9. DOCUMENTATION OF STATISTICAL METHODS

Statistical Analysis Plan

- Statistical Analysis Plan Parts A and B V2.0 02Oct2017
    - The Statistical Analysis Plan for Parts A and B underwent one revision and V2.0 is provided.
- Statistical Analysis Plan Part C V1.0 14Dec2017

Sage Therapeutics, Inc

Statistical Analysis Plan

Methods

Protocol 217-ETD-201/NCT02978781

Part A and Part B

A PHASE 2A, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY EVALUATING THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SAGE-217 IN THE TREATMENT OF SUBJECTS WITH ESSENTIAL TREMOR (ET)

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Version: Version 2.0

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2 LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
ADL	activities of daily living
AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BLQ	below the limit of quantification
%CV	percent coefficient of variation
CI	confidence interval
C-SSRS	Columbia-Suicide Severity Rating Scale
DEQ-5	Drug Effects Questionnaire
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
ET	essential tremor
FCS	full conditional specification
HIV	human immunodeficiency virus
ICF	informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
LLOQ	lower limit of quantitation
LS	least-squares
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
QoL	quality of life
QTcF	QT-interval for ECG corrected for heart rate (Fridericia)
QUEST	Quality of Life in Essential Tremor Questionnaire
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
SSS	Stanford Sleepiness Scale
TEAE	treatment emergent adverse event
TETRAS	TRG Essential Tremor Rating Assessment Scale
ULOQ	upper limit of quantitation
VAS	visual analogue scale
WHO-DDE	World Health Organization Drug Dictionary Enhanced

3 INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis of the study and is based on the approved clinical study protocol, dated September 5, 2017, Version 5.0, incorporating Amendment 4for Study 217-ETD-201. Part A and Part B of this study are analyzed according to this SAP. Part C will be analyzed according to a separate SAP.

This SAP addresses the safety, efficacy, and pharmacokinetics (PK) objectives of the study and describes the planned safety, efficacy, and PK statistical analyses and data presentations.

The statistical plan described hereafter is an *a priori* plan and will be submitted to file before any analysis of data pertaining to Sage Study 217-ETD-201 (Part A and Part B) is performed. The SAP is to be finalized and approved before database lock.

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.3 or higher) for Windows.

Pharmacokinetic parameter estimation will be performed using Phoenix WinNonlin® software (Version 6.4 or later; Pharsight, Cary, NC) on individual plasma concentration-time data.

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

There are 2 SAGE-217 formulations given in this study: subjects who consent before the approval of Protocol Version 4.0 (Amendment 3) by the Institutional Review Board (IRB) will receive the oral solution formulation for the duration of the study; subjects who consent after Protocol Version 4.0 (Amendment 3) is approved by the IRB will receive the capsule formulation for the duration of the study.

Due to the small number of subjects enrolled under Protocol Version 3.0 (Amendment 2) or earlier data collected for these subjects dosed with oral solution will only be listed, except where indicated otherwise. All objectives and analyses described herein therefore are with respect to subjects enrolled under Protocol Version 4.0 (Amendment 3) or later. It is anticipated that all the subjects enrolled in Part B are after Protocol Version 4.0 and will be dosed with capsules only.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study (Part A and Part B) is to compare the effect of 7 days of administration of SAGE-217 Capsules to placebo on the change in tremor severity, as measured by the change from randomization (Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of Kinesia kinetic tremor scores across both sides of the body) at Day 14.

4.2 Secondary Objectives

The secondary objectives of this study are to compare the effect of 7 days of administration of SAGE-217 Capsules to placebo on the following endpoints:

- Tremor severity as assessed by the change from randomization (Day 8) in the Kinesia upper limb total score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral “wing beating” postural tremor, and kinetic tremor item scores from both sides of the body) and individual item scores at Day 14;
- Tremor severity as measured by the change from randomization (Day 8) in TRG Essential Tremor Rating Assessment Scale (TETRAS) upper limb total score (ie, the sum of TETRAS Performance Subscale item 4 scores [4a, 4b, and 4c] from both sides of the body) and individual TETRAS Performance Subscale upper limb item scores at Day 14;

- Tremor severity as assessed by the change from randomization (Day 8) in other TETRAS Performance Subscale scores at Day 14;
- Safety and tolerability as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event (AE) reporting;
- Sleepiness as assessed by the Stanford Sleepiness Scale (SSS) score;
- Mood as assessed by the Bond-Lader visual analogue score (VAS) Mood Scale; and
- How the subject feels after taking the study drug as assessed by Drug Effects Questionnaire (DEQ-5) ratings.

The above objectives, with the exception of safety as assessed by AEs, will only be listed for SAGE-217 Oral Solution since sufficient data will not be available for any further analysis.

In addition, the PK objective of this study is to assess the PK profile of SAGE-217 in plasma samples following administration of SAGE-217 Capsules. Pharmacokinetic data for subjects treated with SAGE-217 Oral Solution will be listed only.

4.3 Other Objectives

The other objectives of the study are to compare the effect of 7 days of administration of SAGE-217 Capsules to placebo on:

- Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring), as assessed by the Empatica Wristband E4. Tremor oscillation, as assessed by multidimensional accelerometer measurements (ie, raw accelerometer values) using the Empatica Wristband E4.
- Quality of life (QoL), as assessed by TETRAS activities of daily living (ADL), Quality of Life in Essential Tremor Questionnaire (QUEST), and video recording assessment of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis).

In addition, PK and pharmacodynamic (PD) modelling assessment of the relationship between plasma exposure of SAGE-217 and change from baseline in Kinesia scores may be assessed.

The above objectives will only be listed for SAGE-217 Oral Solution since sufficient data will not be available for any further analysis.

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

The following efficacy endpoints are planned to be assessed only in subjects taking the capsules.

5.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the change from randomization (Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of Kinesia kinetic tremor scores from both sides of the body) at Day 14.

5.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include the following:

- Change from randomization (Day 8) in the Kinesia upper limb total score and individual item scores at Day 14 and all other time points;

- Change from randomization (Day 8) in TETRAS kinetic tremor score, TETRAS Performance Subscale upper limb total score, and individual TETRAS Performance Subscale upper limb item scores at Day 14 and all other time points; and
- Change from baseline in other TETRAS Performance Subscale scores measured at Day 14 and all other time points.

5.1.3 Other Efficacy Endpoints

The other efficacy endpoints of this study include the following:

- Change from baseline in TETRAS ADL and QUEST scores at Day 14.

5.2 Safety Endpoints

The safety endpoints of this study for subjects taking capsules (except where specified otherwise) include the following:

- Frequency and severity of AEs (including subjects on oral solution for Part A);
- Safety and tolerability as assessed by changes from baseline in vital signs measurements, clinical laboratory data, ECG parameters, and incidences of suicidal ideation using the C-SSRS;
- Change from baseline in sleepiness as assessed by the SSS scores;
- Change from baseline in mood as assessed by the Bond-Lader VAS Mood Scale; and
- DEQ-5 ratings.

5.3 Other Endpoints

The PK endpoints include plasma concentrations of SAGE-217 and metabolites for subjects taking capsules as follows:

- Mean plasma concentrations and parameters (area under the concentration-time curve from time 0 to last time point [AUC_{0-t}], area under the concentration-time curve from time 0 to infinity [$AUC_{0-\infty}$], maximum plasma concentration [C_{max}], time to reach maximum concentration [t_{max}], and terminal half-life [$t_{1/2}$], as appropriate) of SAGE-217 and possible metabolites.

6 STUDY DESIGN

6.1 Overall Design

This study is a 3-part, multicenter, Phase 2a study to evaluate the efficacy, safety, tolerability, and PK of SAGE-217 in approximately 60 adult subjects with essential tremor (ET). Subjects who consent before the approval of Protocol Version 4.0 (Amendment 3) by the IRB will receive the oral solution formulation for the duration of the study; subjects who consent after Protocol Version 4.0 (Amendment 3) is approved by the IRB will receive the capsule formulation for the duration of the study.

Part A of the study is an open-label design with morning dosing for 7 days. Part B of the study is a double-blind, placebo-controlled, randomized withdrawal design. Subjects will be exposed to study drug (SAGE-217 or placebo) for up to 14 days and will be followed for an additional 14 days after the administration of the last dose. Part C of the study is an open-label design with evening dosing (and morning and evening dosing beginning on Day 4) for up to 14 days.

During the Screening Period (Day -28 to Day -1), after signing the informed consent form (ICF), subjects will be assessed for study eligibility and the severity of each subject's ET will be evaluated using TETRAS. Eligible subjects will return to the clinical study unit on Day -1.

The study will be conducted in 3 parts; however, only Part A and Part B will be discussed in this SAP (Part C will be discussed in a separate SAP):

- **Part A:** Beginning on Day 1, all subjects will receive open-label SAGE-217 in the morning with food for 7 days. Subjects will receive SAGE-217 10 mg on Day 1, SAGE-217 20 mg on Day 2, and SAGE-217 30 mg from Day 3 to Day 7, with dose adjustments for severe AEs judged by the Investigator to be related to study drug.
- **Part B:** In order to qualify for Part B of the study, a subject must tolerate a dose of ≥10 mg of SAGE-217, and the subject must have responded to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor (item 4c) combined score predose on Day 8. Eligible subjects will be randomized in a 1:1 fashion to receive SAGE-217 or placebo for 7 days beginning on Day 8. All doses of study drug will be administered with food. Subjects randomized to SAGE-217 or placebo will receive their maximum (tolerated) dose as determined in Part A in the morning with food.

Dose adjustments will only be allowed during Part A of the study. A dose will be considered not tolerated if the subject experiences a severe AE considered to be related to the study drug by the Investigator. If a dose is not tolerated, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the open-label dosing period (ie, subjects who are unable to tolerate SAGE-217 30 mg will receive SAGE-217 20 mg and subjects who are unable to tolerate SAGE-217 20 mg will receive SAGE-217 10 mg). The dose tolerated on Days 5, 6, and 7 of Part A will be considered the maximum dose for that subject. Subjects who require dose adjustments on Days 5, 6, or 7 of Part A will not progress to Part B.

Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part A and Part B (Sections 12.1.1 and 12.1.2, respectively).

6.2 Sample Size and Power

Approximately 60 subjects will be enrolled in Part A to yield at least 40 randomized subjects for Part B. A total sample size of 34 evaluable subjects (ie, 17 per group) will have 80% power to detect a difference in means of 3.0 on the primary endpoint assuming that the common standard deviation is 3.0 using a 2-sample t-test with a 0.05 two-sided significance level. Assuming a 15% non-evaluability rate, 20 subjects per group will be randomly assigned to treatment. The number of subjects in each treatment group is also thought to be sufficient to assess preliminary safety and tolerability following multiple doses of SAGE-217.

6.3 Randomization

Part A is open-label with no control group; therefore, there will be no randomization or blinding. Once it has been determined that a subject meets eligibility criteria, the subject will be sequentially assigned a subject number. Subject identification numbers will consist of the site number (eg, “01”) followed by subject number with leading zeroes (eg, “001”; the subject identification number would then be “01-001”).

Part B of the study is a double-blind, placebo-controlled, randomized withdrawal design. Subjects who tolerate a dose of ≥10 mg of SAGE-217 in Part A and respond to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor combined score predose on Day 8, will be randomly assigned in a 1:1 fashion to receive SAGE-217 or placebo according to a computer-generated randomization schedule. Once it has been determined that a subject meets eligibility criteria for randomization, the subject will be sequentially assigned a randomization number from the randomization schedule provided to the unblinded pharmacist. Randomization numbers will consist of a 4-digit number starting with 1001.

Subject randomization (including subject identifier, randomization number, and treatment assigned) will be provided in a listing.

6.4 Blinding and Unblinding

Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist, who will prepare the study drug according to the randomization schedule, will be unblinded.

The randomization schedule will be generated prior to the start of the study. The randomization schedule will be generated using SAS® Software (release 9.3 or higher). Only the clinic pharmacist, who is responsible for preparing the study drug for administration, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual study drug contents to the investigator, who should also alert Sage of the emergency. In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the electronic case report form (eCRF). If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study.

