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9. STATISTICAL METHODS INTERIM ANALYSIS PLAN

The Statistical Analysis Plan Methods were modified once; Version 2.0 (dated 01 August 2017) is provided.

Sage Therapeutics, Inc.

Statistical Analysis Plan

Methods

Protocol 217-PRK-201

A PHASE 2, TWO-PART STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF SAGE-217 IN SUBJECTS WITH PARKINSON'S DISEASE

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2 LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
AE	adverse event
AM	morning
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
BLQ	below the limit of quantification
BMI	body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CBC	complete blood count
CI	confidence interval
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
HIV	human immunodeficiency virus
IA	interim analysis
MedDRA	Medical Dictionary for Regulatory Activities
MDS-UPDRS	Movement Disorder Society – United Parkinson's Disease Rating Scale
MMRM	mixed effect model repeated measures
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
[redacted]	[redacted]
PD	Parkinson's Disease
[redacted]	[redacted]
PK	pharmacokinetic
PT	preferred term
QTcF	QT-interval for ECG corrected for heart rate (Fridericia)
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SSS	Stanford Sleepiness Scale
TEAE	treatment emergent adverse event
ULOQ	upper limit of quantitation
WHO-DD	World Health Organization Drug Dictionary

3 INTRODUCTION

This amended statistical analyses plan (SAP) is for the final analysis of the study (Part A and Part B) and is based on the approved clinical study protocol, dated 08 JUN 2017, Version 5.0, incorporating Amendment 4

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 approved prior to any analysis of data pertaining to Sage's study 217-PRK-201 Part A and prior to any analysis of data pertaining to Part B.

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. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

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

Separate listings, tables, and figures will be created for Part A and Part B. 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 Part A is to evaluate the safety and tolerability of SAGE-217 Oral Solution.

The primary objective of Part B is to evaluate the effect of SAGE-217 capsules as an adjunct to antiparkinsonian agent(s) on the severity of Parkinson's Disease (PD) tremor symptoms.

4.2 Secondary Objectives

The secondary objectives of Part A are:

- To evaluate the effect of SAGE-217 Oral Solution on the severity of PD motor symptoms after withdrawal of Levodopa or Carbidopa-Levodopa (Levodopa/Carbidopa).
- To evaluate the effect of SAGE-217 Oral Solution exposure length on the severity of PD motor symptoms after withdrawal of Levodopa/Carbidopa.

The secondary objectives of Part B are:

- To evaluate the effect of SAGE-217 capsules as an adjunct to antiparkinsonian agent(s) on motor and non-motor symptoms of PD.
- To evaluate the safety and tolerability of SAGE-217 Capsules.

4.3 Pharmacokinetic Objectives

- **Part A:** To assess the pharmacokinetic (PK) profile of SAGE-217 Oral Solution in plasma samples.
- **Part B:** To assess the PK profile of SAGE-217 Capsules utilizing a population PK approach.

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

There are no primary efficacy endpoints in Part A.

The primary endpoint of Part B is improvement in PD tremor as assessed by changes in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II/III tremor score (defined as the sum of MDS-UPDRS items 2.10, 3.15, 3.16, 3.17, and 3.18).

5.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of Part A are:

- Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS – Part III (Motor Examination) total score.

The secondary efficacy endpoints of Part B are:

- Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS – Part III total score.
- Improvement in PD nonmotor and motor aspects of experiences of daily living as assessed by the MDS-UPDRS – Part I and Part II scores, respectively.
- Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS – Parts I-IV total score.

5.1.3 Other Efficacy Endpoints

[redacted]

5.2 Safety Endpoints

The primary endpoint of Part A is safety and tolerability as assessed by frequency and severity of adverse events (AEs) and changes from baseline in vital signs, clinical laboratory data, electrocardiogram (ECG)

parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS). In addition, sleepiness/sedation as assessed by Stanford Sleepiness Scale.

The secondary safety endpoint of Part B is the frequency and severity of AEs and changes in vital signs, clinical laboratory data, ECG parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).

