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SAGE THERAPEUTICS INCORPORATED

Statistical Analysis Plan

Methods

Protocol Number 217-MDD-302

STUDY TITLE: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF SAGE-217 WITH A FIXED, REPEATED TREATMENT REGIMEN ON RELAPSE PREVENTION IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

Author of SAP: [redacted]

Version: Version 1

Version Date of SAP: 23 April 2020

Sponsor: Sage Therapeutics, Inc.

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Protocol Number: 217-MDD-302

Authorization Signature Page

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of SAGE-217 with a Fixed, Repeated Treatment Regimen on Relapse Prevent in Adults with Major Depressive Disorder

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2. LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
AE	adverse event
ANCOVA	Analysis of Covariance
ATC	anatomical therapeutic chemical
BLQ	below the limit of quantitation
BMI	body mass index
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
[redacted]	[redacted]
[redacted]	[redacted]
DB	Double-Blind
[redacted]	[redacted]
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
[redacted]	[redacted]
eCRF	electronic case report form
[redacted]	[redacted]
EOS	End of study
EOT	end of treatment
ET	early termination
FAS	Full Analysis Set
FSH	follicle stimulating hormone
GEE	Generalized estimating equations
[redacted]	[redacted]
HAM-D	Hamilton Rating Scale for Depression
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus

Abbreviation or specialist term	Explanation
HIV	human immunodeficiency virus
ICF	informed consent form
[redacted]	[redacted]
IRAC	Independent Relapse Adjudication Committee
IRT	Interactive voice technology
[redacted]	[redacted]
[redacted]	[redacted]
LFT	Liver Function Tests
LLOQ	lower limit of quantification
LS	Least Squares
KM	Kaplan-Meier
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
OL	Open-Label
PCS	Potentially clinically significant
PCSC	potentially clinically significant change
PHQ-9	9-Item Patient Health Questionnaire
[redacted]	[redacted]
[redacted]	[redacted]
PT	preferred term
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
RCI	Reliable Change Index
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

Abbreviation or specialist term	Explanation
SD	standard deviation
SE	standard error
SI	International System of Units
SOC	system organ class
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
WHO-DD	World Health Organization-Drug Dictionary
[redacted]	[redacted]

3. INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis of 217-MDD-302 study, and is based on clinical study protocol, version 2.0, dated 27 August 2019. There have been 4 country-specific amendments approved, but no subject has been enrolled under those amenments in the specific countries. Therefore, those amendments were not applicable for the basis of this SAP.

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

4. STUDY OBJECTIVES

4.1. Primary Objective

The primary objective of Study 217-MDD-302 is to evaluate the efficacy of SAGE-217 with a fixed, repeated treatment regimen in the prevention of relapse in subjects with major depressive disorder (MDD) who have responded to open-label (OL) treatment with SAGE-217.

4.2. Secondary Objective

The secondary objective of Study 217-MDD-302 is to evaluate the long-term safety and tolerability of a fixed, repeated treatment regimen of SAGE-217 up to 1 year.

[redacted]

5. STUDY ENDPOINTS

5.1. Primary Endpoint

The primary efficacy endpoint of this study is the time to relapse during the Double-Blind (DB) Phase (days; from first dose in the first period of the DB phase to relapse [date] during the DB Phase).

5.2. Secondary Endpoints

The secondary endpoints of this study are:

- Percentage of subjects who relapse during the DB Phase
- Change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at the end of each 14-day treatment period in the DB Phase
- HAM-D response at the end of each 14-day treatment period in the DB Phase, defined as a $\geq$ 50% reduction in HAM-D total score from baseline
- HAM-D remission at the end of each 14-day treatment period in the DB Phase, 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 period in the DB Phase
- Change from baseline in Clinical Global Impression – Severity (CGI-S) score at the end of each 14-day treatment period in the DB Phase
- Change from baseline in the 9-item Patient Health Questionnaire (PHQ-9) score at the end of each 14-day treatment period in the DB Phase
- Time to relapse during the DB Phase (days; from first dose of study drug in DB Phase to relapse [date] during the DB Phase) for subjects who achieved HAM-D remission in the OL Phase
- Incidence of treatment-emergent adverse events (TEAEs)

[redacted]

6. STUDY DESIGN

6.1. Overall Design

Study 217-MDD-302 has an OL Phase followed by a randomized, DB, placebo-controlled phase to assess the effect of SAGE-217 monotherapy in a fixed, repeated treatment regimen versus placebo on relapse prevention in adult subjects with MDD who are not currently taking antidepressants. Randomization is carried out in a 1:1 ratio to receive SAGE-217 30 mg or matched placebo.

This study will consist of a Screening Phase of up to 4 weeks, an Open-Label Phase of 8 weeks, and a DB Phase of 40 weeks.

The Screening Phase begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. The diagnosis of MDD must be made according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Clinical Trial Version (SCID-5CT) performed by a qualified healthcare professional. Subjects will undergo preliminary screening procedures at the Screening Visit to determine eligibility, including completion of the Montgomery-Åsberg Depression Rating Scale (MADRS), HAM-D, and CGI-S.

Beginning on Day 1 of the OL Phase, eligible subjects will self-administer a single dose of study drug once daily in the evening with food, on an outpatient basis, for 14 consecutive

days. Subjects who complete the OL Phase (through Day 56) with no significant tolerability issues as judged by the Investigator and who exhibited a HAM-D response, defined as a ≥50% reduction from baseline in HAM-D total score, at visits on Day 15, 28, 42, 56 will be eligible for the DB Phase. One excursion of <50% reduction from baseline (but total score ≤21) in HAM-D total score or one missing HAM-D total score at visit on Day 28 or Day 42, will be permitted for eligibility to the DB Phase. Non-responders to SAGE-217 will be discontinued from the study.

Beginning on Day 1 of the DB Phase, eligible subjects from OL phase will be randomized to receive SAGE-217 30 mg or matching placebo in a 1:1 ratio. The 40-week DB Phase consists of five 14-day treatment periods, each separated by a 6-week follow-up period. The end of each follow-up period coincides with the first visit of the next treatment period. During the 14-day treatment periods, subjects will self-administer a single dose of study drug once daily in the evening with food, on an outpatient basis.

During the follow-up periods of the DB Phase, depressive symptoms will be monitored every 7 (+3) days via remote PHQ-9. If the PHQ-9 score is ≥10, the subject will return to the site as soon as possible to be assessed by the clinician-administered HAM-D. If the HAM-D is ≥18 at this visit, the subject will return to the site in 7 to 14 days to be reassessed by the HAM-D. If the HAM-D remains ≥18, the subject will be considered to have relapsed at this visit. Subjects that meet relapse criteria (see Section 9.3.1.1) will not be eligible for further randomized treatment periods and should return for follow-up visits as outlined in the protocol. Subjects that meet relapse criteria during a treatment period and discontinue treatment early should return to the site for an EOT visit, and thereafter, should return for follow-up visits (see Appendix A Follow-up for Subjects that Meet Relapse Criteria). Final determination of relapse will be made by an Independent Relapse Adjudication Committee (IRAC) for events other than 2 consecutive HAM-D scores ≥ 18 assessed 7 to 14 days apart. Subjects will return to the study center during each of the phases as outlined in Appendix A.

If at any time during the study, 30 mg SAGE-217 is not tolerated, as assessed by the occurrence of a severe adverse event (AE) judged by the Investigator to be related to the study drug, the dose will be reduced to 20 mg and continued for the remainder of the treatment period. Dose adjustments related to moderate AEs will be at the discretion of the Investigator. Subsequent treatment period will begin with the 30-mg dose, regardless of whether a subject required a dose adjustment in a previous treatment period. Subjects who cannot tolerate the 20-mg dose at any time will be terminated from the study upon completion of an end of treatment (EOT) visit as soon as possible, and an early termination (ET) visit 7 days later.

6.2. Sample Size and Power

The randomization in the DB phase is 1:1, with 150 subjects randomized in each treatment arm – placebo and SAGE-217. Assuming a relapse rate of 34% in the placebo arm and 17% in the SAGE-217 arm for a fixed 40-week repeated treatment regimen (Hazard ratio = 0.448), this sample size will provide a 90% power with 0.05 level of significance in comparing time to relapse (through comparison of survival curves) by log-rank test. Further, assuming that only 55% of the subjects dosed in the OL Phase will qualify as responders to be randomized in the DB Phase, 546 subjects will need to be dosed in the OL Phase.

6.3. Interim Analysis

An interim analysis is planned when about 50% of the expected relapse events occur (ie, 34 of 67 expected relapse events) to estimate the hazard ratio and to re-estimate (increase) the sample size if needed. No early stopping or sample-size reduction is planned within this interim analysis. This unblinded interim analysis will be performed by an independent third party, external to the sponsor, with specific directions on how to conclude depending on the range of the observed hazard ratio. The final analysis will be performed after the last randomized subject completes (or ET) the study. Further details will be provided in a separate Interim Analysis Plan.

6.4. Randomization

This study contains an OL Phase followed by a randomized, DB, placebo-controlled phase. Subjects who complete the OL Phase with no significant tolerability issues as judged by the Investigator and who meet HAM-D response criteria will be randomized in a 1:1 ratio to receive SAGE-217 30 mg or matched placebo.

Randomization schedules will be generated by an independent statistician. The allocation to treatment group (SAGE-217 30 mg or placebo) will be based on the randomization schedule. Randomization will be performed centrally via an interactive response technology (IRT) system.

6.5. Blinding and Unblinding

This study contains a randomized, double-blind, placebo-controlled phase. Subjects, clinicians, and the study team will be blinded to treatment allocation during the study. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding.

During the DB Phase, the blind is to be broken by the Investigator only when the safety of a subject is at risk and the treatment plan is dependent on the study drug received. Unless a subject is at immediate risk, the Investigator must make diligent attempts to contact Sage

prior to unblinding the study drug administered to a subject. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage as soon as possible and no later than the next business morning. In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the electronic case report form (eCRF). If the subject or study center personnel has been unblinded, the subject will be permanently discontinued from the study.

An independent third party will be unblinded to conduct an interim analysis to re-estimate the sample size with specific directions on how to conclude depending on the range of hazard ratio observed (Section 6.2). The decision will be communicated to Sage personnel only in terms of "no change in sample size necessary" or "increase the sample size to XXX"; hence Sage personnel will remain blinded.

7. MODIFICATIONS

7.1. Modifications to the Approved Clinical Study Protocol

[redacted] mentioned in the protocol will not be derived within the scope of this analysis plan; for details, please refer to Section 8.5 below.

The population, defined in the protocol as the Enrolled Set is not used in the SAP, because it is redundant to the Safety Set – both describe subjects, who received at least one dose of study drug.

7.2. Modifications to the Approved Statistical Analysis Plan

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

7.3. Modifications to the Approved DMC Charter

Not applicable.

8. ANALYSIS SETS

8.1. Randomized Set

The Randomized Set is defined as all subjects who are randomized in the DB Phase.

8.2. Safety Set

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

8.3. Period Specific Safety Set

Period Specific Safety Set X (where X=1, 2, 3, 4, 5) is defined as all subjects who were administered study drug during the DB Study Period X (See Section 9.1.2).

8.4. Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized subjects in the Safety Set with a valid baseline and at least 1 post-baseline HAM-D total score in the DB Phase.

