.2.21.1	Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Ideation	Safety Set

Listing 16.2.21.2	Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Behavior	Safety Set
Listing 16.2.22	Physical Examination	Safety Set

Index of Figures

Figure 14.2.5.6	Sensitivity Analysis: Bar Chart of Hamilton Rating Scale for Depression (HAM-D) Response over Time, by Antidepressant Use at Baseline – Study Period 1	Safety Set
Figure 14.2.5.7	Sensitivity Analysis: Bar Chart of Hamilton Rating Scale for Depression (HAM-D) Response at Day 15 over Study Periods, by Antidepressant Use at Period-Specific Baseline	Full Analysis Set
Figure 14.2.6	Bar Chart of Hamilton Rating Scale for Depression (HAM-D) Remission over Time, by Study Period	Full Analysis Set
Figure 14.2.6.1	Bar Chart of Hamilton Rating Scale for Depression (HAM-D) Remission over Time – Study Period 1	Safety Set
Figure 14.2.6.2	Bar Chart of Hamilton Rating Scale for Depression (HAM-D) Remission over Time, by Antidepressant Use at Baseline – Treatment Cycle 1	Safety Set
Figure 14.2.6.3	Bar Chart of Hamilton Rating Scale for Depression (HAM-D) Remission at Day 15 over Different Study Periods, by Antidepressant Use at Period-Specific Baseline	Safety Set for Study Period 1, Full Analysis Set for Study Periods 2-5
Figure 14.2.6.4	Sensitivity Analysis: Bar Chart of Hamilton Rating Scale for Depression (HAM-D) Remission over Time, by Study Period	Full Analysis Set
Figure 14.2.6.5	Sensitivity Analysis: Bar Chart of Hamilton Rating Scale for Depression (HAM-D) Remission over Time – Study Period 1	Safety Set
Figure 14.2.6.6	Sensitivity Analysis: Bar Chart of Hamilton Rating Scale for Depression (HAM-D) Remission over Time, by Antidepressant Use at Baseline – Study Period 1	Safety Set
Figure 14.2.6.7	Sensitivity Analysis: Bar Chart of Hamilton Rating Scale for Depression (HAM-D) Remission at Day 15 over Study Periods, by Antidepressant Use at Period-Specific Baseline	Full Analysis Set
Figure 14.2.7	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Total Score over Time by Study Period	Full Analysis Set
Figure 14.2.7.1	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Total Score over Time by Study Period – High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.7.2	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Total Score over Time by FAS Subjects Dosed in Each Study Period	Full Analysis Set
Figure 14.2.7.2.1	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Total Score over Time by FAS Subjects Dosed in Each Study Period - High Dose vs 30mg Cohort	Full Analysis Set

Figure 14.2.7.3	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Total Score over Time – Study Period 1	Safety Set
Figure 14.2.8	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Core Subscale Score over Time by Study Period	Full Analysis Set
Figure 14.2.8.1	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Core Subscale Score over Time by Study Period – High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.8.2	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Core Subscale Score over Time by FAS Subjects Dosed in Each Study Period	Full Analysis Set
Figure 14.2.8.2.1	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Core Subscale Score over Time by FAS Subjects Dosed in Each Study Period - High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.9	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Anxiety Subscale Score over Time by Study Period	Full Analysis Set
Figure 14.2.9.1	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Anxiety Subscale Score over Time by Study Period – High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.9.2	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Anxiety Subscale Score over Time by FAS Subjects Dosed in Each Study Period	Full Analysis Set
Figure 14.2.9.2.1	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Anxiety Subscale Score over Time by FAS Subjects Dosed in Each Study Period - High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.10	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Bech-6 Subscale Score over Time by Study Period	Full Analysis Set
Figure 14.2.10.1	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Bech-6 Subscale Score over Time by Study Period – High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.10.2	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Bech-6 Subscale Score over Time by FAS Subjects Dosed in Each Study Period	Full Analysis Set