Subjects randomized to SAGE-217 will receive their maximum dose as determined in Part A in the morning with food. Subjects randomized to the placebo arm will represent randomized withdrawal (withdrawal from SAGE-217 treatment they received in Part A).

7 MODIFICATIONS

7.1 Modifications to the Approved Clinical Study Protocol

The following changes from the clinical study protocol (version 5.0, dated September 5, 2017) have been made in the SAP:

The protocol describes an evaluable population consisting of all randomized subjects with at least 1 post-baseline Kinesia assessment. This analysis set has been removed in the SAP as the evaluable population is expected to be similar to the efficacy population (see Section 8.1). Therefore, the Evaluable Population as defined in the protocol will not be used for efficacy analysis.

The protocol also mentions that center will be included in the mixed effects repeated measures model of the primary endpoint and key secondary endpoints. Center has been removed from the model in the SAP (see Section 9.3.1.3) as the number of subjects per center are likely to be small and could lead to model convergence issues.

The protocol specifies that change from baseline in TETRAS ADL and QUEST scores at Day 14 are exploratory endpoints; however, as per Sponsor request, these are going to be analyzed as other endpoints instead of exploratory.

The protocol specifies the addition of a Part C; Part C will be analyzed in a separate SAP.

7.2 Modifications to the Approved Statistical Analysis Plan

The following changes have been made to the SAP Version 1.0 (28 March 2017) as a result of Protocol Version 4.0 (Amendment 3):

- Change of title and version of protocol that the SAP is based upon;
- Change of Sage Therapeutics statistical signatory;
- All endpoints and analyses changed to be based on subjects on the capsules instead of oral solution;
- Clarification of analysis populations to indicate if based on oral solution or capsule;
- Minor formatting/administrative changes.

The following changes have been made to the SAP Version 1.0 (28 March 2017) as a result of Protocol Version 5.0 (Amendment 4):

- Addition of text referencing Part C, although Part C is not described herein.

7.3 Modifications to the Approved DMC Charter

Not applicable.

8 ANALYSIS POPULATIONS

Subjects included in the below analysis populations (and reason for exclusion, if applicable) will be provided in a listing.

8.1 Efficacy Population

The Efficacy Population (Part A; Capsule) will consist of all subjects who complete at least one dose of the capsule formulation in Part A and have at least one postdose efficacy evaluation. The Efficacy Population (Part A; Capsule) will be used to analyze all Part A-Capsule efficacy data.

The Efficacy Population (Part B; Capsule) will consist of all subjects who complete at least one dose of the capsule formulation in Part B and have at least one post-randomization efficacy evaluation. The Efficacy Population (Part B; Capsule) will be used to analyze all other efficacy data.

No efficacy populations will be defined for the Oral Solution.

8.2 Safety Population

The Safety Population (Part A; Both Formulations) will consist of all subjects who are administered open-label study drug of either the oral solution or capsule formulation. The Safety Population (Part A; Capsule) will consist of all subjects who are administered open-label study drug of the capsule formulation. The Safety Population (Part B; Capsule) will consist of all subjects who are administered double-blind study drug of the capsule formulation. These populations will be used to provide descriptive summaries of safety in each respective part. Summaries of safety that are not part-specific will be based on Safety Population (Part A; Capsule). Summaries of safety that include both formulations will be based on Safety Population (Part A; Both Formulations).

8.3 PK Population

The PK Population (Part A; Both Formulations) will consist of all subjects in the Safety Population (Part A; Both Formulations) with a sufficient number of plasma samples with quantifiable concentration of SAGE-217 in Part A. The PK Population (Part A; Capsule) will consist of all subjects in the Safety Population (Part A; Capsule) with a sufficient number of plasma samples with quantifiable concentration of SAGE-217 in Part A. The PK Population (Part B; Capsule) will consist of all subjects in the Safety Population (Part B; Capsule) with a sufficient number of plasma samples with quantifiable concentration of SAGE-217 in Part B. The PK Population will be used to summarize PK data in each respective study part.

9 STATISTICAL ANALYSIS

9.1 General Considerations

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variables will be summarized using the number and proportion of each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment group.

The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (standard deviation) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place unless otherwise specified. Assessments done on unscheduled visits will not be summarized but will be listed.

Treatment group (ie, randomized treatment for efficacy summaries, treatment received otherwise) is defined as SAGE-217 or Placebo. Tolerated dose is defined as SAGE-217 10 mg, SAGE-217 20 mg, or SAGE-217 30 mg (Section 6.1).

Data from subjects taking the oral solution will be primarily presented in the data listings; however, subject disposition, demographics, and AE data for Part A will be summarized by formulation (oral solution and capsule). Otherwise, all background summaries will be presented by treatment group and overall subjects, unless otherwise specified. All safety summaries will be presented by overall subjects for Part A and treatment group for Part B. All efficacy summaries will be presented by overall subjects for Part A and treatment group for Part B. Pharmacokinetic data will be presented by overall subjects for Part A and tolerated dose for active treatment only for Part B.

All final, planned analyses identified in the protocol and in this SAP will be performed after all relevant study data have been processed and integrated into the analysis database, analysis populations have been finalized, and the database has been locked. Any post-hoc, exploratory analysis performed to support planned study analyses, which were not identified in this SAP, will be documented and reported in Section 9.8 of the CSR. Any results from these unplanned analyses (post-hoc), including analyses based on data collected but not analyzed (Section 7.1), will also be clearly identified in the text of the CSR.

All collected data will be presented in listings and will be sorted by subject.

If partial dates occur, the convention for replacing missing dates for the purposes of calculating derived variables is as follows:

For partial AE and medication start dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the year is known, but the month or month and day is unknown, then:
    - If the year matches the year of first dose date, then impute as the month and day of the first dose date.
    - Otherwise, assign 01 January
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the first dose date, then impute as the day of the first dose date.
    - Otherwise, assign 01

For partial AE and medication end dates:

- If the year is unknown, then do not impute the date but assign as missing value.
- If the year is known, but the month or month and day is unknown, then:
    - If the year matches the year of the last date of the study (date of last contact if subject lost to follow-up; date of completion or early termination otherwise), then impute as the month and day of the last date of the study.
    - Otherwise, assign 31 December.
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the last date of the study, then impute as the day of the last date of the study.

- Otherwise, assign the last day of the month.

No missing data will be imputed unless otherwise specified.

In general, for quantitative safety laboratory values reported as '<X' or '≤X', the lower limit of quantitation (LLOQ) will be used for analysis (ie, a value of X will be used in the analysis for lab values reported as '<X' or '≤X'). Similarly, for safety quantitative laboratory values reported as '>X' or '≥X', the upper limit of quantitation (ULOQ) will be used for analysis (ie, a value of X will be used in the analysis for lab values reported as '>X' or '≥X').

For analysis purposes, repeat laboratory rest results will not be used unless the original laboratory value is missing or indicated as invalid, in which case the first non-missing repeat laboratory value will be used for data analysis.

The last observation recorded before receiving the first dose of study drug on Day 1 in Part A will be used as the baseline observation for all calculations of change from baseline. The last observation recorded before receiving the first dose of study drug before randomization on Day 8 in Part B will be used as the randomization observation for all calculations of change from randomization.

9.2 Background Characteristics

9.2.1 Subject Disposition

All subjects who sign the ICF will be accounted for in this study.

Subject disposition will be summarized separately for each study part, as follows:

- For Part A, the number of subjects enrolled (ie, signed informed consent); treated; completed Part A; withdrew from Part A (including reason for withdrawal); and included in each Part A analysis population will be summarized by overall subjects within formulation.
- For Part B, the number and percentage of subjects who were randomized; treated; completed Part B; withdrew from Part B (including reason for withdrawal); and included in each Part B analysis population will be summarized by treatment group and overall subjects.
- Additionally, the previous Part B summary will be repeated by tolerated dose within treatment group.

All disposition information will be included in a listing.

9.2.2 Demographics and Baseline Characteristics

Demographics, such as age, gender, child-bearing potential, race, and ethnicity, and baseline characteristics such as height, weight, body mass index (BMI), and time (years) since ET diagnosis (from date of ICF), will be summarized by overall subjects within formulation in Part A and treatment group in Part B.

Categorical summaries, such as gender, childbearing potential, race, and ethnicity, will be summarized using frequency and percentage. Subjects who marked more than one race will be summarized in a "More than One Race" category. Continuous summaries, such as age, height, weight, BMI, and time since ET diagnosis, will be summarized using mean, standard deviation (SD), median, minimum, and maximum. The demographic and baseline characteristics table will be generated for subjects in the Safety Population.

Hepatitis, human immunodeficiency virus (HIV), pregnancy, alcohol, cotinine, caffeine, and drug screening results will be listed, but not summarized as they are considered part of the inclusion/exclusion criteria.

Medical history, coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 18.1 or higher), will be listed.

9.2.3 Prior and Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) (Version September 1, 2015 or later).

Frequencies and percentages of medications used in the study will be summarized as follows:

- Prior medication: medication taken before the date of first dose of open-label study drug (including medications with a missing start date but a non-missing end date in this time period).
- Concomitant medication: a medication with a start date on or after the first dose of open-label study drug (even if end date is missing) and on or before the last dose of study drug, or medications with a start date before the first dose of open-label study drug that are ongoing or with a stop date on or after the first dose of open-label study drug, will be considered concomitant. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Concomitant medications will be assigned to the study part in which they are being taken. A concomitant medication with a start date before the first dose of double-blind study drug will be assigned to Part A (including medications with missing start dates with either a missing end date or an end date before first dose of double-blind study drug). A concomitant medication with a start date on or after the first dose of double-blind study drug will be assigned to Part B. If a concomitant medication assigned to Part A continues to be taken through Part B, then the medication will be assigned to both parts of the study as appropriate. If the start and stop dates of the concomitant medications do not clearly define the part during which a medication was taken, it will be assumed to be taken in both parts. Details of prior and concomitant medications will be listed by study part, subject, start date, and verbatim term. All medications will be summarized by Anatomic Therapeutic Chemical (ATC) class and preferred term (PT). Furthermore, prior medications will be summarized by overall subjects; and concomitant medications will be summarized by overall subjects (Part A) and treatment group (Part B) for subjects taking capsules. Subjects will be counted once per ATC and PT in each study part.

Medication summaries will be based on the Safety Populations.

9.2.4 Study Drug Exposure

Study drug dosing information will be listed.

9.2.5 Study Drug Compliance

Study drug noncompliance such as missing visits, interruptions in the schedule of administration, and nonpermitted medications will be listed in the protocol deviations listing.

9.3 Efficacy Analysis

The primary efficacy variable for this study is change from randomization in accelerometer-based Kinesia kinetic tremor combined score in Part B; change from baseline for Part A will also be evaluated.

The secondary efficacy variables for this study include change from baseline (Part A) and change from randomization (Part B) in:

- Kinesia upper limb total and individual item scores
- TETRAS total and individual upper limb item scores
- TETRAS Performance Subscale scores

The other efficacy variables for this study include change from baseline (Part A) and change from randomization (Part B) in:

- TETRAS ADL scores

- QUEST scores

All efficacy analyses will be conducted on the Efficacy Population, only for subjects taking capsules.

9.3.1 Analysis of Primary Efficacy Variable

9.3.1.1 Description of Primary Efficacy Variable

The primary outcome measure is the change from randomization in accelerometer-based Kinesia kinetic tremor combined score, based on the Day 14, predose measurement.

In order to measure essential tremor amplitude, subjects will wear a wireless ring motion sensor (ie, Kinesia). The motion sensor uses three orthogonal accelerometers and three orthogonal gyroscopes to monitor three-dimensional motion. Data are then transmitted from the sensor to a computer using Bluetooth technology. These measures of three-dimensional motion for each maneuver are then converted to Kinesia scores, which have been shown to correlate with corresponding clinician-rated TETRAS scores (ie, forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor on both sides of the body) (Giovanni, Giuffrida, Adam, Davidson, & Jankovic, 2010). Each Kinesia score ranges from 0 to 4; higher scores indicate more severe tremor. The Kinesia assessment is completed in conjunction with the TETRAS Performance Subscale Item 4 assessment.

In Part A, Kinesia will be performed on Day -1 (three assessments separated by at least 30 minutes); a single assessment will be performed predose and 2 and 8 hours postdose on Days 1, 2, 3, and 7. In Part B, a single Kinesia reading will be performed predose and 2 and 8 hours postdose on Days 8, 9, and 14, and any time during the visit on Day 21.