[redacted]

9. STATISTICAL ANALYSIS

9.1. General Considerations

Unless otherwise specified, continuous endpoints will be summarized with n, mean standard deviation (SD), median, minimum (min) and maximum (max). If the measurements in the source (raw) data are integers, then the corresponding mean and median will be presented to 1 decimal place and the SD to 2 decimal places. If the measurements are obtained to 1 decimal place, then the mean and median will be presented to 2 decimal places and the SD to 3 decimal places; and so forth. Minimum and maximum will be displayed as reported in the source (raw) data. In addition, change from baseline values (visit value – baseline value) will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages. Percentages will be presented to 1 decimal place unless otherwise specified; the denominator of percentages will be the number of subjects in the analysis set used unless specified otherwise.

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

All summaries and figures will be provided by treatment group, unless stated otherwise. Efficacy data are analyzed by the treatment the subject is randomized to receive. Safety data are analyzed by the actual treatment received. During the DB Phase, this is determined by the highest strength of drug the subject received at any point of time during the study, irrespective of the number of days of exposure. For example, if a subject received placebo for

8 days and SAGE-217 for 7 days, the actual treatment for the subject is SAGE-217. Unless specified otherwise, analyses using Safety Set will use actual treatment received.

All subject data, including those derived, will be presented in the subject data listings. In general, the subject data listings will be sorted by subject number and assessment visit and date (and time, if applicable). The treatment will be identified for each subject.

For the purpose of all efficacy analyses, the DB baseline is defined as the last non-missing measurement prior to the first dose of study drug in DB Phase, unless stated otherwise. If the time of an assessment is collected, baseline will be the latest assessment prior to the time of first dose of blinded study drug administration. If the time of an assessment is not collected, the assessment on Day 1 of the Treatment Period 1 is assumed to be prior to dosing if the protocol mentions that this assessment needs to be before dosing or it is collected as "pre-dose".

For the purpose of all safety analyses, the OL baseline is defined as the last non-missing measurement prior to the first dose of study drug in OL Phase, unless stated otherwise. If the time of an assessment is collected, OL baseline will be the latest assessment prior to the time of first dose study drug administration. If the time of an assessment is not collected or is missing, the assessment on Day 1 of the OL Phase is assumed to be prior to dosing

Period-specific baseline (for each Treatment Period X) is defined as the last non-missing measurement before the first dose of study drug taken in Period X.

9.1.1. 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 after Day 1, study day = visit date – Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date – Day 1 date. Thus, study days for screening visit are negative numbers. There is no "Day 0".

9.1.2. Study Period Definition

Starting date/time = date/time when a subject receives the first dose of the study drug in the period X (as recorded in the Study Drug Administration page) with > 0 capsules consumed, X=OL, DB1, DB2, DB3, DB4, DB5

End date/time = Right before Study Period (X+1) starting date/time if the subject did not discontinue the study before the start of Study Period X+1; or =date of Study

Completion/Discontinuation if the subject discontinued study before the start of Treatment Period X+1

9.1.3. Missing Data

All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. Efficacy analyses will use sensitivity analyses and/or windowing of visits to assess the impact of missing data. Safety analyses will not impute missing data, except for windowing of visits. Imputation of missing data in scoring of questionnaires is discussed in respective sections below. Handling of missing or incomplete dates have been discussed in Appendix C.

9.2. Background Characteristics

9.2.1. Subject Disposition

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

The summaries of subject disposition will include the number of subjects who were screened, who screen failed, and who received study drug in the Open-Label Phase, who were randomized in the DB Phase, and who received study drug in the Double-Blind Phase. The subject disposition summary will also include the number of subjects who completed each phase (including number of responders and non-responders in the OL Phase), who prematurely withdrew from each phase, primary reasons for not completing each phase, who completed treatment in each phase, who discontinued treatment prematurely, and primary reasons for discontinuing treatment, and the number of subjects who relapsed. Study completion summary and treatment completion summary will be based on subjects who received study drug (Safety Set). Percentages will be calculated based on Safety Set. These data will be provided by treatment group. For subjects randomized in the Double-Blind Phase, randomized treatment group will be used.

If a subject is rescreened because the subject was 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.

A subject is considered completed the Open-Label Phase (OL Completer) if he or she has completed 2 weeks of SAGE-217 treatment and 6 weeks of follow-up, including the Day 56 visit.

A subject who is OL Completer is considered a responder if the following conditions are satisfied:

- The HAM-D total score at Day 15 visit is reduced $\geq$ 50% compared to the baseline, AND

- The HAM-D total score at Day 56 visit is reduced ≥ 50% compared to the baseline, AND
- Either
  - (The HAM-D total score at Day 28 and Day 42 visits are both reduced ≥ 50% compared to the baseline) OR
  - (The HAM-D total score at Day 28 visit is reduced ≥ 50% compared to the baseline) AND (the HAM-D total score at Day 42 visit is reduced < 50% compared to the baseline yet the score is ≤ 21 or the score is missing), OR;
  - (The HAM-D total score at Day 42 visit is reduced ≥ 50% compared to the baseline) AND (the HAM-D total score Day 28 visit is reduced < 50% compared to the baseline yet the score is ≤ 21 or the score is missing).

A subject is considered completed Double Blind Phase (DB Completer) if he or she completed all five double-blind treatment periods, including the last follow up visit and is derived from the study conclusion CRF page with the completion question answered 'Yes'.

A subject is marked as completing the treatment if the prematurely discontinued question in the treatment discontinuation CRF page is answered 'No'.

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 during the Double-Blind Phase will include the number of subjects at the beginning of each treatment period, dosed in each treatment period, who discontinued treatment during each treatment period, primary reason for discontinuing the treatment, and who completed the treatment period. This will be provided for the Randomized Set.

Using the 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.

A separate data listing will be provided for subjects in the Safety Set regarding whether they met all eligibility criteria (if not, which ones were not met).

9.2.2. Protocol Deviations

Protocol deviations identified during site monitoring will be captured on eCRF and categorized by the study team as major and minor deviations, without any unblinding information. The major deviations are further categorized as major-efficacy, major-safety and major-GCP deviations. The protocol deviations by category will be provided in a listing for all subjects in the Safety Set.

9.2.3. Demographics and Baseline Characteristics

The following analyses will use the Safety Set and the FAS (using randomized treatment).

Demographic data (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized by Study Phase and treatment group and pooled treatment groups, where applicable. Highest education level will be categorized in the summary tables as follows:

- Less than 12^{th} grade
- 12th grade diploma or GED
- Some college but no degree
- Associate degree
- Bachelor's degree
- Master's degree
- Professional degree
- Doctoral degree

Baseline subgroups are defined for the following categories:

- Race (Black or African American, White, Other)
- Gender (Female, Male)
- Age (18-24, 25-50, 51-65 years)
- BMI ($\leq$18.4, 18.5-24.9, 25-29.9, $\geq$30 kg/m^2)

Diagnostic labs are part of screening. A data listing using the Safety set will be provided. The diagnostic screening test results that will be included in this listing are provided in Table 1.

Table 1: Diagnostic Screening Test Results

Diagnostic		
Serum	**Urine**	**Breathalyzer**
Hepatitis B	Drug screen: including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine	Alcohol

Diagnostic		
Serum	**Urine**	**Breathalyzer**
Hepatitis C	Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: urine hCG	
Reflex HCV RNA		
HIV-1 and -2		
Female subjects who 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		

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

9.2.4. Medical/Surgical History

The following analyses will use the Safety Set.

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 years 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 Appendix C.

Medical/surgical history collected at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0 or higher. Medical/surgical history data will be summarized by system organ class (SOC) and preferred term (PT). A summary of medical/surgical history that are ongoing at the time of screening will be provided separately.

Subject history of psychiatric disorders and family psychiatric history will be summarized; the data will be provided in listings.

9.2.5. 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, any GABAergic medications taken 12 months prior to screening, and non-psychotropic medications taken within 30 days prior to screening will also be collected. All medications will be coded using World Health Organization-Drug dictionary (WHO-DD) March 2018 or later.

Medications will be presented according to whether they were 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 Appendix C. Note that it is possible for a medication to be both 'prior' and 'concomitant'.

Concomitant medications will be further divided by treatment period as follows (if time is missing, the date will be used for this algorithm):

- On-treatment concomitant medications in 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 in period X, AND that were ongoing at the time of first dose of study drug in the study period X.
- Post-treatment concomitant medications in 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 and before the investigator determined relapse event (See Table 2 in Section 9.3.1.1)
- Post-relapse concomitant medications are all medication with a start date on or after the investigator determined relapse.

Prior and concomitant medication use will be summarized by anatomical therapeutic chemical (ATC) level 1 and Standard Medication Name.

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 an end date is available.

9.2.6. 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. Total drug exposure will be calculated separately for OL and DB Phases. For the DB Phase the total drug exposure will be computed by summing up the exposure across all DB treatment periods. If the subject skips the dose on any of the days, the dose taken for that day is 0 mg.

Total exposure duration to study drug (in days) will be calculated separately for OL and DB Phases. For the DB Phase the total exposure duration for each treatment period is defined as: Date of last dose in the specific period – date of first dose in the specific period + 1. Note that this includes 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 treatment periods.

Total drug exposure and total exposure duration will be summarized descriptively. Study drug exposure will also be summarized descriptively by study phase and treatment period. Number of doses taken will be presented in categories: less than 11 doses, from 11 to 14 doses, and >14 doses (by study period). Number and % of subjects with less than 11 doses will be presented per study period.

9.2.7. Study Drug Adherence

The following analyses will use the Safety Set. Study drug adherence (%) is defined as the number of capsules taken, divided by the number of capsules planned to be taken, times 100. Adherence will also be used to summarize subjects into the three categories as follows:

- Number of subjects with adherence <75%
- Number of subjects with adherence from 75% (inclusively) to 100% (inclusively)
- Number of subjects with adherence >100%

The schedule of study drug is one capsule per day, so the planned number of days for study drug intake is the same as the number of capsules planned to be taken. The planned number of days for study drug intake is defined as follows:

1. If the subject discontinues treatment within Day 2 and Day 14 (both inclusive), the planned number of days is the last dose day of study drug.
2. If the subject does not discontinue treatment, the planned number of days is 14.

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.

9.3. Efficacy Analysis

9.3.1. Definition of Efficacy Variables

9.3.1.1. Relapse

Relapse will be determined during the Double-Blind Phase. A summary of all events for which a subject may be considered to have relapsed is presented in Table 2 below.

Table 2: Summary of Relapse Events

Event	Requires review by IRAC?
2 consecutive HAM-D scores ≥18 assessed 7 to 14 days apart	No
Any worsening of depression requiring hospitalization	Yes
Any Investigator-determined risk of suicide	Yes
Worsening of overall depressive symptoms as measured by CGI-S ≥4 and an increase from baseline in CGI-S score of ≥ 2points	Yes
PHQ-9 score ≥10 and subsequent subject withdrawal from study	Yes
Single PHQ-9-triggered HAM-D score ≥18 and subsequent subject withdrawal from study	Yes

Final determination of relapse will be made by an Independent Relapse Adjudication Committee (IRAC) for events other than 2 consecutive HAM-D scores ≥18 assessed 7 to 14 days apart.

Subjects who have 2 consecutive HAM-D total scores ≥18 during a treatment period are encouraged to complete the treatment period. Subjects who experience any of the first 4 events described in the table above will not be eligible for further randomized treatment periods; these subjects may receive treatment as clinically indicated by their physician and should return to the site for follow-up visits as outlined in the protocol. Summaries will be provided for subjects who relapse only.