5.3 Other Endpoints

Plasma concentrations of SAGE-217, and possibly SAGE-217 metabolites, will be measured, and PK parameters will be derived.

6 STUDY DESIGN

6.1 Overall Design

This study is a 2-part, multicenter, Phase 2 study to evaluate the safety, tolerability, PK, and efficacy of SAGE-217. Part A of the study is an open-label design with morning (AM) dosing of SAGE-217 for 4 days in up to 18 adult subjects with PD of moderate severity who respond to immediate-release oral Levodopa and are on stable dose. Part B of the study is an open-label design with evening (PM) dosing of SAGE-217 Capsules for 7 days in up to 15 adult subjects with PD. Subjects that participate in Part A are eligible to participate in Part B if all eligibility criteria for Part B are met and they tolerated at least 20 mg SAGE-217 in Part A. Subjects will be followed for an additional 7 days after the administration of the last dose in Part A and Part B.

There are two parts to the study:

- **Part A:** Open Label with AM dosing (4 days).

  All subjects will continue to take their antiparkinsonian agents including immediate-release oral Levodopa on the day of admission (Day -1) and in the AM only on the following 3 days (Days 1 to 3). All subjects will stop their immediate-release oral Levodopa on Day 4 and will start on a 30 mg dose of SAGE-217 Oral Solution administered in the AM with food, as outlined in Section 9.1.1 of the protocol. Subjects not tolerating 30 mg will receive 20 mg, and subjects not tolerating 20 mg will receive 10 mg on subsequent days (Section 7.4 of the protocol). The dose received on Day 7 will be defined as the tolerated dose for that subject. Subjects not tolerating 10 mg will not be able to continue in the study and may be replaced. Subjects will be followed for an additional 7 days (Day 14) after the administration of the last dose. Levodopa treatment will be resumed on Day 8 and continue through Day 14.

  Rescue treatment (oral Levodopa or other antiparkinsonian agent at Investigator's discretion) will be allowed, if needed, on all days (Days 1 to 7).

  Part A is designed to determine the tolerated dose of SAGE-217 Oral Solution for each subject and to assess whether SAGE-217 exhibits efficacy in subjects with PD of moderate severity in order to inform the conduct of Part B.

- **Part B:** Open-label with PM dosing of SAGE-217 Capsules, for 7 days, as an adjunct to antiparkinsonian agent(s).

  Subjects on a stable dose of antiparkinsonian agent(s) will continue taking them for the duration of the study. Anticholinergics and/or amantadine will be discontinued by Day -6 and Day -10, respectively.

  Screening may occur between Day -28 and Day -2, but subjects must be admitted on Day -1 for selected pre-dose assessments (eg, clinical laboratory assessments, assessment of tremor). All subjects will take SAGE-217 Capsules, 20 mg, at 8PM on Days 1 and 2. On Day 3, subjects

tolerating the initial dose (ie, those who do not experience a severe AE judged by the Investigator to be related to study drug) will receive a dose increase (SAGE-217, 30 mg), at 8PM and continuing each subsequent evening at 8PM for the remainder of the dosing period (ending on Day 7).

If on Day 3 or any time thereafter, the 30 mg dose is not tolerated, assessed by occurrence of a severe AE judged by the Investigator to be related to study drug, the dose on the next day must be reduced to 20 mg and continued for the remainder of the dosing period. Subjects who cannot tolerate the 20 mg dose at any time will be discontinued and replaced.

All doses of SAGE-217 will be administered with food as outlined in Section 9.1.2 of the protocol. For antiparkinsonian agents, administration with or without food will be determined by the Investigator.

Subjects will receive SAGE-217 for up to 7 days and will be followed for an additional 7 days after the administration of the last dose.

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

6.2 Sample Size and Power

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A at least through Day 14 to inform the conduct of Part B. Up to 15 subjects will be enrolled in Part B in order for 10 subjects to complete the study (tolerate at least 20 mg SAGE-217 for the duration of the dosing period).

6.3 Randomization

Not applicable as Part A and Part B are open-label, single arm.

6.4 Blinding and Unblinding

Not applicable as Part A and Part B are open-label.