9.3.1.2 Visit Windows for the Primary Endpoint

For efficacy analyses, unscheduled measurements will only be included if a scheduled measurement is not available and the unscheduled measurement falls on the same study day. Due to the short duration of this study, this is not anticipated to occur.

9.3.1.3 Primary Analysis

The difference between treatment groups in change from randomization to post-randomization in Kinesia kinetic tremor combined score from Part B will be evaluated by a mixed model for repeated measures (MMRM) with change from randomization of the Kinesia kinetic tremor combined scores as the dependent variable, and treatment group, study visit, and treatment group by study visit interaction as fixed effects, and the randomization (Day 8 predose) value as a covariate. An unstructured covariance matrix will be used to model the within-subject correlation. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

In case of convergence issues, other covariance structures will be used including (but not limited to) autoregressive (AR (1)), compound symmetry (CS), and variance components (VC) with each model fit to find the covariance structure with the best fit. The fit statistics will be compared for all covariance structures; the structure with the smallest Akaike information criterion will be retained as the preferred model.

In comparing the visit value to randomization, least-squares (LS) mean change from randomization will be presented along with associated 95% CI and *P* values. In comparing treatments (SAGE-217 minus placebo), LS mean differences in change from randomization will be presented along with associated 95% CI and pairwise treatment *P* values.

9.3.1.4 Supportive Analyses

For all subjects, observed values and change from baseline in Kinesia kinetic tremor combined score will be summarized for all Part A time points by overall subjects. For subjects entering Part B, observed values and change from baseline (Part A time points) / change from randomization (Part B time points) in

Kinesia kinetic tremor combined score will be summarized for all time points by treatment group. For Part B, additional summaries may be performed by tolerated dose.

9.3.1.5 Multiplicity Adjustment

Not applicable.

9.3.1.6 Sensitivity Analysis

Not applicable.

9.3.1.7 Subgroup Analyses

Not applicable.

9.3.2 Analysis of Secondary Efficacy Variables

9.3.2.1 Kinesia Upper Limb Scores

Description of Kinesia Upper Limb Scores

The accelerometer-based Kinesia upper limb total score is the sum of Kinesia scores (ie, forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor) from both sides of the body. The upper limb individual item question score for each side of the body ranges from 0 to 4, with higher scores indicating more tremors/greater tremor amplitude.

Analysis of Kinesia Upper Limb Scores

For all subjects, observed values and change from baseline in Kinesia upper limb individual item and total scores will be summarized for all Part A time points by overall subjects. For subjects entering Part B, observed values and change from baseline (Part A time points) / randomization (Part B time points) in the Kinesia upper limb individual item and total scores will be summarized by treatment group.

The difference between treatment groups will be analyzed using the MMRM model as described for the primary analysis (Section 9.3.1.3) for post-randomization time points only.

9.3.2.2 TETRAS Upper Limb Scores

Description of TETRAS Upper Limb Scores

Items 4a (forward outstretched postural tremor), 4b (lateral "wing beating" postural tremor), and 4c (kinetic tremor), assessed on both sides of the body, comprise the TETRAS Performance Subscale upper limb scores. The TETRAS kinetic tremor combined score is the sum of the item 4c scores from both sides of the body. The TETRAS Performance Subscale upper limb total score is the sum of all item 4 scores from both sides of the body (Elble, Comella, & al, 2012).

In Part A, TETRAS Performance Subscale upper limb scores will be assessed at Screening and on Day -1 (three assessments separated by at least 30 minutes); a single assessment will be performed predose and 2, 3, and 8 hours postdose on Days 1, 2, 3, and 7. In Part B, TETRAS Performance Subscale upper limb scores will be assessed at predose and 2, 3, and 8 hours postdose on Days 8, 9, and 14, and any time during the visit on Day 21.

Analysis of TETRAS Upper Limb Scores

For all subjects, observed values and change from baseline in TETRAS kinetic tremor combined score, upper limb individual item scores, and upper limb total score will be summarized for all Part A time points by overall subjects. For subjects entering Part B, observed values and change from baseline (Part A time points) / randomization (Part B time points) in TETRAS kinetic tremor combined score, upper limb individual item scores, and upper limb total scores will be summarized by treatment group.

The difference between treatment groups will be analyzed using the MMRM model as described for the primary analysis (Section 9.3.1.3) for post-randomization time points only.

9.3.2.3 TETRAS Performance Subscale (Items 6, 7, and 8) Scores

Description of TETRAS Performance Subscale (Items 6, 7, and 8) Scores

The TETRAS Performance Subscale score includes the following 9 items: head tremor, face (including jaw) tremor, voice tremor, upper limb tremor, lower limb tremor, Archimedes spirals, handwriting, dot approximation task, and standing tremor (Elble, Comella, & al, 2012). However, only Archimedes spirals (item 6), handwriting (item 7), and dot approximation task (item 8) assessments, in addition to upper limb tremor as described above, were performed for this study.

In Part A, TETRAS Performance Subscale items 6, 7, and 8 will be assessed on Day -1 and predose on Day 7. In Part B, TETRAS Performance Subscale items 6, 7, and 8 will be assessed at predose on Day 14 and any time during the visit on Day 21.

Analysis of TETRAS Performance Subscale (Items 6, 7, and 8) Scores

For all subjects, observed values and change from baseline in TETRAS Performance Subscale scores will be summarized for all Part A time points by overall subjects. For subjects entering Part B, observed values and change from baseline in TETRAS Performance Subscale scores will be summarized by treatment group.

The difference between treatment groups will be analyzed using the MMRM model as described for the primary analysis (Section 9.3.1.4 & 9.3.1.3) for all post-baseline time points.

9.3.3 Analysis of Exploratory Efficacy Variables

9.3.3.1 TETRAS ADL

Description of TETRAS ADL

The QoL as assessed by the TETRAS ADL Subscale includes the following 12 items: speaking; feeding with a spoon; drinking from a glass; hygiene; dressing; pouring; carrying food trays, plates, or similar items; using keys; writing; working; overall disability with the most affected task; and social impact (Elble, Comella, & al, 2012). Each individual item question score ranges from 0 to 4, where higher scores indicate worse QoL. The total score is derived as the sum of all of the individual items scores, with a maximum total score of 48. If one of the individual item scores is missing, the total score will be set to missing.

In Part A, the TETRAS ADL Subscale will be assessed on Day -1 and predose on Day 7. In Part B, the TETRAS ADL Subscale will be assessed at predose on Day 14 and any time during the visit on Day 21.

Analysis of TETRAS ADL

For all subjects, observed values and change from baseline in TETRAS ADL scores will be summarized for each item score and total score for all Part A time points by overall subjects. For subjects entering Part B, observed values and change from baseline in TETRAS ADL scores will be summarized for each item score and total score for all time points by treatment group.

9.3.3.2 QUEST

Description of QUEST

The QUEST is a brief, ET-specific QoL scale in which subjects rate the extent to which tremor impacts a function or state (30 questions), waking hours with tremor in any part, tremor self-assessment rating tremor severity in various body parts (head, voice, right arm/hand, left arm/hand, right leg/foot, and left leg/foot), health status, and overall QoL, along with 4 questions gathering general information describing work status and issues occurring in the past month (tremor interference with sexual satisfaction, side effects from tremor medication, and satisfaction of tremor control achieved by medication) (Tröster, Pahwa, Fields, Tanner, & Lyons, 2005). The extent to which tremor impacts a function or state is rated as never/no, rarely, sometimes, frequently, always/yes, and not applicable. Tremor severity is rated as none, mild, moderate, marked, or severe. Perceived health and overall QoL are rated on a scale of 0 to 100 in 5-point increments, where 0=very poor health and 100=excellent/perfect health.

For the 30-question component of the QUEST, the questions will be scored in 5 dimensions: Communication (questions 1-3); Work and Finances (questions 4-9); Hobbies and Leisure (questions 10-12); Physical (questions 13-21); and Psychosocial (questions 22-30).

The dimension scoring algorithm is as follows:

$$Dimension\ Score = \frac{Total\ applicable\ points\ for\ each\ dimension}{Total\ possible\ points\ (\#\ of\ applicable\ questions\ \times\ 4) for\ each\ dimension}$$

The point values assigned to each question are as follows: 0 = “Never/No”; 1 = “Rarely”; 2 = “Sometimes”; 3 = “Frequently”; 4 = “Always/Yes”; blank = Not Applicable (question is not counted toward applicable points or questions) (Movement Disorders Society Rating Scales, n.d.).

In Part A, QUEST will be assessed on Day -1 and Day 7. In Part B, QUEST will be assessed on Day 14.

Analysis of QUEST

For all subjects, observed values and change from baseline in QUEST scores will be summarized for each dimension score for all Part A time points by overall subjects. For subjects entering Part B, observed values and change from baseline in QUEST scores will be summarized for each dimension score for all time points by treatment group.

9.4 Safety Analysis

Safety will be evaluated through incidence and severity of AEs, as well as observed values and changes from baseline in vital signs, clinical laboratory measures (including shifts from baseline), ECG parameters, suicidal ideation using the C-SSRS, and the SSS. Safety summaries will be presented for subjects taking the capsule formulation, unless otherwise specified.

For Part A, safety endpoints will be summarized by overall subjects, unless otherwise specified (eg, by the type of formulation). For Part B, safety endpoints will be summarized by treatment group (ie, SAGE-217 or placebo). All safety data will be presented in individual subject data listings. Safety analysis will be conducted for the Safety Population.

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Abnormality/ Clinical Significance
AEs	X			
CMs	X			

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Abnormality/ Clinical Significance
Labs		X	X	*
ECG		X	X	*
Vital Signs		X	X	
C-SSRS		X	X	
SSS		X	X	
VAS		X	X	
DEQ-5		X	X	
X = Safety Assessment will be summarized in tables * = Safety Assessment will be summarized in individual subject data listings				

9.4.1 Adverse Events

Adverse events (AEs) will be coded using the MedDRA coding system (version 19.1 or higher). The analysis of AEs will be based on the concept of treatment-emergent AEs (TEAEs). A TEAE for Part A is defined as an AE with onset after the start of open-label study drug, or any worsening of a pre-existing medical condition/AE with onset after the start of open-label study drug and until 14 days after the last dose or start of double-blind study drug, whichever is earlier. A TEAE for Part B is defined as an AE with onset after the start of double-blind study drug, or any worsening of a pre-existing medical condition/AE with onset after the start of double-blind study drug and until 14 days after the last dose. Any TEAEs occurring in the follow-up period after last dose of study drug will be summarized based on the last dose of study drug taken.

Adverse events will be assigned to the study part in which they first occur. An AE with a start date before the first dose of double-blind study drug will be assigned to Part A (including AE with missing start dates with either a missing end date or an end date before first dose of double-blind study drug). An AE with a start date on or after the first dose of double-blind study drug will be assigned to Part B. If the start and stop dates of the AE do not clearly define the part during which an AE first occurred, it will be assumed to be occurring in both parts.

A summary of the number and percentage of subjects with TEAEs will be provided separately for each study part. The summary for Part A will present data from subjects on both formulations, by overall subjects within formulation. The summary for Part B will be presented by treatment group. Frequencies and percentages of the following will be included:

- Any TEAE
- Severe TEAEs
- Possibly or Probably Related TEAEs
- TEAEs Leading to Discontinuation

- TEAEs Leading to Death
- Serious AEs (SAEs)

In Part A, the incidence of TEAEs will be summarized by the following, for overall subjects:

- SOC and PT (including subjects on both formulations)
- PT
- Dose, Day, and PT
- SOC, PT, and Maximum Severity
- SOC, PT, and Relationship to Study Drug

In Part B, the incidence of TEAEs will be summarized by the following, for subjects entering Part B:

- Treatment group, SOC, and PT
- Treatment group and PT
- Treatment group, Dose, Day, and PT
- Treatment group, SOC, PT, and Maximum Severity
- Treatment group, SOC, PT, and Relationship to Study Drug

Incidences will be presented by descending frequency of SOC (where applicable), then in order of decreasing frequency of PT (within SOC, if applicable; first for SAGE-217 then placebo), and then alphabetically within PT where the incidence is the same. The presentation of TEAEs by dose, day, and PT will include counts of TEAEs that started on that particular day. For Part A, the dose of the TEAE will correspond to the dose the subject was on at the start of the TEAE. For Part B, the dose of the TEAE will correspond to either tolerated dose (subjects receiving SAGE-217) or placebo (subjects receiving placebo).