Time to relapse is defined as the number of days from first dose of study drug in DB Phase to relapse: Date of relapse – date of first dose in DB phase + 1

9.3.1.2. 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. The assessment schedule is presented in Appendix A. The 17-item HAM-D comprises individual ratings related to the following symptoms: depressed mood (sadness, hopeless, helpless, worthless), feelings of guilt, suicide, insomnia (early, middle, late), work and activities, retardation (slowness of thought and speech; impaired ability to concentrate; decreased motor activity), agitation, anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis, loss of weight, and insight. Each item is scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression. The score for each item will be summed to compute a total score, which ranges from 0 to 52. If more than 3 individual items are missing a response, the HAM-D total score will not be calculated and will be left as missing. If less than or equal to 3 individual item scores are missing, the missing item scores will be imputed by the mean of all other available item scores, or the maximum possible values for the missing responses, whichever is smaller, to calculate the HAM-D total score.

Four HAM-D subscale scores will be calculated as the sum of the individual rating scores related to each subscale, divided by the total possible score within the subscale, multiplied by 100, and rounded to a whole number. If more than one item is missing or HAM-D total score is missing, the subscale score is left as missing; if one item on a particular subscale is missing, but has been imputed for the calculation of the total score, the imputed value from the total score calculation will be used in the subscale score calculation for that item. Table 3 describes the subscale score calculations:

Table 3: 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.

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

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

9.3.1.3. 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 only rated at post-treatment assessments as described in Appendix A. 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.

9.3.1.4. Clinical Global Impression – Severity (CGI-S)

The Clinical Global Impression - Severity (CGI-S) uses a 7-point Likert scale to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating as 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=extremely ill.

9.3.1.7. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a 9-item subject-rated depressive symptom severity scale. Subjects will complete the PHQ-9 via web browser every 7 days (± 3 days). 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: 1 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.

9.3.2. Visit Windows

The scheduled visits will not be windowed and will be used at nominal visit value for analysis purposes. The unscheduled, end-of-treatment (EOT) and early termination (ET) visit will be mapped to a scheduled visit for analysis. Unscheduled visits that happen on or before EOT visit date (including EOT visit) will be mapped using the date of collection/assessment and Day 1 first dose date as a basis to determine study day and then study day will be mapped to the intended visit according to the visit windows specified in Table 3 below. Unscheduled visits after EOT visit date, including ET visit, will be windowed using relative days since last dose date; the mapping will follow Table 4 below. 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, 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.

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 will remain in the database and will be included in the listings.

Table 4 displays windows for efficacy analysis.

Table 4: Visit Windows for Efficacy Analysis

Phase	Scheduled Visit in Protocol (in Period)	Target Study Day in Protocol (in Period)	Study Day Window for Visit in Analysis
Screening	Screening	Day -1	Days (-28) to (-1)
OL	First Dose	Day 1 (pre-dose)	Day 1 (pre-dose)
	Day 8 ± 1 day	Day 8	Day 2 – Day 11
	Day 15 ± 1 day	Day 15	Day 12 – Day 17
	Day 21 / last OL dose + 7 days ± 1 day	Day 21 / last OL dose + 7 days	Day 18 - Day 23 / last OL dose date +4 days, +9 days
	Day 28 / last OL dose + 14 days ± 1 day	Day 28 / last OL dose + 14 days	Day 24 - Day 35 / last OL dose date +10 days, +21 days
	Day 42 ± 1 day / last OL dose + 28 days ± 1 day	Day 42 / last OL dose + 28 days	Day 36 – Day 48 / last OL dose date + 22 days, +34 days
DB Treatment 1	Day 56 ± 1 day (Day 1)	Day 56 (Day 1)	Day 56 (DB Treatment 1 Day 1 pre-dose)
	Day 63 ± 1 day (Day 8)	Day 63 (Day 8)	Day 57 – Day 66 (DB Treatment 1 Day 2 – Day 11)
	Day 70 ± 1 day (Day 15)	Day 70 (Day 15)	Day 67 – Day 72 (DB Treatment 1 Day 12 – Day 17)
	Day 76 / last DB Treatment 1 dose + 7 days ± 3 days (Day 21)	Day 76 / last DB Treatment 1 dose + 7 days (Day 21)	Day 73 – Day 79 (DB Treatment 1 Day 18 – Day 23) / last DB Treatment 1 dose + 4 days, + 9 days
DB Treatment 2	Day 111 ± 3 days (Day 1)	Day 111 (Day 1)	Day 111 (DB Treatment 2 Day 1 pre-dose)
	Day 118 ± 1 day (Day 8)	Day 118 (Day 8)	Day 112 – 121 Day (DB Treatment 2 Day 2 – Day 11)

Phase	Scheduled Visit in Protocol (in Period)	Target Study Day in Protocol (in Period)	Study Day Window for Visit in Analysis
	Day 125 ± 1 day (Day 15)	Day 125 (Day 15)	Day 122 – Day 127 (DB Treatment 1 Day 12 – Day 17)
	Day 131 / last DB Treatment 2 dose + 7 days ± 3 days (Day 21)	Day 131 / last DB Treatment 2 dose + 7 days (Day 21)	Day 128 – Day 133 (DB Treatment 2 Day 18 – Day 23) / last DB Treatment 2 dose + 4 days, + 9 days
DB Treatment 3	Day 166 ± 3 days (Day 1)	Day 166 (Day 1)	Day 166 (DB Treatment 3 Day 1 pre-dose)
	Day 173 ± 1 day (Day 8)	Day 173 (Day 8)	Day 167 – 176 Day (DB Treatment 3 Day 2 – Day 11)
	Day 180 ± 1 day (Day 15)	Day 180 (Day 15)	Day 177 – Day 182 (DB Treatment 3 Day 12 – Day 17)
	Day 186 / last DB Treatment 3 dose + 7 days ± 3 days (Day 21)	Day 186 / last DB Treatment 3 dose + 7 days (Day 21)	Day 183 – Day 188 (DB Treatment 3 Day 18 – Day 23) / last DB Treatment 3 dose + 4 days, + 9 days
DB Treatment 4	Day 221 ± 3 days (Day 1)	Day 221 (Day 1)	Day 221 (DB Treatment 4 Day 1 pre-dose)
	Day 228 ± 1 day (Day 8)	Day 228 (Day 8)	Day 222 – 231 Day (DB Treatment 4 Day 2 – Day 11)
	Day 235 ± 1 day (Day 15)	Day 235 / last DB Treatment 4 dose + 7 days (Day 15)	Day 232 – Day 237 (DB Treatment 4 Day 12 – Day 17)
	Day 241 / last DB Treatment 4 dose + 7 days ± 3 days (Day 21)	Day 241 (Day 21)	Day 238 – Day 243 (DB Treatment 4 Day 18 – Day 23) / last DB Treatment 4 dose + 4 days, + 9 days
DB Treatment 5	Day 276 ± 3 days (Day 1)	Day 276 (Day 1)	Day 276 (DB Treatment 5 Day 1 pre-dose)

Phase	Scheduled Visit in Protocol (in Period)	Target Study Day in Protocol (in Period)	Study Day Window for Visit in Analysis
	Day 283 ± 1 day (Day 8)	Day 283 (Day 8)	Day 277 – 286 Day (DB Treatment 5 Day 2 – Day 11)
	Day 290 ± 1 day (Day 15)	Day 290 (Day 15)	Day 287 – Day 292 (DB Treatment 5 Day 12 – Day 17)
	Day 296 / last DB Treatment 5 dose + 7 days ± 3 days (Day 21)	Day 296 / last DB Treatment 5 dose + 7 days (Day 21)	Day 293 – Day 298 (DB Treatment 5 Day 18 – Day 23) / last DB Treatment 5 dose + 4 days, + 9 days
	Day 331 ± 3 days (Day 56)	Day 331 / last DB Treatment 5 dose + 42 days (Day 56)	Day 328 – Day 334 (DB Treatment 5 Day 53 – Day 58) / last DB Treatment 1 dose + 39 days, + 44 days

Note: Study day and study day windows for unscheduled visits, EOT and ET for subjects who have discontinued treatment prematurely, visit dates that are ≥4 days from the last dose of study drug in that period will apply windows based on last dose date in that period (ie, visit date – last dose date + 1 >4).

The PHQ-9 scale is collected via web browser every 7 days (±3 days) beginning on Day 1 of the OL Phase. Visit windows will be used for each visit for this scale. Day 8 will have a window of Day 3 to Day 11 with a target of Day 8. Day 15 will have a window of Day 12 to Day 18 with a target of Day 15. Windows for every 7 days will be used. The score closest to the target will be used. If two scores are in the window equal distance from the target, the later score will be used for the analysis. All visits will be included in the listing.

9.3.3. Analysis of Efficacy Variable(s)

The FAS will be used for all efficacy summary tables in DB phase; for OL phase summaries, Safety Set will be used. Subjects will be analyzed according to randomized treatment. Summaries of endpoints will be provided by each scheduled visit whenever applicable.

The primary endpoint of this study is time to relapse during the double-blind (DB) Phase (as defined in Section 5.1).The properties of the primary estimand for this study are described as follows:

Variable of interest: time to relapse during the DB phase.

Population of interest: adult subjects with MDD.

Summary Measure: Kaplan–Meier (KM) estimate of the survival function

Handling of Intercurrent Events: intercurrent events (treatment discontinuation) will be captured through the censorship scheme of the KM estimate.

The following summary of the following efficacy endpoints will be provided:

- Time to relapse during the DB Phase
- Time to relapse during the DB Phase for subjects who achieved HAM-D Remission by the end of the OL Phase (days from first dose of study drug in DB Phase to relapse during DB Phase)
- Percentage of subjects who relapse during the DB Phase
- HAM-D total score – observed, change from baseline, percent change from baseline, change from phase-specific baseline, percent change from phase-specific baseline
- HAM-D subscale scores – observed, change from baseline, percent change from baseline, change from phase-specific baseline, percent change from phase-specific baseline
- HAM-D individual item score — observed, change from baseline, percent change from baseline, change from phase-specific baseline, percent change from phase-specific baseline
- HAM-D response – missing response not accounted
- HAM-D response – missing response counted as 'No response'
- HAM-D remission – missing remission not accounted
- HAM-D remission – missing remission counted as 'No remission'
- CGI-I score – observed
- CGI-I response
- CGI-S scores – observed and change from baseline, change from phase-specific baseline

[redacted]

- PHQ-9 score – observed (including categories), change from baseline, change from phase-specific baseline

9.3.3.1. Kaplan-Meier Analysis

Time to relapse endpoints will be analyzed using the Kaplan-Meier estimates of the survival curves for each treatment arm, along with the median time to relapse. A two-sided log-rank test will be used to compare the survival curves at a significance level of 0.05. The following censorship scheme will be used:

- A subject will be censored at the subject's last day in the database if the subject did not relapse.
- If the investigator-determined relapse is not confirmed by the Independent Relapse Adjudication Committee (IRAC), then the subject will be censored at the date of the investigator-determined relapse.

9.3.3.2. Mixed Effects Model for Repeated Measures

The change from baseline will be summarized by randomized treatment group and each scheduled time point where the evaluation has been made. A mixed effects model for repeated measures (MMRM) will be used for analysis. The model will include treatment (SAGE-217 or placebo), period-specific baseline value, assessment time point, and time point-by-treatment as explanatory variables for each treatment period. All explanatory variables will be treated as fixed effects. All post-baseline time points for the specific study period will be included in the model.