Figure 14.2.10.2.1	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Bech-6 Subscale Score over Time by FAS Subjects Dosed in Each Study Period - High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.11	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Maier Subscale Score over Time by Study Period	Full Analysis Set
Figure 14.2.11.1	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Maier Subscale Score over Time by Study Period – High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.11.2	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Maier Subscale Score over Time by FAS Subjects Dosed in Each Study Period	Full Analysis Set
Figure 14.2.11.2.1	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Maier Subscale Score over Time by FAS Subjects Dosed in Each Study Period - High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.12	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Total Score over Time by Study Period and Antidepressant Use at Period-specific Baseline	Full Analysis Set
Figure 14.2.12.1	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Total Score over Time by Study Period and Antidepressant Use at Period-Specific Baseline – High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.12.2	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Hamilton Rating Scale for Depression (HAM-D) Total Score over Time by Antidepressant Use at Baseline - Study Period 1	Safety Set
[redacted]		

Figure 14.2.14.1	Forest Plot of Change from Period-Specific Baseline at Day 15 in Hamilton Rating Scale for Depression (HAM-D) Total Score for Subgroups by Study Period	Full Analysis Set
Figure 14.2.14.2	Forest Plot of Change from Period-Specific Baseline at Day 15 in Hamilton Rating Scale for Depression (HAM-D) Subscale Scores by Study Period	Full Analysis Set
Figure 14.2.14.3	Forest Plot of Change from Period-Specific Baseline at Day 15 in Hamilton Rating Scale for Depression (HAM-D) Total Score for Subgroups - Study Period 1	Safety Set
Figure 14.2.14.4	Forest Plot of Change from Period-Specific Baseline at Day 15 in Hamilton Rating Scale for Depression (HAM-D) Subscale Scores - Study Period 1	Safety Set
Figure 14.2.15	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Clinical Global Impression – Severity (CGI-S) Score over Time by Study Period	Full Analysis Set
Figure 14.2.15.1	Line Plot of Mean (±SD) Change from Period-Specific Baseline in Clinical Global Impression - Severity (CGI-S) Score over Time by Study Period – High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.15.2	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Clinical Global Impression - Severity (CGI-S) Score over Time by FAS Subjects Dosed in Each Study Period	Full Analysis Set
Figure 14.2.15.2.1	Line Plot of Mean (±SD) Percent Change from Period-Specific Baseline in Clinical Global Impression - Severity (CGI-S) Score over Time by FAS Subjects Dosed in Each Study Period - High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.16.1	Line Plot of Mean (±SD) of HAM-D Total Score over Current and Subsequent Study Periods for Responders at Day 15 from Current Treatment Cycle	Full Analysis Set
Figure 14.2.16.1.1	Line Plot of Mean (±SD) of HAM-D Total Score over Current and Subsequent Study Periods for Responders at Day 15 from Current Treatment Cycle - High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.16.2	Line Plot of HAM-D Total Score over Time for Responders at Day 15 of the Latest Treatment Cycle by Subjects who Had Been Dosed in Exactly X Treatment Cycles	Full Analysis Set
Figure 14.2.16.2.1	Line Plot of HAM-D Total Score over Time for Responders at Day 15 of the Latest Treatment Cycle by Subjects who Had Been Dosed in Exactly X Treatment Cycles - High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.16.3	Bar Chart of HAM-D Responders/Non-Responders at Day 15 with % of Non-Responders at Day 15 in Previous Cycle	Full Analysis Set
Figure 14.2.16.4	Bar Chart of HAM-D Responders/Non-Responders at Day 15 with % of Responders at Day 15 in Previous Cycle	Full Analysis Set

Figure 14.2.17.1	Kaplan-Meier Plot of Relapse (Days) by Study Period	Safety Set for Study Period 1, Full Analysis Set for Study Periods 2-5
Figure 14.2.17.1.1	Kaplan-Meier Plot of Relapse (Days) by Study Period - High Dose vs 30 mg Cohort	Safety Set for Study Period 1, Full Analysis Set for Study Periods 2-5
Figure 14.2.17.2	Kaplan-Meier Plot of Durability of Study Drug Effect, Measured by HAM-D (Days), by Study Period	Safety Set for Study Period 1, Full Analysis Set for Study Periods 2-5
Figure 14.2.17.2.1	Kaplan-Meier Plot of Durability of Study Drug Effect, Measured by HAM-D (Days), by Study Period - High Dose vs 30 mg Cohort	Safety Set for Study Period 1, Full Analysis Set for Study Periods 2-5
[redacted]		
Figure 14.2.18	Kaplan-Meier Plot of Time to End of Follow-up (Days)	Full Analysis Set
Figure 14.2.18.1	Kaplan-Meier Plot of Time to End of Follow-up (Days) - High Dose vs 30mg Cohort	Full Analysis Set
Figure 14.2.19	Kaplan-Meier Plot of Time to First HAM-D total score >=20 after Cycle 1 Day 15 Response	Full Analysis Set
Figure 14.2.19.1	Kaplan-Meier Plot of Time to First HAM-D total score >=20 after Cycle 1 Day 15 Response - High Dose vs 30mg Cohort	Full Analysis Set