All AEs, SAEs (including those with onset or worsening before the start of open-label study drug), AEs leading to discontinuation, and AEs leading to death through the Day 28 visit will be listed in separate tables.

9.4.2 Clinical Laboratory

All summaries of laboratory values will be presented using SI units. Continuous hematology, chemistry, and urinalysis results will be listed by subject and timing of collection. Observed values and change from baseline at each time point in Part A will be summarized by overall subjects taking the capsule formulation. For subjects entering Part B, observed values and change from baseline at each time point will be summarized by treatment group. Shifts from baseline will also be summarized by overall subjects (Part A) and treatment group (Part B). Clinically significant abnormal findings will be reported as AEs.

9.4.3 Electrocardiogram

The following 12-ECG parameters will be listed for each subject: heart rate, PR interval, QRS duration, QT interval, and QTcF interval (derived as QT interval / $(\text{RR interval})^{1/3}$). Any clinically significant abnormalities or changes in ECGs should be listed as an AE. Observed values and change from baseline at each time point in Part A will be summarized by overall subjects for Part A taking the capsule formulation. 12-ECG data for subjects taking oral solution will be listed only. For subjects entering Part B, observed values and change from baseline at each time point will be summarized by treatment group. Additionally, the number and percentage of subjects with a QTcF value meeting various clinical significance criteria (raw QTcF >450 msec, >480 msec, and >500 msec; change from baseline QTcF >30

msec and >60 msec) will be summarized separately for each study part: by overall subjects for Part A and by treatment group for Part B.

9.4.4 Vital Signs

Vital sign results (body temperature, heart rate, respiratory rate, supine and standing diastolic blood pressure, supine and standing systolic blood pressure, and pulse oximetry) will be listed by subject and timing of collection. Observed values and change from baseline at each time point in Part A will be summarized by overall subjects taking the capsule formulation. Vital sign data for subjects taking oral solution will be listed only. For subjects entering Part B, observed values and change from baseline at each time point will be summarized by treatment group.

9.4.5 Physical Examination

Screening physical examination results for Part A that are clinically significant will be listed in the medical history listing. Post-screening physical examination results for that are clinically significant will be listed in the AE listing. A listing will be provided containing information on when physical examination occurred and reason it was not done if applicable.

9.4.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the study using the C-SSRS (Posner, Brown, Stanley, & al, 2011). This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicidal ideation and behavior, and a post-baseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes “yes” or “no” responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

Suicidality data collected on the C-SSRS will be listed for all subjects. Tables will include results from the Suicidal Ideation and Suicidal Behavior sections of the C-SSRS. Frequencies and percents of subjects with a response of “Yes” at any point on the Suicidal Ideation and Suicidal Behavior items will be summarized by overall subjects for Part A taking the capsule formulation. All C-SSRS data for subjects taking oral solution will be listed only, and by treatment group for Part B. Both baseline (“pre-treatment”) and post-baseline (“post-treatment”) results will be presented.

9.4.7 Stanford Sleepiness Scale (SSS)

The SSS is a subject-rated scale designed to quickly assess how alert a subject is feeling (Hoddes, Dement, & Zarcone, 1972). Degrees of sleepiness and alertness are rated on a scale of 1 to 7, where the lowest score of 1 indicates the subject is “feeling active, vital, alert, or wide awake” and the highest score of 7 indicates the subject is “no longer fighting sleep, sleep onset soon; having dream-like thoughts”.

Sedation data collected on the SSS will be listed for all subjects. Mean total score over time will be represented graphically by overall subjects in Part A (taking the capsule formulation) and by treatment group in Part B. All SSS data for subjects taking oral solution will be listed only. Observed values and change from baseline at each time point in Part A will be summarized by overall subjects. For subjects entering Part B, observed values and change from baseline at each time point will be summarized by treatment group.

9.4.8 Bond-Lader Visual Analogue Scale (VAS)

Mood will be assessed using the Bond-Lader VAS Mood Scale. This is a 16-part self-administered questionnaire that employs a 100-mm VAS to explore different aspects of self-reported mood (Bond & Lader, 1974). The 16 different mood ranges include:

1. 0 = “Alert” to 100 = “Drowsy”;
2. 0 = “Calm” to 100 = “Excited”;

3. 0 = “Strong” to 100 = “Feeble”;
4. 0 = “Muzzy” to 100 = “Clear-headed”;
5. 0 = “Well-coordinated” to 100 = “Clumsy”;
6. 0 = “Lethargic” to 100 = “Energetic”;
7. 0 = “Contented” to 100 = “Discontented”;
8. 0 = “Troubled” to 100 = “Tranquil”;
9. 0 = “Mentally slow” to 100 = “Quick-witted”;
10. 0 = “Tense” to 100 = “Relaxed”;
11. 0 = “Attentive” to 100 = “Dreamy”;
12. 0 = “Incompetent” to 100 = “Proficient”;
13. 0 = “Happy” to 100 = “Sad”;
14. 0 = “Antagonistic” to 100 = “Amicable”;
15. 0 = “Interested” to 100 = “Bored”; and
16. 0 = “Withdrawn” to 100 = “Gregarious”.

In order to directly compare VAS results across the 16 items, items 4, 6, 8, 9, 10, 12, 14, and 16 will be reverse-scored by subtracting the scores from 100. In order to normalize the results, the scores will be converted to $\log_e$ (after setting any scores of 0 to 1), with a resulting range of 0 to 4.605. Based on the factor loadings from Table 4 of the Bond and Lader article, the following equations will be used to compute the 3 factor scores:

- Alertness = $0.827X_1 + 0.618X_3 + 0.755X_4 + 0.642X_5 + 0.776X_6 + 0.635X_9 + 0.792X_{11} + 0.593X_{12} + 0.614X_{15}$;
- Contentedness = $0.677X_7 + 0.697X_8 + 0.823X_{13} + 0.738X_{14} + 0.594X_{16}$; and
- Calmness = $0.845X_2 + 0.677X_{10}$,

  where X_i represents a subject’s item score after normalization, and i represents the item number from the entire scale (in order from 1-16).

Bond-Lader VAS results will be listed for all subjects. Observed values and change from baseline at each time point in Part A will be summarized by parameter (including the 3 factor scores) and overall subjects taking the capsule formulation. All Bond-Lader VAS data for subjects taking oral solution will be listed only. Observed values and change from baseline at each time point in Part B will be summarized by parameter (including the 3 factor scores) and treatment group.

9.4.9 Drug Effects Questionnaire (DEQ-5)

The DEQ-5 will be administered as follows:

1. Do you FEEL a drug effect right now?
2. Are you HIGH right now?
3. Do you DISLIKE any of the effects that you are feeling right now?
4. Do you LIKE any of the effects that you are feeling right now?
5. Would you like MORE of the drug you took, right now?

The answers are recorded on a 100-mm VAS, with the answer for each being “Not at all” and “Extremely” at the extremes. There will be options to record “Not applicable” for questions 3 and 4 if no drug effects are felt and for question 5 prior to administration of study medication.

The DEQ-5 results will be listed for all subjects. Since no baseline (before first dose of open-label study drug) values were recorded, only raw values at each time point will be summarized by parameter and

overall subjects for Part A taking the capsule formulation, and by parameter and treatment group for Part B. All DEQ-5 data for subjects taking oral solution will be listed only.

9.5 Pharmacokinetic Analysis

For plasma concentration data, all values below the limit of quantification (BLQ) will be set to 0 for summary statistics and graphs. Individual plasma concentrations of SAGE-217 will be summarized at each time point using descriptive statistics, including number of subjects, mean, SD, median, maximum, minimum, percent coefficient of variation (%CV), and geometric mean. Part A data will be summarized by overall subjects, and Part B data will be summarized by tolerated dose for subjects who received SAGE-217. Individual concentration plots and mean data graphs will be produced for the intensive PK sampling (Days 1 and 7 for Part A and Day 8, predose through Day 14, predose [ie, trough concentrations] for Part B). All graphs will be presented using both linear and semi-logarithmic scales. The above descriptive summary will be performed for the PK population.

All SAGE-217 plasma concentrations for both formulations will be presented in a by-subject listing.

Pharmacokinetic parameter estimation will be performed using Phoenix WinNonlin® software (Version 6.4 or later; Pharsight, Cary, NC) on individual plasma concentration-time data. For the PK parameter calculation, BLQ plasma concentrations occurring before t_{max} will be set to 0, with the exception of a BLQ value occurring between two measurable concentrations, in which case it will be set to missing. BLQ plasma concentrations occurring after t_{max} will be set to missing. Pharmacokinetic parameter estimates and summaries will be completed for subjects in the PK population having sufficient measurable concentrations to define the profile.

Pharmacokinetic parameter estimates for Part A as based on Day 1 and Day 7 intensive sampling, including C_{max}, t_{max}, λ_Z, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{1/2,}$ where appropriate and as data permit, and for Part B, including C_{min}, will be summarized using descriptive statistics, including arithmetic and geometric means, SD, %CV, median, minimum, and maximum. Part A data will be summarized by overall subjects, and Part B data will be summarized by tolerated dose within active treatment group. As t_{max} is a categorical variable, only the median and the range will be reported.

Wherever necessary and appropriate, PK parameters may be dose-adjusted to account for individual differences in dose.

A graph comparing change from baseline (Part A) at Day 7 in accelerometer-based Kinesia combined and upper limb total scores and time-matched PK concentrations over time (ie, 0, 2, and 8 hours postdose) may be produced for overall subjects in the PK Population.

All PK summaries will only include subjects on the capsule formulation.

10 SUMMARY OF INTERIM ANALYSES

Not applicable.

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12 LIST OF APPENDICES

12.1 Appendix A: Schedule of Assessments

12.1.1 Part A (Open-Label)

Visit Days	Screening (Day -28 to Day -1)	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Informed consent	X								
Inclusion/exclusion	X	X							
Demographics	X								
Medical history	X								
Physical examination	X								
Body weight/height	X								
Drug/alcohol screen [a]	X	X							
Complete blood count/ serum chemistry [b]	X	X	X	X					
Pregnancy test	X (serum)	X (urine)							
Urinalysis [b]	X	X	X	X					
Hepatitis & HIV screen	X								
Exploratory biochemistry sample [c]	O				O				O
Genetic sample [d]	O								
Vital signs [e]	X	X	X	X	X	X	X	X	X
Pulse oximetry [e]		X	X	X	X	X	X	X	X
12-lead ECG [f]	X		X	X	X	X			X
C-SSRS [g]	X	X	X			X	X	X	X
SSS [h]			X	X	X	X	X	X	X

Visit Days	Screening (Day -28 to Day -1)	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Bond-Lader-VAS [i]			X	X					X
DEQ-5 [j]			X						X
Kinesia (accelerometer) [k]		X	X	X	X				X
TETRAS upper limb items [k]	X	X	X	X	X				X
TETRAS (ADL Subscale and items 4, 6, 7, and 8 of Performance Subscale) [l]		X							X
Empatica Wristband E4 [m]		X	X	X	X				X
QUEST		X							X
Plasma PK samples [n]			X	X	X	X	X	X	X
Administer study drug [o]			X	X	X	X	X	X	X
Adverse events	X								
Prior/concomitant medications [p]	X								
Videos [q]		X							X

ADL = activities of daily living; C-SSRS = Columbia-Suicide Severity Rating Scale; DEQ-5 = Drug Effects Questionnaire; ECG = electrocardiogram; HIV = human immunodeficiency virus; O = optional; PK = pharmacokinetic; QUEST = Quality of Life in Essential Tremor Questionnaire; SSS = Stanford Sleepiness Scale; TETRAS = TRG Essential Tremor Rating Assessment Scale; VAS = visual analogue score

[a] A urine sample for assessment of selected drugs (sedative/hypnotics [eg, opioids], cotinine, and caffeine) and a breath sample for alcohol screen will be collected at screening and Day -1.