Model-based point estimates (i.e., least squares [LS] mean, 95% confidence intervals, and unadjusted p-values) will be reported where applicable. An unstructured (UN) covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz, compound symmetry or Autoregressive (1) [AR (1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR (1) structure, no results will be reported. The sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS when the covariance structure is not UN. The p-value will be interpreted at 5% level of significance.

Line plot of model-based LS Mean and standard error (SE) over time will be prepared for change from baseline in HAM-D total score, HAM-D subscale scores, and PHQ-9 score.

9.3.3.3. Generalized estimating equation (GEE) models

For the analysis of binary endpoints, the estimand is the odds ratio. Generalized estimating equation (GEE) methods will be used for the analysis of binary endpoints, such as HAM-D Response and HAM-D Remission. GEE models will include terms for treatment (SAGE-217, Placebo), baseline value, assessment time point, and time point-by-treatment as explanatory

variables for each study period X. Model-based point estimates (ie, odds ratios), 95% confidence intervals, and unadjusted p-values will be reported, unless otherwise stated.

9.4. Safety Analysis

The secondary objective is to evaluate the safety and tolerability of SAGE-217 as assessed by the incidence and severity of adverse events; [redacted]. Safety analyses will be conducted using the Safety Set, unless specified otherwise. Safety and tolerability will be summarized for the OL Phase using the Safety Set. The data will be presented by the actual treatment received rather than the treatment to which the subject has been randomized; for definition of actual treatment assignment, see Section 9.1. The safety data will be presented for SAGE-217 irrespective of dose for each study phase (OL and DB), and for each DB Study Period X.

The assessment schedule is presented in Appendix A . 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 4 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 9.3.2.

The safety endpoints and variables considered in the summary tables for this study are summarized in Table 5.

Table 5: Safety endpoints and variables in the summary tables

Safety Evaluation	Incidence	Observed Value	Change from Baseline	Abnormality/Clinical Significance (CS)	Potentially Clinical Significance (PCS)
AEs	X				
[redacted]					

Note: PCS criteria are outlined in sections 9.4.2-9.4.4
X = to be summarized in tables
Z = to be presented in listings only

9.4.1. 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 AEs will be coded using MedDRA version 21.0 or higher.

A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset on or after the start 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 after the first dose of study drug in the treatment period 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 period but within 1 day after the last dose of study drug in the same period.
- A follow-up period TEAE in study period X is defined as an adverse event with onset more than 1 day after the last dose but before the first dose in the next study period.
- A TEAE in Study Period X includes treatment period TEAEs and follow-up period TEAEs within the study period X.

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. For imputation of missing AE dates, please refer to Appendix C.

An overview summary table of TEAE by study phase and period will present the number and percentage of subjects as well as the number of events for the following for the Open-Label Phase and for the Double-Blind Phase using Safety Analysis Set:

- TEAE
    - Treatment Period TEAE
    - Follow-up Period TEAE
- TEAE by maximum severity (severe>moderate>mild)
- TEAE leading to discontinuation of study drug
- TEAE leading to dose reduction

- TEAE leading to withdrawal from the study
- SAE
- Death

Incidence of TEAEs in following categories 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 tables will be sorted by decreasing frequency in SAGE-217 group, then alphabetically. All AE summaries described below will be provided for the Open-Label Phase and for the Double-Blind Phase using the Safety Analysis Set. Tables for the Double-Blind Phase will be summarized by treatment arm.

- TEAE
- OL Phase TEAE
- OL Phase Treatment Period TEAE
- OL Phase Follow-up Period TEAE
- DB Phase TEAE
- DB Phase TEAE by Study Period
- DB Phase Treatment Period TEAE by Study Period
- DB Phase Follow-up Period TEAE by Study Period
- OL Phase TEAE by maximum severity
- DB Phase TEAE by maximum severity
- OL Phase TEAE by relationship
- DB Phase TEAE by relationship
- Serious TEAEs
- OL Phase Period Serious TEAEs
- OL Phase Treatment Period Serious TEAE
- OL Phase Follow-up Period Serious TEAE
- DB Phase Serious TEAE
- DB Phase Serious TEAE by Study Period
- DB Phase Treatment Period Serious TEAE by Study Period

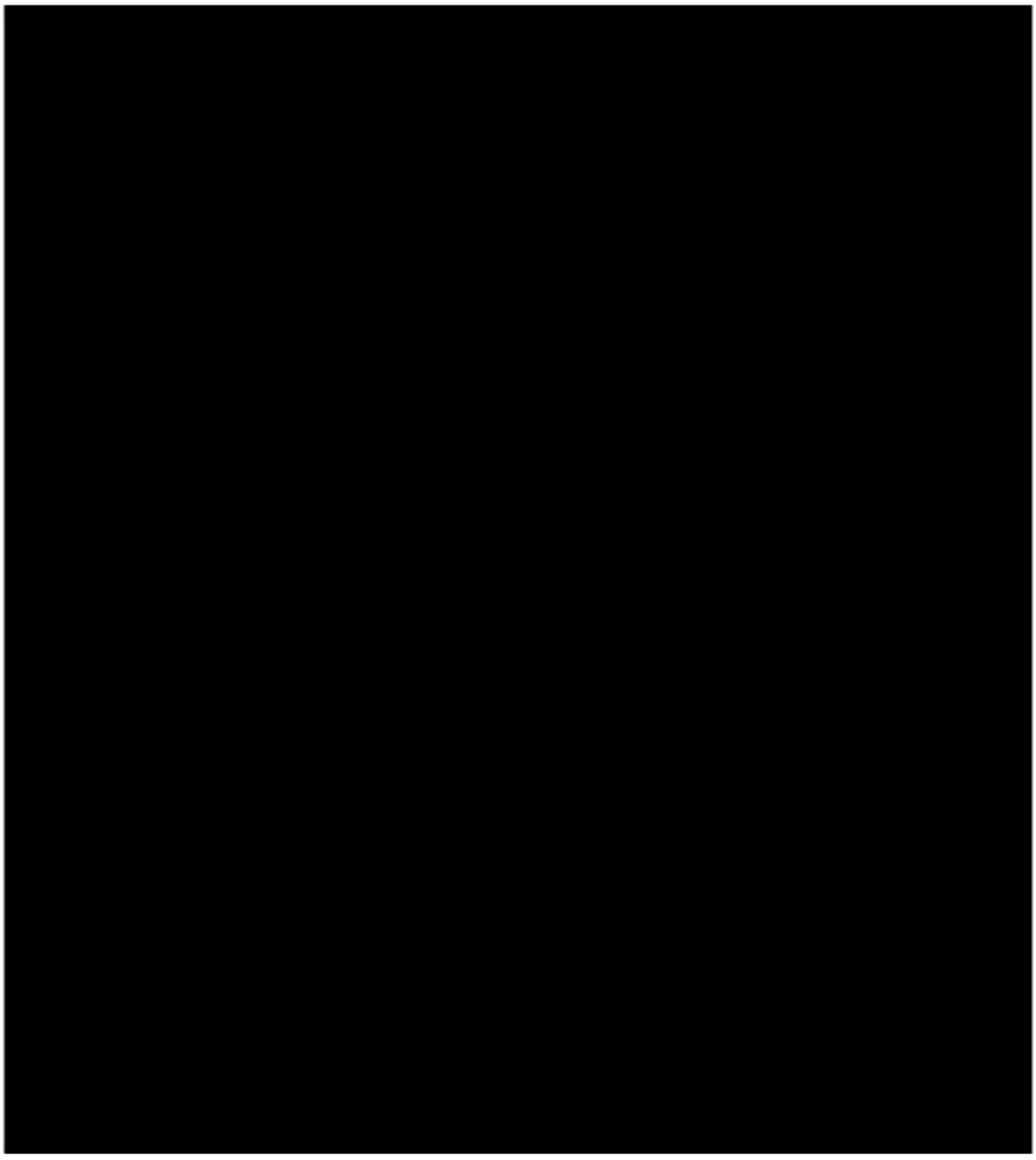
- DB Phase Follow-up Period Serious TEAE by Study Period
- OL Phase TEAEs leading to discontinuation of study drug
- DB Phase TEAEs leading to discontinuation of study drug
- OL Phase TEAEs leading to withdrawal from the study
- DB Phase TEAEs leading to withdrawal from the study

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

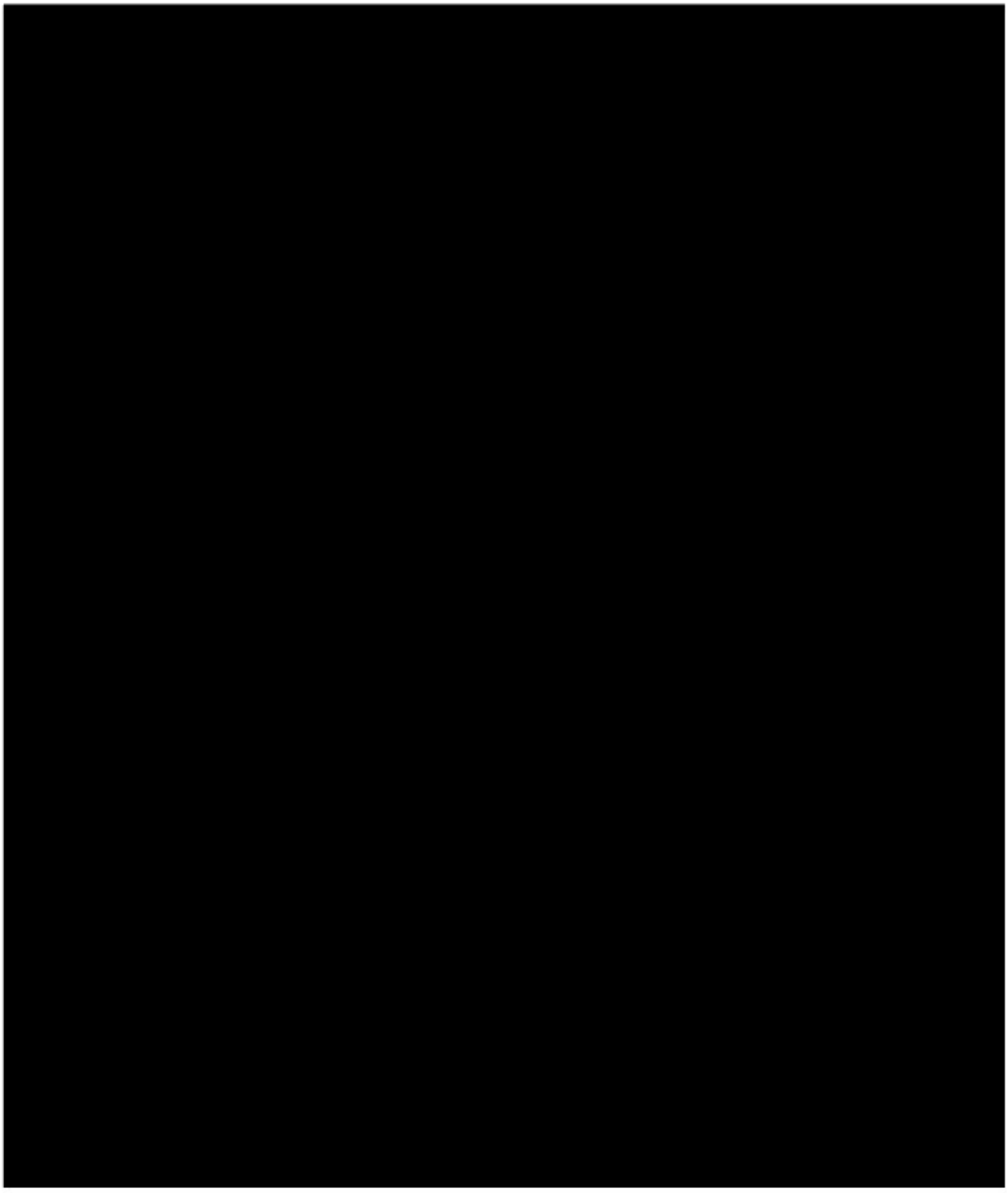
A summary of most common TEAE just by preferred term where the incidence is more than 2% in any treatment group will be provided for the OL Phase and the DB Phase, sorted by decreasing frequency first by SAGE-217.