DocuSign

Certificate Of Completion

Envelope Id: 083988BA2BD84038A87E1E055DD97C3E
Status: Completed
Subject: Complete with DocuSign: Sage 217-MDD-303 Final SAP Methods v3.0 21Jul2023.docx
Source Envelope:
Document Pages: 90
Signatures: 7
Envelope Originator:
Certificate Pages: 6
Initials: 0
[redacted]
AutoNav: Enabled
[redacted]
EnvelopeId Stamping: Enabled
IP Address: [redacted]
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Record Tracking

Status: Original
21-Jul-2023 | 08:06
Holder: [redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: DDAF10A1-376A-455A-9CFD-CF2F69AA698C Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 21-Jul-2023 | 08:11 Viewed: 21-Jul-2023 | 10:01 Signed: 21-Jul-2023 | 10:02
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Security Level: Email, Account Authentication (Required), Login with SSO	[redacted] Signature Adoption: Pre-selected Style Signature ID: 92E67E8B-BDDC-44E9-BC56-A6850815A6F4 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 21-Jul-2023 | 08:11 Resent: 21-Jul-2023 | 10:56 Viewed: 21-Jul-2023 | 10:58 Signed: 21-Jul-2023 | 11:00
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 95A42B3B-78C2-4820-B3C9-63A26F4312B3 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 21-Jul-2023 | 08:11 Viewed: 21-Jul-2023 | 09:33 Signed: 21-Jul-2023 | 09:35
Electronic Record and Signature Disclosure:		

Signer Events	Signature	Timestamp
Not Offered via DocuSign		
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: A9EFCEB1-3639-4EC4-8D3A-1C13B23CD8DA Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 21-Jul-2023 | 08:11 Resent: 21-Jul-2023 | 10:56 Viewed: 21-Jul-2023 | 11:02 Signed: 21-Jul-2023 | 11:04
Electronic Record and Signature Disclosure: Accepted: 21-Jul-2023 | 11:02 ID: ffbf5371-9d1f-4350-815d-db9c0ff776f4		
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 4CB4D7BF-3097-4239-AC1B-C40A2362AF78 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 21-Jul-2023 | 08:11 Viewed: 21-Jul-2023 | 08:22 Signed: 21-Jul-2023 | 08:23
Electronic Record and Signature Disclosure: Accepted: 20-Jul-2021 | 11:15 ID: fd75acbc-bffa-47ad-933d-bb55286e892e		
[redacted] [redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: FFC23379-D63F-4A4A-B9ED-9236C39354B6 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 21-Jul-2023 | 08:11 Viewed: 21-Jul-2023 | 09:02 Signed: 21-Jul-2023 | 10:47
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
[redacted] [redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 89BBDD29-A7B4-4DDA-8896-FB74228A3343 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 21-Jul-2023 | 08:11 Viewed: 21-Jul-2023 | 09:25 Signed: 21-Jul-2023 | 09:26
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	21-Jul-2023 | 08:11
Envelope Updated	Security Checked	21-Jul-2023 | 10:56
Certified Delivered	Security Checked	21-Jul-2023 | 09:25
Signing Complete	Security Checked	21-Jul-2023 | 09:26
Completed	Security Checked	21-Jul-2023 | 11:04
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Sage Therapeutics - Part 11 (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Sage Therapeutics - Part 11:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: marcel@sagerx.com

To advise Sage Therapeutics - Part 11 of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at marcel@sagerx.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Sage Therapeutics - Part 11

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to marcel@sagerx.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Sage Therapeutics - Part 11

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to marcel@sagerx.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Sage Therapeutics - Part 11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Sage Therapeutics - Part 11 during the course of your relationship with Sage Therapeutics - Part 11.