[b] Screening and safety laboratory tests will be performed at screening, Day -1, predose on Day 1, and predose on Day 2.

[c] An optional blood sample for exploratory biochemistry, where consent is given.

[d] An optional genetic sample for biomarker testing, where consent is given.

[e] Vital signs (heart rate, respiratory rate, temperature, and supine [for at least 5 minutes prior to the measurement] and standing [for at least 2 to 3 minutes] systolic and diastolic blood pressure) and pulse oximetry will be performed at screening (vital signs only) and Day -1, predose and at 1, 2, 3, 4, 6, and 8 hours postdose on Days 1, 2, 3, and 4, and predose on Days 5, 6, and 7. Vital signs and pulse oximetry assessments will be performed within ±10 minutes of the scheduled times.

[f] 12-lead ECGs will be performed at screening, predose, and at 1 and 8 hours (±10 minutes) postdose on Days 1, 2, 3, 4, and 7.

[g] The C-SSRS will be performed at screening, on Day -1, 8 hours (±1 hour) postdose on Day 1, predose on Day 4, and on Days 5, 6, and 7. Baseline/Screening version of C-SSRS should be used on day of screening and Since Last Visit version should be used on all subsequent time points.

[h] The SSS will be performed predose and at 1, 2, 3, 4, 6, and 8 hours postdose on Days 1, 2, 3, and 4, and predose only on Days 5, 6, and 7. The SSS is to be performed within ±10 minutes of the scheduled times.

[i] The Bond-Lader VAS will be performed predose and 2 hours (±10 minutes) postdose on Days 1, 2, and 7.

[j] The DEQ-5 will be performed 2 hours (±10 minutes) postdose on Days 1 and 7.

[k] Kinesia and TETRAS upper limb items will be performed at screening (TETRAS upper limb items only), on Day -1 (three assessments separated by at least 30 minutes); single assessments will be performed predose and 2 and 8 hours (±30 minutes) postdose on Days 1, 2, 3, and 7. In addition, the TETRAS upper limb items will be performed, while wearing the Empatica Wristband E4, on Day -1 and 3 hours (±30 minutes) postdose on Days 1, 2, 3, and 7. All three maneuvers in the upper limb assessments (items 4a, 4b, and 4c) will be completed for both arms, first for the RIGHT arm and then for the LEFT.

[l] TETRAS (ADL Subscale and items 4, 6, 7, and 8 of Performance Subscale) will be performed on Day -1 and predose (±30 minutes) on Day 7.

[m] The Empatica Wristband E4 will be worn during the study visits while in clinic on Days -1, 1, 2, 3, and 7. With the exception of during the TETRAS upper limb assessments, the Empatica Wristband E4 will be worn on the wrist that, of the two arms, exhibits more severe tremor symptoms. During the TETRAS upper limb assessments on Day -1 and 3 hours (±30 minutes) postdose on Days 1, 2, 3, and 7, the Empatica Wristband E4 will be worn on the wrist corresponding to the side of the body being assessed.

[n] Plasma pharmacokinetic samples will be taken predose (±5 minutes) and 0.25, 0.5, 1, 2, 4, and 8 hours postdose on Days 1 and 7 and predose on Days 2, 3, 4, 5, and 6.

[o] Study drug will be administered in the morning with food.

[p] To include those taken within 2 weeks prior to informed consent and throughout the study.

[q] Videos of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis) will be taken on Day -1and predose on Day 7.

12.1.2 Part B (Randomized Withdrawal)

Visit Days	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Follow-up Day 21±1 day [a] (Early Termination Visit)	End of Study Day 28±1 day
Randomization	X								
Complete blood count/ serum chemistry [b]	X	X						X	
Pregnancy test [c]	X (urine)								X (urine)
Urinalysis [b]	X	X						X	
Vital signs [d]	X	X	X	X	X	X	X	X	
Pulse oximetry [d]	X	X	X	X	X	X	X	X	
12-lead ECG [e]	X	X	X				X	X	
C-SSRS [f]	X			X	X	X	X	X	X
SSS [g]	X	X	X	X	X	X	X	X	
Bond-Lader-VAS [h]	X	X					X	X	
DEQ-5 [i]	X						X		
Kinesia (accelerometer) [j]	X	X					X	X	
TETRAS upper limb items [j]	X	X					X	X	
TETRAS (ADL Subscale and items 4, 6, 7, and 8 of Performance Subscale) [k]							X	X	
Empatica Wristband E4 [l]	X	X					X	X	
QUEST							X		
Plasma PK samples [m]	X	X	X	X	X	X	X		

Visit Days	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Follow-up Day 21±1 day [a] (Early Termination Visit)	End of Study Day 28±1 day
Administer study drug [n]	X	X	X	X	X	X	X		
Adverse events	X								
Concomitant medications [o]	X								
Videos [p]							X	X	

ADL = activities of daily living; C-SSRS = Columbia-Suicide Severity Rating Scale; DEQ-5 = Drug Effects Questionnaire; ECG = electrocardiogram; HIV = human immunodeficiency virus; PK = pharmacokinetic; QUEST = Quality of Life in Essential Tremor Questionnaire; SSS = Stanford Sleepiness Scale; TETRAS = TRG Essential Tremor Rating Assessment Scale; VAS = visual analogue score

[a] In addition to subjects who complete Part B, subjects who receive at least one dose of study drug and do not complete Part B will have a visit 1 week following the last dose of study drug to assess safety measures.

[b] Safety laboratory tests will be performed predose on Day 8 and Day 9 and anytime during the visit on Day 21.

[c] To be performed predose on Day 8 and anytime during the visit on Day 28.

[d] Vital signs (heart rate, respiratory rate, temperature, and supine [for at least 5 minutes prior to the measurement] and standing [for at least 2 to 3 minutes] systolic and diastolic blood pressure) and pulse oximetry will be performed predose on Day 8 and at 1, 2, 3, 4, 6, and 8 hours postdose on Days 8, 9, and 10, predose on Days 11, 12, 13, and 14, and anytime during the visit on Day 21. Vital signs and pulse oximetry assessments will be performed within ±10 minutes of the scheduled times.

[e] 12-lead ECGs will be performed at 1 and 8 hours (±10 minutes) postdose on Days 8, 9, 10, and 14, and anytime during the visit on Day 21.

[f] The C-SSRS (Since Last Visit version) will be performed 8 hours (±1 hour) postdose on Days 8, 11, 12, 13 and 14 and anytime during the visits on Days 21 and 28.

[g] The SSS will be performed predose and 1, 2, 4, 6, and 8 hours postdose on Days 8, 9, 10, 11, 12, 13, and 14, and anytime during the visit on Day 21. The SSS is to be performed within ±10 minutes of the scheduled times.

[h] The Bond-Lader VAS will be performed predose and 2 hours (±10 minutes) postdose on Days 8, 9, and 14 and anytime during the visit on Day 21.

[i] The DEQ-5 will be performed 2 hours (±10 minutes) postdose on Days 8 and 14.

[j] Kinesia and TETRAS upper limb items will be performed predose, 2 and 8 hours (±30 minutes) postdose on Days 8, 9, and 14, and anytime during the visit on Day 21. In addition, the TETRAS upper limb items will be performed, while wearing the Empatica Wristband E4, 3 hours (±30 minutes) postdose on Days 8, 9, and 14, and anytime during the visit on Day 21. All three maneuvers in the upper limb assessments (items 4a, 4b, and 4c) will be completed for both arms, first for the RIGHT arm and then for the LEFT.

[k] TETRAS ADL Subscale and items 4, 6, 7, and 8 of Performance Subscale will be performed predose (±30 minutes) on Day 14 and anytime during the visit on Day 21.

[l] The Empatica Wristband E4 will be worn during the study visits while in clinic on Days 8, 9, 14, and 21. With the exception of during the TETRAS upper limb assessments, the Empatica Wristband E4 will be worn on the wrist that, of the two arms, exhibits more severe tremor symptoms. During the

TETRAS upper limb assessments 3 hours (±30 minutes) postdose on Days 8, 9, and 14 and anytime during the visit on Day 21, the Empatica Wristband E4 will be worn on the wrist corresponding to the side of the body being assessed.

[m] Plasma pharmacokinetic samples will be taken predose (±5 minutes) on Days 8, 9, 10, 11, 12, 13, and 14.

[n] Study drug will be administered in the morning with food.

[o] To include those taken throughout the study.

[p] Videos of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis) will be taken predose on Day 14 and anytime during the visit on Day 21.

Sage Therapeutics, Inc

Statistical Analysis Plan

Methods

Protocol 217-ETD-201

Part C

A PHASE 2A, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY EVALUATING THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SAGE-217 IN THE TREATMENT OF SUBJECTS WITH ESSENTIAL TREMOR (ET)

Author of SAP: [redacted], MStat

Version: Version 1.0

Date of SAP: 14 DEC 2017

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1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
ADL	activities of daily living
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BLQ	below the limit of quantification
%CV	percent coefficient of variation
CI	confidence interval
CM	concomitant medications
C-SSRS	Columbia-Suicide Severity Rating Scale
DEQ-5	Drug Effects Questionnaire
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
ET	essential tremor
HIV	human immunodeficiency virus
ICF	informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
LLOQ	lower limit of quantitation
LS	least-squares
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
QoL	quality of life
QTcF	QT-interval for ECG corrected for heart rate (Fridericia)
QUEST	Quality of Life in Essential Tremor Questionnaire
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
TEAE	treatment emergent adverse event
TETRAS	TRG Essential Tremor Rating Assessment Scale
ULOQ	upper limit of quantitation
VAS	visual analogue scale
WHO-DDE	World Health Organization Drug Dictionary Enhanced

3 INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis of the study and is based on the approved clinical study protocol, dated September 5, 2017, Version 5.0, incorporating Amendment 4 for Study 217-ETD-201. Part A and Part B of this study were analyzed in a separate SAP. Part C will be analyzed according to this SAP.

This SAP addresses the safety, efficacy, and pharmacokinetics (PK) objectives of the study and describes the planned safety, efficacy, and PK statistical analyses and data presentations.

The statistical plan described hereafter is an *a priori* plan and will be submitted to file before any analysis of data pertaining to Sage Study 217-ETD-201 (Part C) is performed. The SAP is to be finalized and approved before database lock.

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.3 or higher) for Windows.

Pharmacokinetic parameter estimation will be performed using population PK methods.

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study (Part C) is to assess the effect of 14 days administration of SAGE-217 Capsules on tremor severity, as measured by the change from baseline (Day 1) in the accelerometer-based Kinesia upper limb tremor combined score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores from both sides of the body) at Day 15.

4.2 Secondary Objectives

The secondary objectives of this study are to assess the effect of 14 days of administration of SAGE-217 Capsules on the following endpoints:

- Tremor severity, as assessed by the change from baseline (Day 1) in the Kinesia upper limb individual item scores at Day 15;
- Tremor severity, as measured by the change from baseline (Day 1) in the TETRAS upper limb total score (ie, the sum of TETRAS Performance Subscale item 4 scores [4a, 4b, and 4c] from both sides of the body) and individual TETRAS Performance Subscale upper limb item scores at Day 15;
- Tremor severity, as assessed by the change from baseline (Day 1) in the total TETRAS Performance subscale score and other TETRAS Performance Subscale scores measured at Day 15;

4.3 Safety Objectives

- Safety and tolerability as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event (AE) reporting;
- Mood as assessed by the Bond-Lader visual analogue score (VAS) Mood Scale; and
- How the subject feels after taking the study drug as assessed by Drug Effects Questionnaire (DEQ-5) ratings.

In addition, the PK objective of this study is to assess the PK profile of SAGE-217 in plasma samples following administration of SAGE-217 Capsules.

4.4 Exploratory Objectives

The exploratory objectives of the study are to compare the effect of 14 days of administration of SAGE-217 Capsules on:

- Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring), as assessed by the Empatica Wristband E4. Tremor oscillation, as assessed by multidimensional accelerometer measurements (ie, raw accelerometer values) using the Empatica E4 Wristband.
- Quality of life (QoL), as assessed by TETRAS activities of daily living (ADL), Quality of Life in Essential Tremor Questionnaire (QUEST), and video recording assessment of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis).