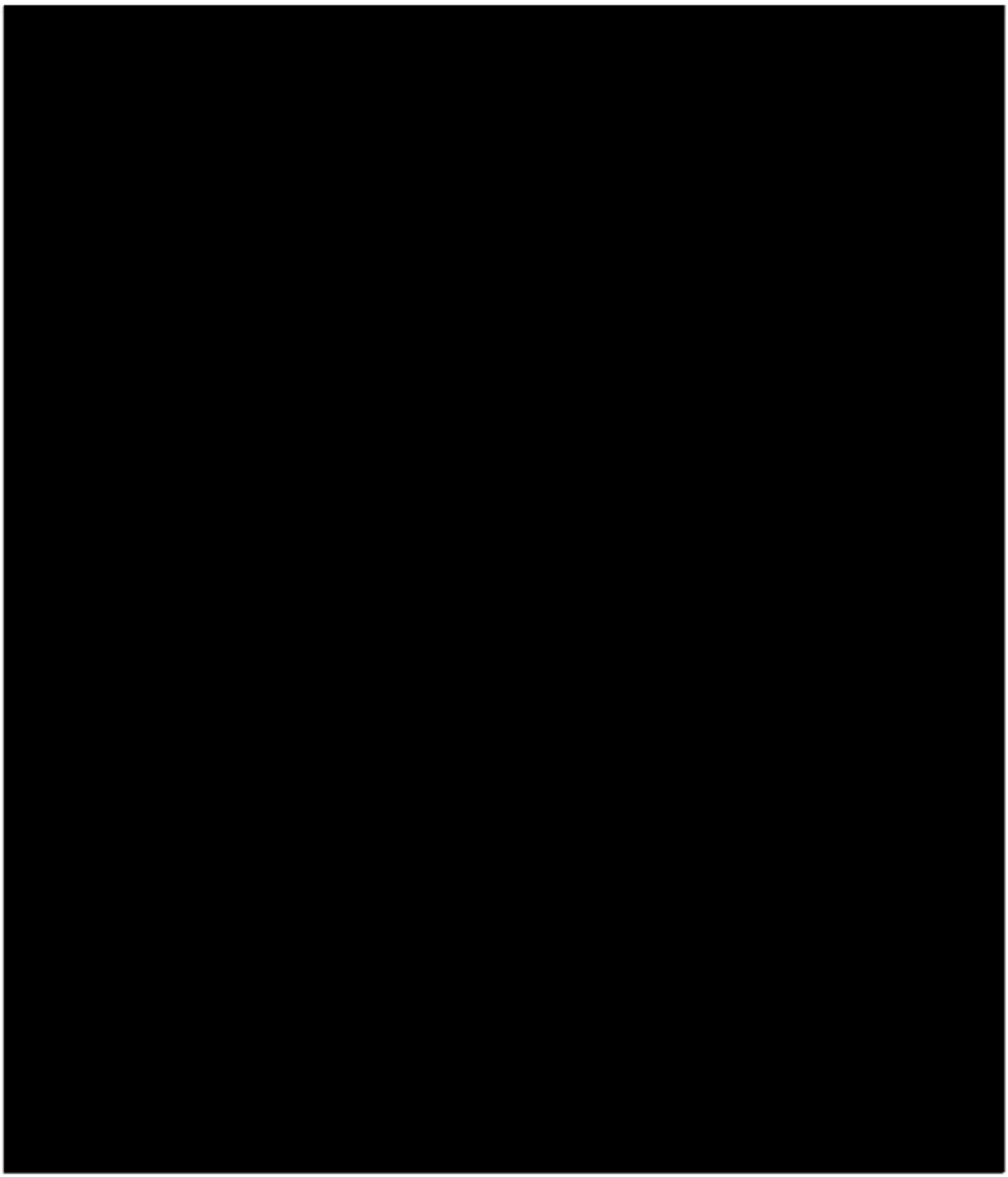
For maximum severity, subjects will be counted only once within each SOC and PT at the maximum severity in the following order: severe> moderate> mild; an AE with missing severity will be omitted from severity presentation. For relationship to study drug, 'related' is defined as relationship being "possible" 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. The incidences will be presented by descending frequency of SOC and then, within a SOC, by PT 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.

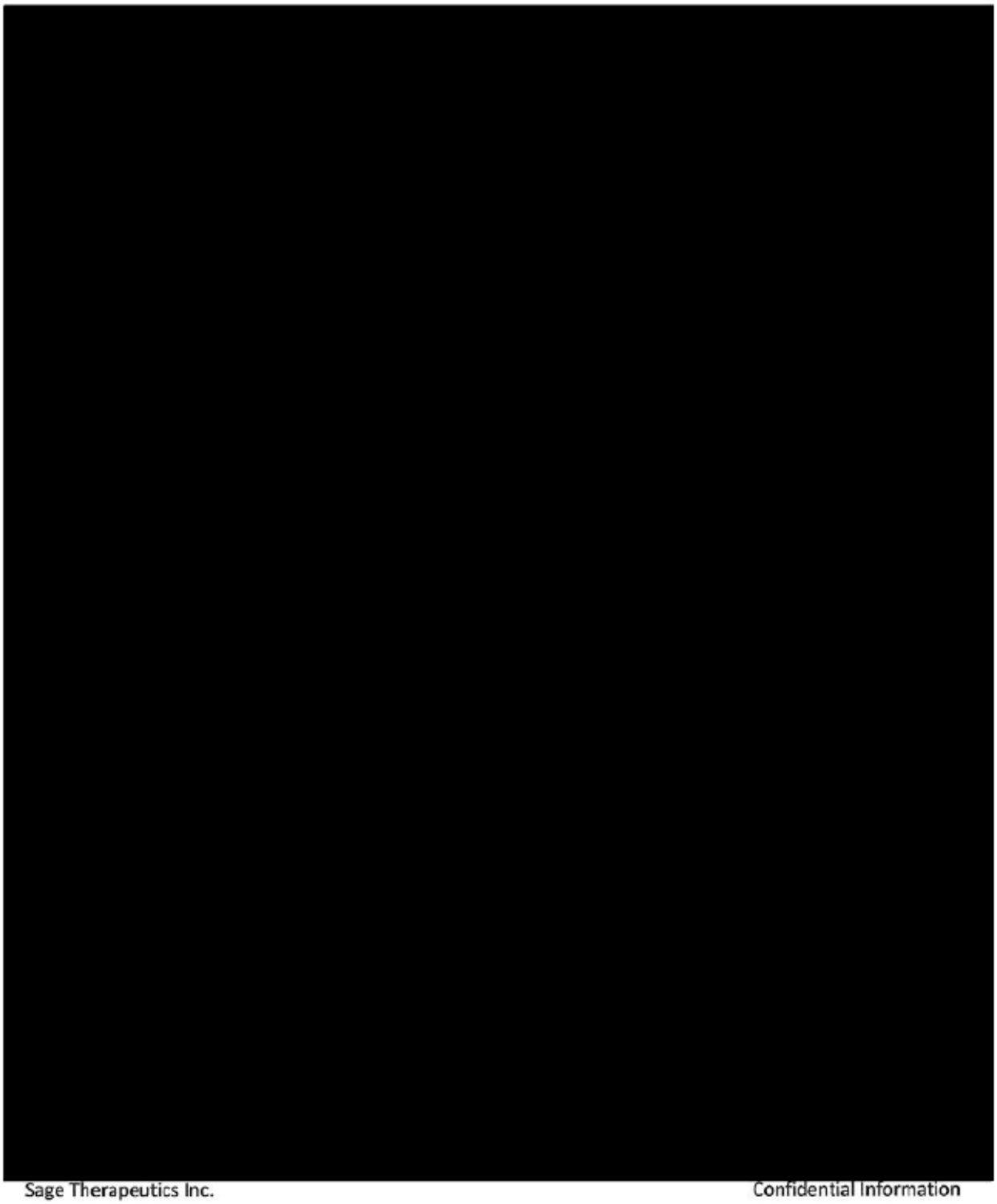
[redacted]



[redacted]