7 MODIFICATIONS

7.1 Modifications to the Approved Clinical Study Protocol

The protocol was amended to version 5.0, dated 08 JUN 2017. Part B was changed from a randomized design to open-label. The inclusion/exclusion criteria, dosing schedule, and assessment time points were updated. Subjects are allowed to remain on antiparkinsonian agent(s) which eliminates the need for rescue medications in Part B. The Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) and Stanford Sleepiness Scale (SSS) assessments were removed from Part B [redacted]

7.2 Modifications to the Approved Statistical Analysis Plan

The Part B sections of this SAP were updated after protocol version 5.0, dated 08 JUN 2017. Part B summaries will be done by overall subjects instead of by treatment sequence. Sections for the [redacted] MDS-UPDRS Part II/III tremor score were added. The Part B MOAA/S, SSS, MMRM, and rescue medication analysis was removed. Separate listings and tables are now being produced for Part A and Part B.

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 will consist of all subjects who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation. Separate populations are defined for each part of the study: Efficacy Population (Part A) will include subjects who fulfill the requirements for inclusion in the Efficacy Population based on Part A results; similarly, Efficacy Population (Part B) will include subjects who fulfill the requirements for inclusion in the Efficacy Population based on Part B results. Efficacy Population (Part A) and Efficacy Population (Part B) will be used to analyze efficacy data in Parts A and B, respectively.

8.2 Safety Population

The Safety Population is defined as all subjects who are administered study drug in a study part. This population will be used to provide descriptive summaries of safety. Safety Population (Part A) and Safety Population (Part B) will be used to analyze safety data in Parts A and B, respectively.

8.3 PK Population

The PK Population will consist of all subjects in the safety population with at least one plasma sample with quantifiable concentration of SAGE-217. The PK population will be separated by study part. PK Population (Part A) will include subjects with at least one plasma sample with quantifiable concentration of SAGE-217 in Part A. PK Population (Part B) will include subjects with at least one plasma sample with quantifiable concentration of SAGE-217 in Part B. These populations will be used to summarize PK data for each respective study part.

9 STATISTICAL ANALYSIS

9.1 General Considerations

Continuous (quantitative) 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. An exception to this will be the by dose AE and medication tables. The denominator for percentage will be the number of subjects dosed at a SAGE-217 mg level on a particular study day. The denominator for percentage in categorical parameter urinalysis laboratory tables will be the number of subjects with an assessment at a given time point.

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 two degrees of precision more than the observed data.

Percentages will be presented to one decimal place unless otherwise specified. Assessments done on unscheduled visits will not be summarized but will be listed. The safety population will be used to provide descriptive summaries of safety. The efficacy population will be used to analyze efficacy data. The PK population will be used to derive PK data. Safety summaries for Part A of the study will be presented by overall subjects. Safety summaries for Part B of the study will be presented by overall subjects.

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 Clinical Study Report (CSR). Any results from these unplanned analyses (post-hoc) 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 and study part.

If partial dates occur, the convention for replacing missing dates for the purposes of calculating derived variables within each study part 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 month or month and day are unknown, then:
    - If the year matches the year of first dose date, then impute the month and day of the first dose date in the study part.
    - Otherwise, assign 01 January
- If the year and month are known, but day is unknown, then:
    - If the month and year match the month and year of the first dose date, then impute the day of the first dose date in the study part.
    - 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 month is unknown, then assign the last day of the year, 31 December. If this results in a date after the last study part date, assign the day and month of the last study date.
- If the day is unknown, then assign the last day of the month.

If an AE has a missing severity or relationship, it will be left as missing. No other missing data will be imputed unless otherwise specified.

In general, for quantitative laboratory values reported as '<' or '≤', 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.

For safety data, the last observation recorded before receiving the first dose on Day 1 in each study part will be used as the baseline observation for all calculations of change from baseline. Separate baselines will be derived for Part A and Part B. Baseline values will only be displayed in safety summaries.

Separate tables, figures, and listings will be produced for Part A and Part B.