In addition, PK and pharmacodynamic (PD) modelling assessment of the relationship between plasma exposure of SAGE-217 and change from baseline in Kinesia scores may be assessed.

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the change from baseline (Day 1) in the accelerometer-based Kinesia upper limb tremor combined score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores from both sides of the body) at Day 15.

5.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include the following:

- Change from baseline in the Kinesia upper limb individual item scores at Day 15 and all other time points;
- Change from baseline in TETRAS Performance Subscale upper limb total score (ie, the sum of TETRAS Performance Subscale item 4 scores [4a, 4b, and 4c] from both sides of the body) and individual TETRAS Performance Subscale upper limb item scores at Day 15 and all other time points; and
- Change from baseline in other TETRAS Performance Subscale scores measured at Day 15 and all other time points.

5.1.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints of this study include the following:

- Change from baseline in TETRAS ADL and QUEST scores at Day 15.

5.2 Safety Endpoints

The safety endpoints of this study include the following:

- Frequency and severity of AEs;
- Safety and tolerability as assessed by changes from baseline in vital signs measurements, clinical laboratory data, ECG parameters, and incidences of suicidal ideation using the C-SSRS;

- Change from baseline in mood as assessed by the Bond-Lader VAS Mood Scale; and
- DEQ-5 ratings.

5.3 Other Endpoints

The PK endpoints include plasma concentrations of SAGE-217 and metabolites for subjects taking capsules as follows:

- Mean plasma concentrations and parameters (area under the concentration-time curve from time 0 to last time point [AUC_{0-t}], area under the concentration-time curve from time 0 to infinity [$AUC_{0-\infty}$], maximum plasma concentration [C_{max}], time to reach maximum concentration [t_{max}], and terminal half-life [$t_{1/2}$], as appropriate) of SAGE-217 and possible metabolites.

6 STUDY DESIGN

6.1 Overall Design

This study is a 3-part, multicenter, Phase 2a study to evaluate the efficacy, safety, tolerability, and PK of SAGE-217 in adult subjects with essential tremor (ET). Subjects who consent before the approval of Protocol Version 4.0 (Amendment 3) by the IRB will receive the oral solution formulation for the duration of the study; subjects who consent after Protocol Version 4.0 (Amendment 3) is approved by the IRB will receive the capsule formulation for the duration of the study. Part A of the study was an open-label design with morning dosing for 7 days. Part B of the study was a double-blind, placebo-controlled, randomized withdrawal design. Subjects were exposed to study drug (SAGE-217 or placebo) for up to 14 days and were followed for an additional 14 days after the administration of the last dose. Part C of the study is an open-label design with evening dosing (and morning and evening dosing beginning on Day 4) for up to 14 days. All subjects in Part C will receive the capsule formulation.

During the Screening Period (Day -28 to Day -1), after signing the informed consent form (ICF), subjects will be assessed for study eligibility and the severity of each subject's ET will be evaluated using TETRAS. Eligible subjects will return to the clinical study unit on Day -1.

The study will be conducted in 3 parts; however, only Part C will be discussed in this SAP (Part A and Part B were discussed in a separate SAP):

- **Part C:** All eligible subjects will start on a 10 mg dose of study drug administered with food in the evening on Day 1, 20 mg with food in the evening on Day 2, and 30 mg with food in the evening on Day 3. Beginning on Day 4 and continuing through Day 14, subjects will receive a 40 mg total daily dose (administered as 10 mg with food in the morning and 30 mg with food in the evening). Study drug will be self-administered by subjects on an outpatient basis for the entire 14-day Treatment Period.

Dose adjustments will be allowed during Part C of the study. A dose will be considered not tolerated if the subject experiences a severe AE or a moderate AE of special interest (sedation, somnolence, dizziness, euphoric mood, confusion, drowsiness, inebriation (feeling drunk), or fatigue) judged by the investigator to be related to study drug. If a dose is not tolerated, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the treatment period. Subjects who cannot tolerate the 20 mg dose on Day 2 will be discontinued. Subjects who do not tolerate 30 mg on Day 3 will receive 20 mg for the remainder of the treatment period (10 mg in the morning and 10 mg in the evening). Subjects who do not tolerate 40 mg on Day 4 or any time thereafter will receive 30 mg for the remainder of the treatment period (10 mg in the morning and 20 mg in the evening).

Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part C (Section 12.1.1).

6.2 Sample Size and Power

For Part C, approximately 15 subjects will be enrolled to ensure at least 10 subjects complete the study (through Day 15). The sample size for Part C was selected based on clinical and not statistical considerations.

6.3 Randomization

Part C is open-label with no control group; therefore, there will be no randomization. Once it has been determined that a subject meets eligibility criteria, the subject will be sequentially assigned a subject number. Subject identification numbers will consist of the site number (eg, "01") followed by subject number with leading zeroes (eg, "001"; the subject identification number would then be "01-001").

6.4 Blinding and Unblinding

Part C is an open-label study with no control group; therefore, there will be no blinding.

7 MODIFICATIONS

7.1 Modifications to the Approved Clinical Study Protocol

The following changes from the clinical study protocol (version 5.0, dated September 5, 2017) have been made in the SAP:

- The protocol describes Part A and Part B; these were analyzed according to a separate SAP.
- This SAP includes safety objectives for assessing mood and how the subject feels after taking the study drug which are not explicitly outlined in the protocol, although the endpoints used to assess the objectives (Bond-Lader VAS Mood Scale and DEQ-5, respectively) are described in the protocol.

7.2 Modifications to the Approved Statistical Analysis Plan

This is the first version of the SAP.

7.3 Modifications to the Approved DMC Charter

Not applicable.

8 ANALYSIS POPULATIONS

Subjects included in the below analysis populations (and reason for exclusion, if applicable) will be provided in a listing.

8.1 Efficacy Population

The Efficacy Population (Part C; Capsule) will consist of all subjects who complete at least one dose of study drug in Part C and have at least one postdose efficacy evaluation. The Efficacy Population (Part C; Capsule) will be used to analyze all Part C-Capsule efficacy data.

8.2 Safety Population

The Safety Population (Part C; Capsule) will consist of all subjects who are administered at least one dose of study drug. This population will be used to provide descriptive summaries of safety.

8.3 PK Population

The PK Population (Part C; Capsule) will consist of all subjects in the Safety Population (Part C; Capsule) with at least one sample with quantifiable plasma concentration of SAGE-217 in Part C. This population will be used to summarize PK data.

9 STATISTICAL ANALYSIS

9.1 General Considerations

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variables will be summarized using the number and proportion of each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment group.

The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (standard deviation) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place unless otherwise specified. Assessments done on unscheduled visits will not be summarized but will be listed.

Treatment group is defined as SAGE-217. For any outputs showing tolerated dose, tolerated dose is defined as SAGE-217 20 mg, SAGE-217 30 mg, or SAGE-217 40 mg (Section 6.1).

The last observation recorded before receiving the first dose of study drug on Day 1 in Part C will be used as the baseline observation for all calculations of change from baseline.

All summaries will be presented by overall subjects, unless otherwise specified.

All final, planned analyses identified in the protocol and in this SAP will be performed after all relevant study data have been processed and integrated into the analysis database, analysis populations have been finalized, and the database has been locked. Any post-hoc analyses performed to support planned study analyses in the clinical study report (CSR), which were not identified in this SAP, will be documented in Section 9.8 of the CSR as a change in the conduct of the study or planned analyses.

All collected data will be presented in listings and will be sorted by subject.

If partial dates occur, the convention for replacing missing dates for the purposes of calculating derived variables is as follows:

For partial AE and medication start dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the year is known, but the month or 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, then impute as the month and day of the first dose date.
    - Otherwise, assign 01 January
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the first dose date, then impute as the day of the first dose date.
    - Otherwise, assign 01

For partial AE and medication end dates:

- If the year is unknown, then do not impute the date but assign as missing value.
- If the year is known, but the month or month and day is unknown, then:

  - If the year matches the year of the last date of the study (date of last contact if subject lost to follow-up; date of completion or early termination otherwise), then impute as the month and day of the last date of the study.
  - Otherwise, assign 31 December.

- If the year and month are known, but the day is unknown, then:
  - If the month and year match the month and year of the last date of the study, then impute as the day of the last date of the study.
  - Otherwise, assign the last day of the month.

No missing data will be imputed unless otherwise specified.

In general, for quantitative safety laboratory values reported as '<X' or '≤X', the lower limit of quantitation (LLOQ) will be used for analysis (ie, a value of X will be used in the analysis for lab values reported as '<X' or '≤X'). Similarly, for safety quantitative laboratory values reported as '>X' or '≥X', the upper limit of quantitation (ULOQ) will be used for analysis (ie, a value of X will be used in the analysis for lab values reported as '>X' or '≥X').

For analysis purposes, repeat laboratory results will not be used unless the original laboratory value is missing or indicated as invalid, in which case the first non-missing repeat laboratory value will be used for data analysis.

9.2 Background Characteristics

9.2.1 Subject Disposition

All subjects who sign the ICF will be accounted for in this study.

Subject disposition will be summarized as follows:

- The number of subjects enrolled (ie, signed informed consent); treated; completed Part C; withdrew from Part C (including reason for withdrawal); and included in each Part C analysis population will be summarized by overall subjects; and
- The number and percentage of subjects enrolled; treated; completed Part C; withdrew from Part C (including reason for withdrawal); and included in each Part C analysis population will be summarized by tolerated dose.

All disposition information will be included in a listing.

9.2.2 Demographics and Baseline Characteristics

Demographics, such as age, gender, child-bearing potential, race, and ethnicity, and baseline characteristics such as height, weight, body mass index (BMI), and time (years) since ET diagnosis (from date of ICF; a missing ET diagnosis month will be imputed as January, and the missing day will be imputed as 01), will be summarized by overall subjects.

Categorical summaries, such as gender, childbearing potential, race, and ethnicity, will be summarized using frequency and percentage. Subjects who marked more than one race will be summarized in a "More than One Race" category. Continuous summaries, such as age, height, weight, BMI, and time since ET diagnosis, will be summarized using mean, standard deviation (SD), median, minimum, and maximum. The demographic and baseline characteristics table will be generated for subjects in the Safety Population.

Hepatitis, human immunodeficiency virus (HIV), pregnancy, alcohol, cotinine, caffeine, and drug screening results will be listed, but not summarized as they are considered part of the inclusion/exclusion criteria.

Medical history, coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 19.1 or higher), will be listed.

9.2.3 Prior and Concomitant Medications

Concomitant medications (CM) will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) (Version September 1, 2015 or later).

Frequencies and percentages of medications used in the study will be summarized as follows:

- Prior medication: medication taken before the date of first dose of open-label study drug (including medications with a missing start date but a non-missing end date in this time period).
- Concomitant medication: a medication with a start date on or after the first dose of open-label study drug (even if end date is missing) and on or before the last dose of study drug, or medications with a start date before the first dose of open-label study drug that are ongoing or with a stop date on or after the first dose of open-label study drug, will be considered concomitant. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Details of prior and concomitant medications will be listed by subject, start date, and verbatim term. All medications will be summarized by Anatomic Therapeutic Chemical (ATC) class Level 3 and preferred term (PT). Furthermore, both prior and concomitant medications will be summarized by overall subjects. Subjects will be counted once per ATC and PT.

Medication summaries will be based on the Safety Population.

9.2.4 Study Drug Exposure and Compliance

For all of the below formulas, *i* = individual subject for the entire treatment period (unless otherwise specified).

- Total drug exposure in mg will be calculated as:

$$\sum_i Actual\ Doses\ Taken\ \ (mg)$$

- Average daily dose (Days 4-14) in mg/day will be calculated as:

$$\frac{\sum_i Actual\ Doses\ Taken\ \ (Days\ 4-14)\ (mg)}{\sum_i Days\ on\ Study\ Drug\ (Days\ 4-14)}$$

  Days 1-3 are excluded since they are dose escalation days.

- Total days of exposure will be calculated as:

$$\sum_i Days\ on\ Study\ Drug$$

- Study drug compliance will be calculated as:

$$\frac{\sum_i Actual\ Doses\ Taken\ \ (mg)}{\sum_i Planned\ Doses\ (mg)} \times 100$$

  where planned doses are summed up to the point of discontinuation (eg, if a subject discontinues early, only planned doses up to that discontinuation day are counted in the denominator).