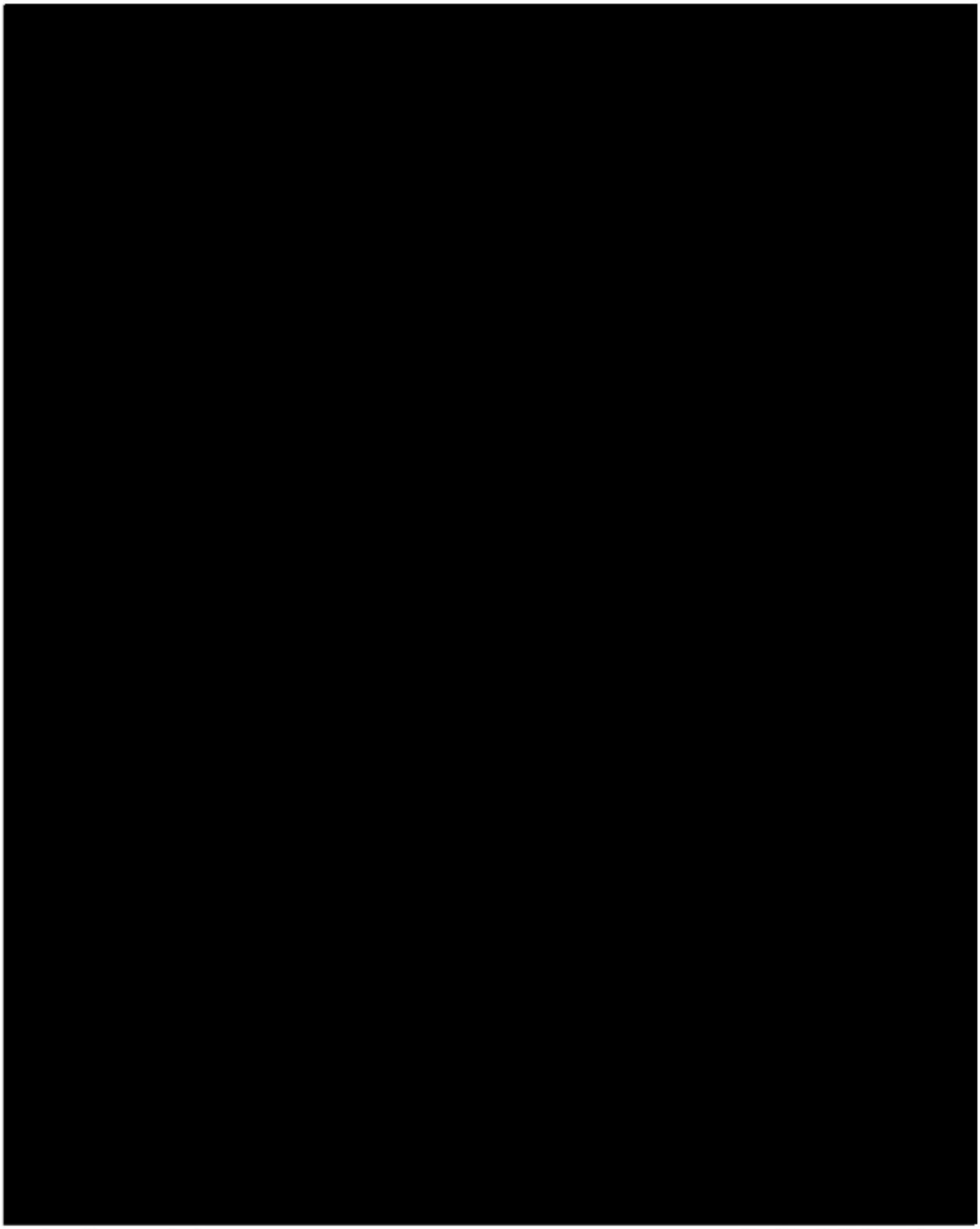


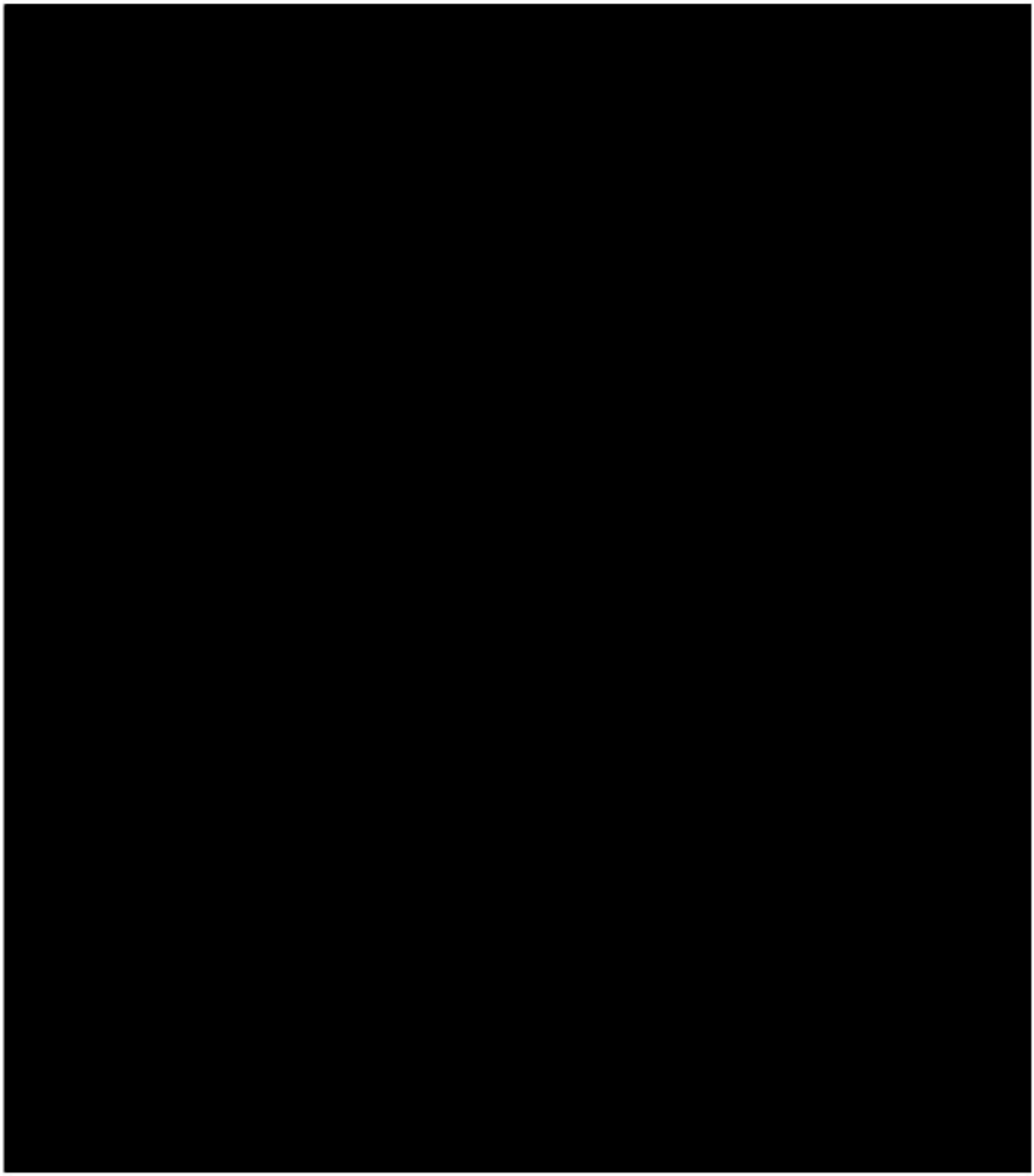
[redacted]

9.4.5. Physical Examination

For the physical examination, only clinically significant abnormalities are captured in the database – for post-baseline observations, these will be reported as adverse events, hence these will be included in AE displays; for pre-baseline observations, these will be reported as medical history, hence these will be included in Medical History displays. The dates of physical examination will be listed to confirm that the examination was done.

[redacted]





9.4.8.3. Derived Variables

9.4.8.3.1. Effect Size

The magnitude of the differences between the treatment and placebo groups, the effect size, will be assessed using Cohen's *d* (Cohen 1988). The equations will be as follows:

$$d = \frac{(\bar{x}_t - \bar{x}_p) * Multiplicand}{Pooled\ SD}$$

$$Pooled\ SD = \sqrt{\frac{(n_t - 1)(SD_t)^2 + (n_p - 1)(SD_p)^2}{n_t + n_p - 2}}$$

Where:

- t = treatment group
- p = placebo group
- n = the sample size of each group
- $\bar{x}$ = descriptive sample mean of each group
- SD = descriptive standard deviation of each group
- The multiplicand equals 1 for tests for which a higher score is indicative of better [redacted] and -1 for tests where a lower score is indicative of better [redacted]

Note: All values for these variables will be shown in the aforementioned table of descriptive statistics.

Effect size $|d|$: <0.2 considered as trivial, 0.2-0.5 considered as small, >0.5-0.8 considered as moderate, >0.8-1.1 considered as large, >1.1 considered as very large (Cohen 1988).

9.4.8.3.2. Standardized Scores

To characterize the nature and magnitude of [redacted] in the study, individual subjects performance on each of the [redacted] will be expressed as a standardized score using the relevant age related normative data (See Table 11 in Appendix D). These analyses will be conducted for the sample enrolled in the open label and double blind phases of the study. The process will be as follows:

- Performance on each [redacted] will be standardized relative to baseline data (i.e., the score will be converted to a z-score by subtracting the study sample's mean at baseline from the score and dividing by the standard deviation (SD) of the study sample's baseline).
- The multiplicand equals 1 for tests for which a higher score is indicative of better [redacted], see Table 2) and -1 for tests where a lower score is indicative of better [redacted]
- The z-score will be calculated as follows:

$$z - Score\ (z_{ijt}) = \frac{(x_{ijt} - \bar{x}_{1t})}{\sigma_{1t}} * Multiplicand$$

Where:

- t = is the test indicator
- i = indexes subject i
- j = indexes the j-th assessment for subject i
- x = [redacted]
- $\bar{x}_{1t}$ = mean performance score of the study sample's baseline for test t
- σ_{1t} = Standard Deviation of the study sample's baseline for test t

9.4.8.3.3. Reliable Change Index (RCI): Comparison of Individual Scores to Baseline

The reliable change index (RCI) is used to assist with interpretation of changes in [redacted]. The RCI itself reflects the magnitude of a standardized difference between two scores (typically the baseline and a post-drug assessment). Essentially, the RCI equation seeks to determine whether differences in scores between two visits are within the range of normal variation in scores. If it is determined that the score is outside the range of normal variation in scores, then the difference between the performance scores from the two assessments is classified as having changed. The range of normal variation in scores for any [redacted] measure is determined from a control population.

In clinical trials, questions about change related to safety are concerned with decline in performance and therefore the statistical decision regarding the RCI is one-tailed. The use of an RCI $\leq$-1.65 cut-off provides a 5% probability of false positive classification for a one-tailed distribution.

The equation for the RCI is as follows:

$$RCI_{mik} = \frac{(Score_{mik} - Score_{m1k}) * Multiplicand}{\sqrt{2} * WSD_k}$$

Where:

- m = subject
- i = assessment (i = 1 means baseline [Study Day 1])
- k = [redacted]
- WSD = Within-Subject Standard Deviation (from [redacted] normative data)

The multiplicand equals 1 for tests for which a higher score is indicative of better [redacted] and -1 for tests where a lower score is indicative of better [redacted]

All RCI scores less than or equal to -1.65 are flagged. This threshold was chosen based on existing literature, which states that an RCI score, an established measure of meaningful [redacted], of ≤ -1.65 is often considered significant at a 90% confidence level (Hinton-Bayre 2010).

RCI scores will only be calculated for the Open-Label phase.

9.4.8.4. Analyses

Open-Label Phase

[redacted] outcome measures, scores, and change from baseline scores (directionality adjusted to ensure positive scores reflect improvement) will be summarized descriptively by assessment for each response group (responder vs. non-responder). To investigate the effect of treatment on [redacted], performance at Day 15 will be compared to OL Baseline using a paired t-test. Effect sizes will also be computed.

Upon completing the OL Phase, subjects will be classified as treatment responders or non-responders. Change from Day 1 (baseline) to Day 15 will be analyzed comparing responders versus non-responders using Analysis of Covariance (ANCOVA) model with OL baseline value as a covariate. The least squares (LS) mean differences between the responses at Day 15 will be estimated along with 95% confidence intervals. Effect sizes will also be generated.

RCI scores will be calculated. For each subject, the number of RCI scores less than or equal to -1.65 will be computed and presented in a listing. Individuals with RCI scores less than or

equal to -1.65 on two or more tests will be identified and their proportions compared between responder and non-responder groups.

A subject listing including scores, change from baseline and RCI scores on each test will be generated.

Double-Blind Phase

[redacted] outcome measures, scores and change from baseline scores (directionally adjusted to ensure positive scores reflect improvement), will be summarized descriptively by treatment group.

All change from baseline scores from the DB Phase (adjusted so that positive scores reflect improvement) will be plotted with box plots by assessment time and treatment group for each test for each study period. Mean and 95% confidence intervals by assessment and treatment group will also be plotted. Change from DB baseline scores (adjusted so that positive scores reflect improvement) will be analyzed using Analysis of Covariance (ANCOVA) model with DB baseline as a covariate. The [redacted] test measurements comparison between SAGE-217 and placebo will be assessed longitudinally for every other Study Period for the following timepoints: pre-dose, end of active treatment period, end of follow up period (see the following table):

Table 10: Scheduled post-baseline visits for the [redacted] endpoints analyses

	Pre-dose	End of treatment period	End of follow up period
Study Period 2	Visit 12	Visit 14	Visit 16
Study Period 4	Visit 20	Visit 22	Visit 24

The LS means differences between the treatment group and placebo will be estimated along with 95% confidence intervals. Effect sizes will be generated for each post-baseline timepoint.