Total drug exposure (mg), average total daily dose (mg/day) (starting at Day 4), total days of exposure, and compliance (%) will be summarized descriptively by overall subjects. Additionally, number of subjects at each tolerated total daily dose (ie, the sum of the final morning and evening doses received by

each subject during Days 4-14) will be summarized. If a subject discontinued after a morning dose (ie, did not receive an evening dose), the previous daily's total daily dose will be considered as the tolerated total daily dose. If a subject only received evening doses, the final evening dose received will be considered as the tolerated total daily dose.

Study drug dosing and compliance information (including details of unplanned dose adjustments) will be listed. Any other study drug noncompliance such as missing visits, interruptions in the schedule of administration, and nonpermitted medications will be listed in the protocol deviations listing.

9.3 Efficacy Analysis

The primary efficacy variable for this study (Part C) is change from baseline in accelerometer-based Kinesia upper limb tremor combined score.

The secondary efficacy variables for this study (Part C) include change from baseline in:

- Kinesia upper limb individual item scores
- TETRAS Performance subscale total and individual upper limb item scores
- Other TETRAS Performance Subscale scores

The other efficacy variables for this study (Part C) include change from baseline in:

- TETRAS ADL scores
- QUEST scores

All efficacy analyses will be conducted on the Efficacy Population.

9.3.1 Analysis of Primary Efficacy Variable

9.3.1.1 Description of Primary Efficacy Variable

The primary outcome measure is the change from baseline in the accelerometer-based Kinesia upper limb tremor combined score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores from both sides of the body), based on the Day 15 measurement.

In order to measure essential tremor amplitude, subjects will wear a wireless ring motion sensor (ie, Kinesia). The motion sensor uses three orthogonal accelerometers and three orthogonal gyroscopes to monitor three-dimensional motion. Data are then transmitted from the sensor to a computer using Bluetooth technology. These measures of three-dimensional motion for each maneuver are then converted to Kinesia scores, which have been shown to correlate with corresponding clinician-rated TETRAS scores (ie, forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor on both sides of the body) (Giovanni, Giuffrida, Adam, Davidson, & Jankovic, 2010). Each Kinesia score ranges from 0 to 4; higher scores indicate more severe tremor. The Kinesia assessment is completed in conjunction with the TETRAS Performance Subscale Item 4 assessment.

In Part C, Kinesia will be performed at pre-PM dose on Days 1 and 8; on Day 15; and at follow-up on Day 21.

9.3.1.2 Visit Windows for the Primary Endpoint

For efficacy analyses, unscheduled measurements will only be included if a scheduled measurement is not available and the unscheduled measurement falls on the same study day. Due to the short duration of this study, this is not anticipated to occur.

9.3.1.3 Primary Analysis

The difference in change from baseline to post-baseline in Kinesia upper limb tremor combined score will be evaluated by a mixed model for repeated measures (MMRM) with change from baseline of the Kinesia upper limb tremor combined scores as the dependent variable, study visit as fixed effect, and the baseline value as a covariate. An unstructured covariance matrix will be used to model the within-subject correlation. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

In case of convergence issues, other covariance structures will be used including (but not limited to) autoregressive (AR (1)), compound symmetry (CS), and variance components (VC) with each model fit to find the covariance structure with the best fit. The fit statistics will be compared for all covariance structures; the structure with the smallest Akaike information criterion will be retained as the preferred model.

In comparing the visit value to baseline, least-squares (LS) mean change from baseline will be presented along with associated 95% CI and *P* values. Since the sample size was not based upon statistical considerations, all *P* values are considered nominal.

9.3.1.4 Supportive Analyses

Observed values, change from baseline, and percent change from baseline in Kinesia upper limb tremor combined score will be summarized for all time points for overall subjects.

9.3.1.5 Multiplicity Adjustment

Not applicable.

9.3.1.6 Sensitivity Analysis

Not applicable.

9.3.1.7 Subgroup Analyses

Not applicable.

9.3.2 Analysis of Secondary Efficacy Variables

9.3.2.1 Kinesia Upper Limb Individual Scores

Description of Kinesia Upper Limb Individual Scores

The accelerometer-based Kinesia upper limb individual scores include the sum from both sides of the body in the following Kinesia areas: forward outstretched postural tremor, lateral “wing beating” postural tremor, and kinetic tremor. The upper limb individual item question score for each side of the body ranges from 0 to 4, with higher scores indicating more tremors/greater tremor amplitude.

Analysis of Kinesia Upper Limb Individual Scores

Observed values, change from baseline, and percent change from baseline in Kinesia upper limb individual item scores will be summarized for all time points by overall subjects.

The change from baseline will be analyzed using the MMRM model as described for the primary analysis (Section 9.3.1.3) for post-baseline time points only.

9.3.2.2 TETRAS Upper Limb Individual and Total Scores

Description of TETRAS Upper Limb Individual and Total Scores

Items 4a (forward outstretched postural tremor), 4b (lateral “wing beating” postural tremor), and 4c (kinetic tremor), assessed on both sides of the body, comprise the TETRAS Performance Subscale upper

limb scores. The TETRAS Performance Subscale upper limb total score is the sum of all item 4 scores from both sides of the body (Elble, Comella, & al, 2012).

In Part C, TETRAS Performance Subscale upper limb scores will be assessed at Screening and on Day -1; pre-PM dose on Days 1 and 8; on Day 15; and at follow-up on Day 21.

Analysis of TETRAS Upper Limb Individual and Total Scores

Observed values , change from baseline, and percent change from baseline in TETRAS upper limb individual item and total scores will be summarized for all time points by overall subjects.

The change from baseline will be analyzed using the MMRM model as described for the primary analysis (Section 9.3.1.3) for post-baseline time points only.

9.3.2.3 TETRAS Performance Subscale Individual and Total Scores

Description of TETRAS Performance Subscale Individual and Total Scores

The TETRAS Performance Subscale score includes the following 9 items: head tremor, face (including jaw) tremor, voice tremor, upper limb tremor, lower limb tremor, Archimedes spirals, handwriting, dot approximation task, and standing tremor (Elble, Comella, & al, 2012). However, only Archimedes spirals (item 6), handwriting (item 7), and dot approximation task (item 8) assessments, in addition to upper limb tremor as described above, were performed for this study. The TETRAS Performance Subscale total score is the sum of all item 4, 6, 7, and 8 scores from both sides of the body

In Part C, TETRAS Performance Subscale items 6, 7, and 8 will be assessed at Screening and on Day -1; pre-PM dose on Days 1 and 8; on Day 15; and at follow-up on Day 21.

Analysis of TETRAS Performance Subscale Individual and Total Scores

Observed values, change from baseline, and percent change from baseline in TETRAS Performance Subscale individual item and total scores will be summarized for all time points by overall subjects.

The change from baseline will be analyzed using the MMRM model as described for the primary analysis (Section 9.3.1.3) for all post-baseline time points.

9.3.3 Analysis of Exploratory Efficacy Variables

9.3.3.1 TETRAS ADL

Description of TETRAS ADL

The QoL as assessed by the TETRAS ADL Subscale includes the following 12 items: speaking; feeding with a spoon; drinking from a glass; hygiene; dressing; pouring; carrying food trays, plates, or similar items; using keys; writing; working; overall disability with the most affected task; and social impact (Elble, Comella, & al, 2012). Each individual item question score ranges from 0 to 4, where higher scores indicate worse QoL. The total score is derived as the sum of all of the individual items scores, with a maximum total score of 48. If one of the individual item scores is missing, the total score will be set to missing.

In Part C, the TETRAS ADL Subscale will be assessed at pre-PM dose on Days 1 and 8; on Day 15; and follow-up on Day 21.

Analysis of TETRAS ADL

Observed values, change from baseline, and percent change from baseline in TETRAS ADL scores will be summarized for each item score and total score for all time points by overall subjects.

9.3.3.2 QUEST

Description of QUEST

The QUEST is a brief, ET-specific QoL scale in which subjects rate the extent to which tremor impacts a function or state (30 questions), waking hours with tremor in any part, tremor self-assessment rating tremor severity in various body parts (head, voice, right arm/hand, left arm/hand, right leg/foot, and left leg/foot), health status, and overall QoL, along with 4 questions gathering general information describing work status and issues occurring in the past month (tremor interference with sexual satisfaction, side effects from tremor medication, and satisfaction of tremor control achieved by medication) (Tröster, Pahwa, Fields, Tanner, & Lyons, 2005). The extent to which tremor impacts a function or state is rated as never/no, rarely, sometimes, frequently, always/yes, and not applicable. Tremor severity is rated as none, mild, moderate, marked, or severe. Perceived health and overall QoL are rated on a scale of 0 to 100 in 5-point increments, where 0=very poor health and 100=excellent/perfect health.

For the 30-question component of the QUEST, the questions will be scored in 5 dimensions: Communication (questions 1-3); Work and Finances (questions 4-9); Hobbies and Leisure (questions 10-12); Physical (questions 13-21); and Psychosocial (questions 22-30).

The dimension scoring algorithm is as follows:

$$Dimension\ Score = \frac{Total\ applicable\ points\ for\ each\ dimension}{Total\ possible\ points\ (\#\ of\ applicable\ questions\ \times\ 4) for\ each\ dimension}$$

The point values assigned to each question are as follows: 0 = “Never/No”; 1 = “Rarely”; 2 = “Sometimes”; 3 = “Frequently”; 4 = “Always/Yes”; blank = Not Applicable (question is not counted toward applicable points or questions) (Movement Disorders Society Rating Scales, n.d.).

In Part C, QUEST will be assessed on Days 1, 8, 15, and 21.

Analysis of QUEST

Observed values, change from baseline, and percent change from baseline in QUEST scores will be summarized for each dimension score for all time points by overall subjects.

9.4 Safety Analysis

Safety will be evaluated through incidence and severity of AEs, as well as observed values and changes from baseline in vital signs, clinical laboratory measures (including shifts from baseline), ECG parameters, and suicidal ideation using the C-SSRS.

For Part C, safety endpoints will be summarized by overall subjects, unless otherwise specified. All safety data will be presented in individual subject data listings. Safety analysis will be conducted for the Safety Population.

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Abnormality/ Clinical Significance
AEs	X			
CMs	X			
Labs		X	X	*
ECG		X	X	*

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Abnormality/ Clinical Significance
Vital Signs		X	X	
C-SSRS	X			
VAS		X	X	
DEQ-5		X	X	
X = Safety Assessment will be summarized in tables * = Safety Assessment will be presented in individual subject data listings				

9.4.1 Adverse Events

Adverse events (AEs) will be coded using the MedDRA coding system (version 19.1 or higher). The analysis of AEs will be based on the concept of treatment-emergent AEs (TEAEs). A TEAE for Part C is defined as an AE with onset after the start of open-label study drug, or any worsening of a pre-existing medical condition/AE with onset after the start of open-label study drug and until 14 days after the last dose. Any TEAEs occurring in the follow-up period after last dose of study drug will be summarized based on the last dose of study drug taken.

A summary of the number and percentage of subjects with TEAEs will be provided for overall subjects. Frequencies and percentages of the following will be included:

- Any TEAE
- Maximum severity of TEAEs
- Possibly or Probably Related TEAEs
- TEAEs Leading to Discontinuation
- TEAEs Leading to Death
- Serious AEs (SAEs)

In Part C, the incidence of TEAEs will be summarized by the following, for overall subjects:

- SOC and PT
- PT
- Dose, Day, and PT
- SOC, PT, and Maximum Severity
- SOC, PT, and Relationship to Study Drug

Incidences will be presented by descending frequency of SOC (where applicable), then in order of decreasing frequency of PT (within SOC, if applicable), and then alphabetically within PT where the incidence is the same. The presentation of TEAEs by dose, day, and PT will include counts of TEAEs that started on that particular day. The dose of the TEAE will correspond to the dose the subject was on at the start of the TEAE.

All AEs, SAEs (including those with onset or worsening before the start of open-label study drug), AEs leading to discontinuation, and AEs leading to death through the Day 28 visit will be listed in separate tables.