A subject listing including scores and change from baseline scores (adjusted so that positive scores reflect improvement) on each test and composite will be generated.

[redacted]

[redacted]

10. SUMMARY OF INTERIM AND DMC ANALYSES

Please refer to Section 6.3.

11. REFERENCES

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APPENDIX A. SCHEDULE OF ASSESSMENTS

Screening Period

	Screening Period
Study Day	**-28 to -1**
Visit	**1**
Study Procedure	
Informed Consent	X
Duplicate Subject Check (US only) [a]	X
Inclusion/Exclusion	X
Demographics	X
Medical/Family History	X
SCID-5	X
ICD-10 [b]	X
MGH-ATRQ	X
Serum FSH test [c]	X
Full Physical Examination [d]	X
Body Weight/Height	X
[redacted]	X
Drug & Alcohol Screen [f]	X
Serum Pregnancy Test (all female subjects)	X

	Screening Period
Study Day	**-28 to -1**
Visit	**1**
Study Procedure	
Hepatitis & HIV Screen	X
Subject Training [g]	X
[redacted]	X
[redacted]	X
[redacted]	X
HAM-D [j]	X
MADRS	X
CGI-S	X
Adverse Events/SAEs [k]	X
Prior Medications	X

CGI-S = Clinical Global Impression – Severity; [redacted]; ECG = electrocardiogram; 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; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; SCID-5 = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; SAE = serious adverse event; US = United States

[a] Subjects at US sites will be asked to authorize that their unique subject identifiers be entered into a registry with the intent of identifying subjects who may meet exclusion criteria for participation in another clinical study.

[b] ICD-10 code(s) for the diagnosis of the current major depressive episode to be collected if available.

[c] 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.

[d] A full physical examination will be conducted, including assessment of body systems (eg, head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities), as well as [redacted] and neurological examinations and mental status examinations.

[e] Clinical laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis.

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

[g] Subjects will be trained on use of study drug adherence monitoring and PHQ-9 software applications and devices by site personnel.

[redacted]

[j] The HAM-D is to be completed as early during the visit as possible. The assessment timeframe for HAM-D will refer to past 7 days (1 week).

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

Open-Label and Double Blind Phases

	Open-Label						Double-Blind Treatment & FU 1				Double-Blind Treatment & FU 2				Double-Blind Treatment & FU 3				Double-Blind Treatment & FU 4				Double-Blind Treatment & FU 5				EOS
Study Day	1	8 (±1)	15 (±1)	21 (±1)	28 (±1)	42 (±1)	56 (±1)	63 (±1)	70 (±1)	76 (±3)	111 (±3)	118 (±1)	125 (±1)	131 (±3)	166 (±3)	173 (±1)	180 (±1)	186 (±3)	221 (±3)	228 (±1)	235 (±1)	241 (±3)	276 (±3)	283 (±1)	290 (±1)	296 (±3)	331 (±1)
Visit	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Treatment Period Day	1	8	15/ EOT[a]	21	28	42	56/ 1[b]	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ ET[a]
Study Procedure																											
Inclusion/ Exclusion	X																										
MADRS	X																										

	Open-Label						Double-Blind Treatment & FU 1				Double-Blind Treatment & FU 2				Double-Blind Treatment & FU 3				Double-Blind Treatment & FU 4				Double-Blind Treatment & FU 5				EOS
Study Day	**1**	**8 (±1)**	**15 (±1)**	**21 (±1)**	**28 (±1)**	**42 (±1)**	**56 (±1)**	**63 (±1)**	**70 (±1)**	**76 (±3)**	**111 (±3)**	**118 (±1)**	**125 (±1)**	**131 (±3)**	**166 (±3)**	**173 (±1)**	**180 (±1)**	**186 (±3)**	**221 (±3)**	**228 (±1)**	**235 (±1)**	**241 (±3)**	**276 (±3)**	**283 (±1)**	**290 (±1)**	**296 (±3)**	**331 (±1)**
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Treatment Period Day	**1**	**8**	**15/ EOT[a]**	**21**	**28**	**42**	**56/ 1[b]**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ 1**	**8**	**15/ EOT[a]**	**21**	**56/ ET[a]**
Study Procedure																											
Subject training [c]	X																										
Randomization							X																				
Abbreviated Physical Examination [d]	X			X			X			X	X			X	X			X	X			X	X			X	X
Body Weight	X		X				X		X		X		X		X		X		X		X		X			X	X
[redacted]																											
Drug & Alcohol Screen [f]	X						X				X				X				X				X				
Urine Pregnancy Test [g]	X		X				X		X		X		X		X		X		X		X		X		X		X
[redacted]																											

	Open-Label						Double-Blind Treatment & FU 1				Double-Blind Treatment & FU 2				Double-Blind Treatment & FU 3				Double-Blind Treatment & FU 4				Double-Blind Treatment & FU 5				EOS
Study Day	1	8 (±1)	15 (±1)	21 (±1)	28 (±1)	42 (±1)	56 (±1)	63 (±1)	70 (±1)	76 (±3)	111 (±3)	118 (±1)	125 (±1)	131 (±3)	166 (±3)	173 (±1)	180 (±1)	186 (±3)	221 (±3)	228 (±1)	235 (±1)	241 (±3)	276 (±3)	283 (±1)	290 (±1)	296 (±3)	331 (±1)
Visit	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Treatment Period Day	1	8	15/ EOT[a]	21	28	42	56/ 1[b]	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ ET[a]
Study Procedure																											
[redacted]																											
HAM-D[k]	X	X	X		X	X	X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
CGI-S	X	X	X		X	X	X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
CGI-I		X	X		X	X	X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
[redacted]																											

	Open-Label						Double-Blind Treatment & FU 1				Double-Blind Treatment & FU 2				Double-Blind Treatment & FU 3				Double-Blind Treatment & FU 4				Double-Blind Treatment & FU 5				EOS
Study Day	1	8 (±1)	15 (±1)	21 (±1)	28 (±1)	42 (±1)	56 (±1)	63 (±1)	70 (±1)	76 (±3)	111 (±3)	118 (±1)	125 (±1)	131 (±3)	166 (±3)	173 (±1)	180 (±1)	186 (±3)	221 (±3)	228 (±1)	235 (±1)	241 (±3)	276 (±3)	283 (±1)	290 (±1)	296 (±3)	331 (±1)
Visit	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Treatment Period Day	1	8	15/ EOT[a]	21	28	42	56/ 1[b]	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ 1	8	15/ EOT[a]	21	56/ ET[a]
Study Procedure																											
Study Drug Dispensation	X	X					X	X			X	X			X	X			X	X			X	X			
Study Drug Administration	X (daily for 14 days)						X (daily for 14 days)				X (daily for 14 days)				X (daily for 14 days)				X (daily for 14 days)				X (daily for 14 days)				
Study Drug Accountability/ Return		X	X					X	X			X	X			X	X			X	X			X	X		
PHQ-9[m]	X (every 7 [+3] days)																										
Adverse Events/ SAEs[n]	X																										
Concomitant Medications	X																										

CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; [redacted] ECG = electrocardiogram; EOT = End of Treatment; [redacted] EOS = End of Study; ET = early termination; FU = follow-up; HAM-D = Hamilton Rating Scale for Depression, 17 item; PHQ-9 = 9-item Patient Health Questionnaire; [redacted] SAE = serious adverse event; [redacted]

[a] 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 as scheduled relative to the last day of treatment. Subjects who discontinue treatment early will be terminated from the study upon completion of their final follow-up visit. 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.

[b] The completion of the Open-label Phase for all subjects coincides with the first day of the Double-Blind Phase (Study Day 56, Visit 8). Subjects that do not exhibit a response to SAGE-217 in the Open-label Phase will be terminated from the study on this day upon completion of all assessments.

[c] Subjects will be trained on use of study drug adherence monitoring and PHQ-9 software applications and devices by site personnel.

[d] An abbreviated physical examination will include assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems.

[redacted]

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

[g] Urine pregnancy test for female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal.

[redacted]

[k] The HAM-D is to be completed as early during the visit as possible. The assessment timeframe for HAM-D will refer to the past 7 days (1 week) at Days 28 and 42 of the OL Phase and each Day 56/1 of the DB Phase; "Since Last Visit" will be used for all other visits.

[redacted]

[m] All PHQ-9 assessments will be performed via web browser. The subject will take the first PHQ-9 on Day 1 and then every 7 days thereafter; if the PHQ-9 score is ≥10, the subject will return to the site as soon as possible to be assessed by the clinician-administered HAM-D. If the HAM-D is ≥18 at this visit, the subject will return to the site in 7 to 14 days to be reassessed by the HAM-D. See Visits for Assessment of Relapse for assessments to be conducted at these visits.

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

Visits for Assessment of Relapse

Study Procedure	
Abbreviated Physical Examination [a]	X
[redacted]	
Urine Pregnancy Test [c]	X
[redacted]	
HAM-D [f]	X
CGI-S	X
CGI-I	X
[redacted]	
Adverse Events/SAEs [g]	X
Concomitant Medications	X

[a] An abbreviated physical examination will include assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems.
[redacted]

[c] Urine pregnancy test for female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal.
[redacted]

[f] The HAM-D is to be completed as early during the visit as possible. The assessment timeframe for HAM-D will refer to the past 7 days (1 week) at Days 28 and 42 of the OL Phase and each Day 56/1 of the DB Phase; "Since Last Visit" will be used for all other visits.

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

Follow-up for Subjects that Meet Relapse Criteria

Study Day	**111, 116, 221, 276, 331/EOS (+3)**
Treatment Period Day	**56/1/ET**
Study Procedure	
[redacted]	
Drug & Alcohol Screen	X
[redacted]	
HAM-D	X
CGI-S	X
CGI-I	X
[redacted]	
PHQ-9[a]	X
Adverse Events/SAEs	X
Concomitant Medication	X

[a] The PHQ-9 will be completed by the subject during the visit at the site.

APPENDIX B. DETAILS OF STATISTICAL METHODOLOGY

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

```
ods output lsmeans=estimates diffs=diffs;
proc mixed data=&data;
class trtpn avisitn usubjid;
model chg=base trtpn avisitn trtpn*avisitn / ddfm=kr s;
repeated avisitn / subject=usubjid type=un;
**If type=un does not converge, use type=TOEP;
lsmeans trtpn*avisitn /diff=all cl alpha=0.05;
run;
```

Sample SAS code for Generalized Estimating Equation (GEE):

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

Sample SAS code for Analysis of Covariance (ANCOVA):

```
ods output lsmeans=estimates diffs=diffs;
proc mixed data=&data;
class trtpn;
model chg=base trtpn / ddfm=kr s;
lsmeans trtpn /diff=all cl alpha=0.05;
run;
```

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 as the month and 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 initiation of the treatment.
    - the month of AE onset < the month of initiation of the treatment, then the day will be set to the last day of month.

- 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.

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

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

Prior and Concomitant Medications

For the partial start date of medication:

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

- 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 the month will be set to December. 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.
- 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.

APPENDIX D. [redacted]

[redacted]

APPENDIX E. LIST OF DISPLAYS

Tables

Table Number	Title	Analysis Set
Table 14.1.1.1	Summary of Subject Disposition	All Subjects
Table 14.1.1.2	Summary of Subject Disposition by Study Period during the Double-Blind Phase	Randomized Set
Table 14.1.2.1	Summary of Major Protocol Deviations	Safety Set
Table 14.1.3.1	Summary of Demographics and Baseline Characteristics	Safety Set
Table 14.1.3.3	Summary of Demographics and Baseline Characteristics	Full Analysis Set
Table 14.1.4.1	Summary of Disease History	Safety Set
Table 14.1.5.1	Summary of Medical and Surgical History	Safety Set
Table 14.1.5.2	Summary of Medical and Surgical History ongoing at Screening	Safety Set
Table 14.1.6.1	Summary of Subject History of Psychiatric Disorder	Safety Set
Table 14.1.6.2	Summary of Family History of Psychiatric Disorder	Safety Set
Table 14.1.7.1	Summary of Prior Non-Psychotropic Medications	Safety Set
Table 14.1.7.2	Summary of Concomitant Non-Psychotropic Medications	Safety Set
Table 14.1.7.3	Summary of On-treatment Non-Psychotropic Medications	Safety Set
Table 14.1.7.4	Summary of Post-treatment Non-Psychotropic Medications	Safety Set
Table 14.1.7.5	Summary of On-Treatment Concomitant Non-Psychotropic Medications by Study Period	Safety Set

Table Number	Title	Analysis 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 Post-Relapse Concomitant Non-Psychotropic Medications	Safety Set
Table 14.1.7.8	Summary of Post-Relapse Concomitant Psychotropic Medications	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	Safety Set
Table 14.2.1.1	Summary of Time to First Relapse during the Double-Blind Phase – Kaplan-Meier Analysis	Full Analysis Set
Table 14.2.1.2	Summary of Time to First Relapse during the Double-Blind Phase for Subjects who Achieved Remission during the Open-Label Phase – Kaplan-Meier Analysis	Full Analysis Set
Table 14.2.1.3	Relapse during the Double-Blind Phase	Full Analysis Set
Table 14.2.1.4.5	Relapse during the Double-Blind Phase by Open-Label Phase Baseline HAM-D Total Score Category	Full Analysis Set
Table 14.2.2.1.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Double-Blind Phase Study Visit	Full Analysis Set
Table 14.2.2.1.2	Model-based Results on Hamilton Rating Scale for Depression (HAM-D) Total Score, Change from Baseline by Double-Blind Phase Study Visit	Full Analysis Set
Table 14.2.2.1.3	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Double-Blind Phase Study Period	Full Analysis Set
Table 14.2.2.1.4	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Open-Label Phase Study Visit	Safety Set

Table Number	Title	Analysis Set
Table 14.2.2.1.5	Summary of Hamilton Rating Scale for Depression (HAM-D) Total Score by Post-Relapse Visit	Full Analysis Set Subjects who Relapsed
Table 14.2.2.2.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Subscale Scores by Double-Blind Phase Study Visit	Full Analysis Set
Table 14.2.2.2.2	Model-based Results on Hamilton Rating Scale for Depression (HAM-D) Core Subscale Score, Change from Baseline by Double-Blind Phase Study Visit	Full Analysis Set
Table 14.2.2.2.3	Model-based Results on Hamilton Rating Scale for Depression (HAM-D) Anxiety Subscale Score, Change from Baseline by Double-Blind Phase Study Visit	Full Analysis Set
Table 14.2.2.2.4	Model-based Results on Hamilton Rating Scale for Depression (HAM-D) Bech-6 Subscale Score, Change from Baseline by Double-Blind Phase Study Visit	Full Analysis Set
Table 14.2.2.2.5	Model-based Results on Hamilton Rating Scale for Depression (HAM-D) Maier Subscale Score, Change from Baseline by Double-Blind Phase Study Visit	Full Analysis Set
Table 14.2.2.3.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Subscale Scores by Study Period	Full Analysis Set
Table 14.2.2.3.2	Summary of Hamilton Rating Scale for Depression (HAM-D) Subscale Scores by Open-Label Phase Study Visit	Safety Set
Table 14.2.2.3.3	Summary of Hamilton Rating Scale for Depression (HAM-D) Subscale Scores by Post-Relapse Visit	Full Analysis Set Subjects who Relapsed
Table 14.2.2.3.4	Summary of Hamilton Rating Scale for Depression (HAM-D) Individual Item Score by Double-Blind Phase Study Visit	Full Analysis Set
Table 14.2.2.3.5	Model-based Results on Hamilton Rating Scale for Depression (HAM-D) Individual Item Score, Change from Baseline by Double-Blind Phase Study Visit	Full Analysis Set

Table Number	Title	Analysis Set
Table 14.2.2.3.6	Summary of Hamilton Rating Scale for Depression (HAM-D) Individual Item Score by Double-Blind Phase Study Period	Full Analysis Set
Table 14.2.2.3.7	Summary of Hamilton Rating Scale for Depression (HAM-D) Individual Item Score by Open-Label Phase Study Visit	Safety Set
Table 14.2.2.3.8	Summary of Hamilton Rating Scale for Depression (HAM-D) Individual Item Scores by Post-Relapse Visit	Full Analysis Set Subjects who Relapsed
Table 14.2.2.4.1	Summary of Hamilton Rating Scale for Depression (HAM-D) Response by Double-Blind Phase Study Visit	Full Analysis Set
Table 14.2.2.4.2	Model-based Results on Hamilton Rating Scale for Depression (HAM-D) Response by Double-Blind Phase Study Visit	Full Analysis Set
Table 14.2.2.4.3	Summary of Hamilton Rating Scale for Depression (HAM-D) Response by Double-Blind Phase Study Period	Full Analysis Set
Table 14.2.2.4.4	Summary of Hamilton Rating Scale for Depression (HAM-D) Response by Open-Label Phase Study Visit	Safety Set
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Table Number	Title	Analysis Set
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Table 14.2.2.7.9	Summary of Clinical Global Impression – Severity (CGI-S) by Post-Relapse Visit	Full Analysis Set Subjects who Relapsed
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Table Number	Title	Analysis Set
[redacted]		

Table Number	Title	Analysis Set
[redacted]		
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Table 14.3.1.1.3	Overview of Treatment-Emergent Adverse Events during the Double-Blind Phase	Safety Set

Table Number	Title	Analysis Set
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Table Number	Title	Analysis Set
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Table 14.3.1.6.1	Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Set
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Table 14.3.1.6.4	Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term during the Open-Label Phase Follow-up Period	Safety Set
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Table Number	Title	Analysis Set
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Table 14.3.1.7.1	Summary of Treatment-Emergent Adverse Events leading to Discontinuation of Study Drug by System Organ Class and Preferred Term during the Open-Label Phase	Safety Set
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Table 14.3.1.8.2	Summary of Most Comment (>2%) Treatment-Emergent Adverse Events by Preferred Term during the Double-Blind Phase	Safety Set
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Table Number	Title	Analysis Set
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Table Number	Title	Analysis Set
[redacted]		

Table Number	Title	Analysis Set
[redacted]		

Table Number	Title	Analysis Set
[redacted]		

Table Number	Title	Analysis Set
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[redacted]		

Table Number	Title	Analysis Set
[redacted]		

Table Number	Title	Analysis Set
[redacted]		

Table Number	Title	Analysis Set
[redacted]		

Figures

Figure Number	Title	Analysis Set
Figure 14.2.1.1	Kaplan-Meier Plot of Time to First Relapse during the Double-Blind Phase	Full Analysis Set
Figure 14.2.1.2	Kaplan-Meier Plot of Time to First Relapse during the Double-Blind Phase (Days) for Subjects who Achieved Remission during the Open-Label Phase	Full Analysis Set
Figure 14.2.2.1.2	Line Plot of LS Mean (± SE) Change from Baseline in Hamilton Rating Scale for Depression (HAM-D) Total Score over Time during the Double-Blind Phase	Full Analysis Set

Figure Number	Title	Analysis Set
Figure 14.2.2.2.2	Line Plot of LS Mean (± SE) Change from Baseline in Hamilton Rating Scale for Depression (HAM-D) Core Subscale Score over Time during the Double-Blind Phase	Full Analysis Set
Figure 14.2.2.2.3	Line Plot of LS Mean (± SE) Change from Baseline in Hamilton Rating Scale for Depression (HAM-D) Anxiety Subscale Score over Time during the Double-Blind Phase	Full Analysis Set
Figure 14.2.2.2.4	Line Plot of LS Mean (± SE) Change from Baseline in Hamilton Rating Scale for Depression (HAM-D) Bech-6 Subscale Score over Time during the Double-Blind Phase	Full Analysis Set
Figure 14.2.2.2.5	Line Plot of LS Mean (± SE) Change from Baseline in Hamilton Rating Scale for Depression (HAM-D) Maier Subscale Score over Time during the Double-Blind Phase	Full Analysis Set
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Figure Number	Title	Analysis Set
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Listings

Listing Number	Title	Analysis 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 Phase	Safety Set
Listing 16.2.2.1	Protocol Deviations	Safety Set
Listing 16.2.3.1	Inclusion/Exclusion Criteria Violations	All Subjects
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Listing 16.2.4.2	Baseline Characteristics	Safety Set
Listing 16.2.4.3	Montgomery-Asberg Depression Rating Scale (MADRS)	Safety Set
Listing 16.2.4.4	Diagnostic Laboratory Results	Safety Set
Listing 16.2.4.5	Disease History	Safety Set

Listing Number	Title	Analysis Set
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Listing 16.2.4.7	Subject History of Psychiatric Disorder	Safety Set
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Listing 16.2.4.9.1	Prior and Concomitant Non-Psychotropic Medications	Safety Set
Listing 16.2.4.9.2	Post-Relapse Medications	Safety Set
Listing 16.2.4.9.3	Concomitant Procedures	Safety Set
Listing 16.2.5.1	Study Drug Administration	Safety Set
Listing 16.2.5.2	Study Drug Exposure	Safety Set
Listing 16.2.5.3	Study Drug Adherence	Safety Set
Listing 16.2.6.1	Time to First Relapse during the Double-Blind Phase	Full Analysis Set
Listing 16.2.6.2	Hamilton Rating Scale for Depression (HAM-D)	Safety Set
Listing 16.2.6.3	Clinical Global Impression (CGI) – Improvement	Safety Set
Listing 16.2.6.4	Clinical Global Impression (CGI) – Severity	Safety Set
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Listing 16.2.6.7	Patient Health Questionnaire (PHQ-9)	Safety Set
Listing 16.2.7.1	Adverse Events	Safety Set
Listing 16.2.7.2	Non-fatal Serious Adverse Events	Safety Set

Listing Number	Title	Analysis Set
Listing 16.2.7.3	Adverse Events Leading to Death	Safety Set
Listing 16.2.7.4	Adverse Events with Onset Prior to First Dose of Study Drug	Safety Set
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Listing 16.2.7.6	Adverse Events leading to Premature Withdrawal from the Study	Safety Set
Listing 16.2.7.7	Adverse Events leading to Dose Reduction	Safety Set
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Listing 16.2.8.1.5	Pregnancy Test	Safety Set
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Listing 16.2.8.4	Physical Examination	Safety Set
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Listing Number	Title	Analysis Set
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