9.4.2 Clinical Laboratory

Screening and safety laboratory tests will be performed at screening, Day -1; pre-PM dose on Days 1 and 8; on Day 15; and follow-up on Day 21 and Day 28. All summaries of laboratory values will be presented using SI units. Continuous hematology, chemistry, and urinalysis results will be listed by subject and timing of collection. Observed values and change from baseline at each time point in will be summarized by overall subjects. Shifts from baseline will also be summarized by overall subjects. Clinically significant abnormal findings will be reported as AEs.

9.4.3 Electrocardiogram

12-lead ECGs will be performed at screening, Day -1; pre-PM dose on Days 1 and 8; on Day 15; and follow-up on Day 21 and Day 28. The following 12-ECG parameters will be listed for each subject: heart rate, PR interval, QRS duration, QT interval, and QTcF interval (derived as QT interval / (RR interval)$^{1/3}$). Any clinically significant abnormalities or changes in ECGs should be listed as an AE. Observed values and change from baseline at each time point will be summarized by overall subjects. Additionally, the number and percentage of subjects with a QTcF value meeting any of the following clinical significance criteria will be summarized separately by overall subjects: raw QTcF >450 msec, >480 msec, and >500 msec; change from baseline QTcF >30 msec and >60 msec.

9.4.4 Vital Signs

Vital sign results (body temperature, heart rate, respiratory rate, supine and standing diastolic blood pressure, supine and standing systolic blood pressure, and pulse oximetry) will be performed at screening, Day -1; pre-PM dose on Days 1 and 8; on Day 15; and follow-up on Day 21 and Day 28 and will be listed by subject and timing of collection. Observed values and change from baseline at each time point will be summarized by overall subjects.

9.4.5 Physical Examination

Screening physical examination results for Part C that are clinically significant will be listed in the medical history listing. Post-screening physical examination results that are clinically significant will be listed in the AE listing. A listing will be provided containing information on when physical examination occurred and reason it was not done if applicable.

9.4.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the study using the C-SSRS (Posner, Brown, Stanley, & al, 2011). This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicidal ideation and behavior, and a post-baseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes “yes” or “no” responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

Suicidality data collected on the C-SSRS will be listed for all subjects. Tables will include results from the Suicidal Ideation and Suicidal Behavior sections of the C-SSRS. Frequencies and percentages of subjects with a response of “Yes” at any point on the Suicidal Ideation and Suicidal Behavior items will be summarized by overall subjects. Both baseline (“pre-treatment”) and post-baseline (“post-treatment”) results will be presented.

9.4.7 Bond-Lader Visual Analogue Scale (VAS)

Mood will be assessed using the Bond-Lader VAS Mood Scale at pre-PM dose on Days 1 and 8; on Day 15; and follow-up on Day 21. This is a 16-part self-administered questionnaire that employs a 100-mm VAS to explore different aspects of self-reported mood (Bond & Lader, 1974). The 16 different mood ranges include:

1. 0 = "Alert" to 100 = "Drowsy";
2. 0 = "Calm" to 100 = "Excited";
3. 0 = "Strong" to 100 = "Feeble";
4. 0 = "Muzzy" to 100 = "Clear-headed";
5. 0 = "Well-coordinated" to 100 = "Clumsy";
6. 0 = "Lethargic" to 100 = "Energetic";
7. 0 = "Contented" to 100 = "Discontented";
8. 0 = "Troubled" to 100 = "Tranquil";
9. 0 = "Mentally slow" to 100 = "Quick-witted";
10. 0 = "Tense" to 100 = "Relaxed";
11. 0 = "Attentive" to 100 = "Dreamy";
12. 0 = "Incompetent" to 100 = "Proficient";
13. 0 = "Happy" to 100 = "Sad";
14. 0 = "Antagonistic" to 100 = "Amicable";
15. 0 = "Interested" to 100 = "Bored"; and
16. 0 = "Withdrawn" to 100 = "Gregarious".

In order to directly compare VAS results across the 16 items, items 4, 6, 8, 9, 10, 12, 14, and 16 will be reverse-scored by subtracting the scores from 100. In order to normalize the results, the scores will be converted to $\log_e$ (after setting any scores of 0 to 1), with a resulting range of 0 to 4.605. Based on the factor loadings from Table 4 of the Bond and Lader article, the following equations will be used to compute the 3 factor scores:

- Alertness = $0.827X_1 + 0.618X_3 + 0.755X_4 + 0.642X_5 + 0.776X_6 + 0.635X_9 + 0.792X_{11} + 0.593X_{12} + 0.614X_{15}$;
- Contentedness = $0.677X_7 + 0.697X_8 + 0.823X_{13} + 0.738X_{14} + 0.594X_{16}$; and
- Calmness = $0.845X_2 + 0.677X_{10}$,

  where X_i represents a subject's item score after normalization, and i represents the item number from the entire scale (in order from 1-16).

Bond-Lader VAS results will be listed for all subjects. Observed values and change from baseline at each time point in will be summarized by parameter (including the 3 factor scores) and overall subjects.

9.4.8 Drug Effects Questionnaire (DEQ-5)

The DEQ-5 will be administered at pre-PM dose on Day 8, on Day 15, and follow-up on Day 21, as follows:

1. Do you FEEL a drug effect right now?
2. Are you HIGH right now?
3. Do you DISLIKE any of the effects that you are feeling right now?
4. Do you LIKE any of the effects that you are feeling right now?
5. Would you like MORE of the drug you took, right now?

The answers are recorded on a 100-mm VAS, with the answer for each being "Not at all" and "Extremely" at the extremes. There will be options to record "Not applicable" for questions 3 and 4 if no drug effects are felt and for question 5 prior to administration of study medication.

The DEQ-5 results will be listed for all subjects. Since no baseline (before first dose of open-label study drug) values were recorded, only raw values at each time point will be summarized by parameter and overall subjects.

9.5 Pharmacokinetic Analysis

Plasma pharmacokinetic samples will be taken pre-PM dose on Days 1 and 8, and on Day 15. For plasma concentration data, all values below the limit of quantification (BLQ) will be set to 0 for summary statistics and graphs. Individual plasma concentrations of SAGE-217 will be summarized at each time point using descriptive statistics, including number of subjects, mean, SD, median, maximum, minimum, percent coefficient of variation (%CV), and geometric mean. Pharmacokinetic parameters (eg, C_{max}, AUC, C_{min}) will be derived using population pharmacokinetic methods; the details of this analysis are outside the scope of this SAP and will be provided separately. The population-derived PK parameters will be summarized by overall subjects. Individual concentration plots and mean data graphs will be produced for all time point. All graphs will be presented using both linear and semi-logarithmic scales. The above descriptive summary will be performed for the PK population.

10 SUMMARY OF INTERIM ANALYSES

Not applicable.

11 REFERENCES

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12 LIST OF APPENDICES

12.1 Appendix A: Schedule of Assessments

12.1.1 Part C (Open-Label)

Study Procedure	Study Period / Visit Day						
	Screening		Treatment			Follow-up	
	Day -28 to Day -1	Day -1	Day 1	Day 8	Day 15	Day 21±1 day[b] (Early Termination Visit)	End of Study Day 28±1 day
Informed consent	X						
Inclusion/exclusion	X	X					
Demographics	X						
Medical history	X						
Physical examination	X		X	X	X	X	X
Body weight/height	X						
Drug/alcohol screen[c]	X	X		X			
Complete blood count/ serum chemistry[d]	X	X	X	X	X	X	X
Pregnancy test	X (serum)	X (urine)				X (urine)	X (urine)
Urinalysis[d]	X	X	X	X	X	X	X
Hepatitis & HIV screen	X						
Exploratory biochemistry sample[e]	O			O	O	O	
Genetic sample[f]	O					O	
Vital signs[g]	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X

Study Procedure	**Study Period / Visit Day**						
	Screening		**Treatment**			**Follow-up**	
	Day -28 to Day -1	**Day -1**	**Day 1**	**Day 8**	**Day 15**	**Day 21±1 day[b]** (Early Termination Visit)	**End of Study Day 28±1 day**
C-SSRS[i]	X	X	X	X	X	X	X
Bond-Lader-VAS[j]			X	X	X	X	
DEQ-5[k]				X	X	X	
Kinesia (accelerometer)[l]			X	X	X	X	
TETRAS Performance Subscale[l]	X	X	X	X	X	X	
TETRAS ADL Subscale[m]			X	X	X	X	
Empatica E4 Wristband[n]		X	X	X	X		
QUEST			X	X	X	X	
Plasma PK samples[o]			X	X	X		
Dispense study drug[p]			X	X			
Adverse events/Serious adverse events	X	X					
Prior/concomitant medications[q]	X	X					
Videos[r]			X	X	X	X	
Treatment compliance call[s]			X				

ADL = activities of daily living; C-SSRS = Columbia-Suicide Severity Rating Scale; DEQ-5 = Drug Effects Questionnaire; ECG = electrocardiogram; HIV = human immunodeficiency virus; O = optional; PK = pharmacokinetic; QUEST = Quality of Life in Essential Tremor Questionnaire; TETRAS = TRG Essential Tremor Rating Assessment Scale; VAS = visual analogue score.
Note: Pre-dose assessments refer to the evening dose only.

[a] An unscheduled visit may be needed if a dose adjustment is deemed necessary by the Investigator at any time during the treatment period in order for the adjusted dose to be dispensed.
[b] In addition to subjects who complete Part C, subjects who receive at least one dose of study drug and do not complete Part C will have a visit 1 week following the last dose of study drug to assess safety measures.

[c] A urine sample for assessment of selected drugs (sedative/hypnotics [eg, opioids], cotinine, and caffeine) and a breath sample for alcohol screen will be collected at screening, Day -1 and Day 8.
[d] Screening and safety laboratory tests will be performed at screening, Day -1, predose on Day 1, predose on Day 8, on Day 15, and follow-up on Day 21 and Day 28.
[e] An optional blood sample for exploratory biochemistry, where consent is given.
[f] An optional genetic sample for biomarker testing, where consent is given.
[g] Vital signs (heart rate, respiratory rate, temperature, and supine [for at least 5 minutes prior to the measurement] and standing [for at least 2 to 3 minutes] systolic and diastolic blood pressure) will be performed at screening, Day -1, predose on Day 1 and Day 8, on Day 15, and at follow-up on Day 21 and Day 28.
[h] 12-lead ECGs will be performed at screening, on Day -1, predose on Days 1 and 8, on Day 15, and follow-up on Days 21 and 28.
[i] The C-SSRS will be performed at screening, on Day -1, predose on Days 1 and 8, on Day 15, and follow-up on Days 21 and 28. Baseline/Screening version of C-SSRS should be used on day of screening and Since Last Visit version should be used on all subsequent time points.
[j] The Bond-Lader VAS will be performed predose on Days 1 and 8, on Day 15, and follow-up on Day 21.
[k] The DEQ-5 will be performed predose on Day 8, on Day 15, and follow-up on Day 21.
[l] Kinesia and TETRAS Performance Subscale will be performed at screening and Day -1 (TETRAS Performance Subscale only), and predose on Days 1 and 8, on Day 15, and follow-up on Day 21.
[m] TETRAS ADL Subscale will be performed predose on Days 1 and 8, on Day 15, and follow-up on Day 21.
[n] The Empatica E4 Wristband will be worn at all times (except while bathing) during three 5-day intervals: at the start of the Day -1 visit until the morning of Day 4, at the start of the Day 8 visit until the morning of Day 12, and at the start of the Day 15 visit until the morning of Day 19. The Empatica E4 Wristband will be worn on the wrist that, of the two arms, exhibits more severe tremor symptoms (i.e. tremor-dominant hand), as determined during screening.
[o] Plasma pharmacokinetic samples will be taken predose on Days 1 and 8, and on Day 15.
[p] Study drug will be dispensed at the scheduled clinic visits during the treatment period for outpatient administration daily with food (in the evening on Days 1-3 and in the morning and in the evening on Days 4-14).
[q] To include those taken within 2 weeks prior to informed consent and throughout the study.
[r] Videos of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis) will be taken predose on Day 1 and Day 8, on Day 15, and follow-up on Day 21.
[s] A treatment compliance call will be made within approximately 60 minutes after the scheduled evening dose (between approximately 8:00PM and 9:00PM) on Days 1-14.