9.2 Background Characteristics

9.2.1 Subject Disposition

All subjects who provide informed consent in each study part will be accounted for in this study. The number of subjects screened and enrolled in each study part will be summarized by overall subjects. The number and percentage of subjects completed, and withdrawn from the study, as well as reason for withdrawal, will be summarized by overall subjects in each study part. Additionally, the number and

percentage of subjects in each analysis population will be summarized overall for each study part. Percentages will be calculated using the number of enrolled subjects. 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 PD diagnosis (from informed consent), will be summarized by overall subjects in each study part.

Frequency and percentage of categorical summaries, such as gender, child-bearing potential, race, and ethnicity, will be summarized by overall subjects in each study part. Continuous summaries, such as age, height, weight, BMI, and time since PD diagnosis, will be summarized using mean, standard deviation, median, minimum, and maximum. Separate demographic tables will be generated for the safety population in both parts of the study.

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

Medical history will be listed.

9.2.3 Study Drug Exposure

Study drug dosing information will be listed.

9.2.4 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 endpoints of Part A relate to safety and tolerability; there are no primary efficacy variables for Part A.

The primary efficacy variable for Part B is the MDS-UPDRS Part II/III tremor score.

The secondary efficacy variables for this study include:

- MDS-UPDRS – Part III total score (Parts A and B)
- MDS-UPDRS – Part I and II total scores (Part B only)
- MDS-UPDRS – Parts I-IV total score (Part B only)

The exploratory efficacy variables for this study include:

9.3.1 Analysis of Primary Efficacy Variable

The MDS-UPDRS includes 4 scales, with various subscales. Each item is rated from 0 (normal) to 4 (severe). The four MDS-UPDRS scales are:

Part I: nonmotor experiences of daily living (13 items)

Part II: motor experiences of daily living (13 items)

Part III: motor examination (33 scores based on 18 items [several with right, left or other body distribution scores])

Part IV: Motor complications (6 items)

Scale for the MDS-UPDRS Rating	Description
0 = normal	No symptoms/signs
1 = slight	Symptoms/signs with sufficiently low frequency or intensity to cause no impact on function
2 = mild	Symptoms/signs of frequency or intensity sufficient to cause a modest impact on function
3 = moderate	Symptoms/signs sufficiently frequent or intense to impact considerably, but not prevent, function
4 = severe	Symptoms/signs sufficiently frequent or intense to impact considerably, but not prevent, function

The MDS-UPDRS Part II/III tremor score comprises the sum of MDS-UPDRS items 2.10, 3.15, 3.16, 3.17, and 3.18 and assesses the severity in PD tremor.

Part A Analysis

Not applicable.

Part B Analysis

In Part B, observed values and change from baseline in the tremor score will be summarized by overall subjects in the Efficacy Population (Part B).

9.3.2 Analysis of Secondary Efficacy Variables

The total score for Parts I-IV comprises the sum of the results of the individual item scores. Part III assesses 18 motor categories, some of which include right and left measurements: speech, facial expression, kinetic tremor of hands, rest tremor amplitude, postural tremor of hands, rigidity of neck and four extremities, finger taps, hand movement, pronation/supination, toe tapping, constancy of rest tremor, leg agility, arising from chair, posture, gait, freezing of gait, postural stability, and global spontaneity of movement. The Part III total score will be calculated by the sum of scores from the 18 motor categories.

Part A Analysis

In Part A, observed values in the MDS-UPDRS – Part III total score and in the individual scores will be summarized by overall subjects in the Efficacy Population (Part A). The Part III total score at each time point (2, 4, 8, and 12 hours postdose) will be averaged over the 3-day period for L/C and 4-day period for SAGE-217. Differences between the averaged Part III total score at the 2, 4, 8, and 12 hour postdose time points be analyzed using a paired t-test. The averaged score and the SAGE-217 – L/C subject level differences at each time point will be summarized and a Shapiro-Wilk normality test will be run on the differences prior to the paired t-test. If the normality condition is not satisfied at the 0.05 significance level, a Wilcoxon signed rank test will be used to compare the time points. The same analysis will be performed on the Part III individual scores.

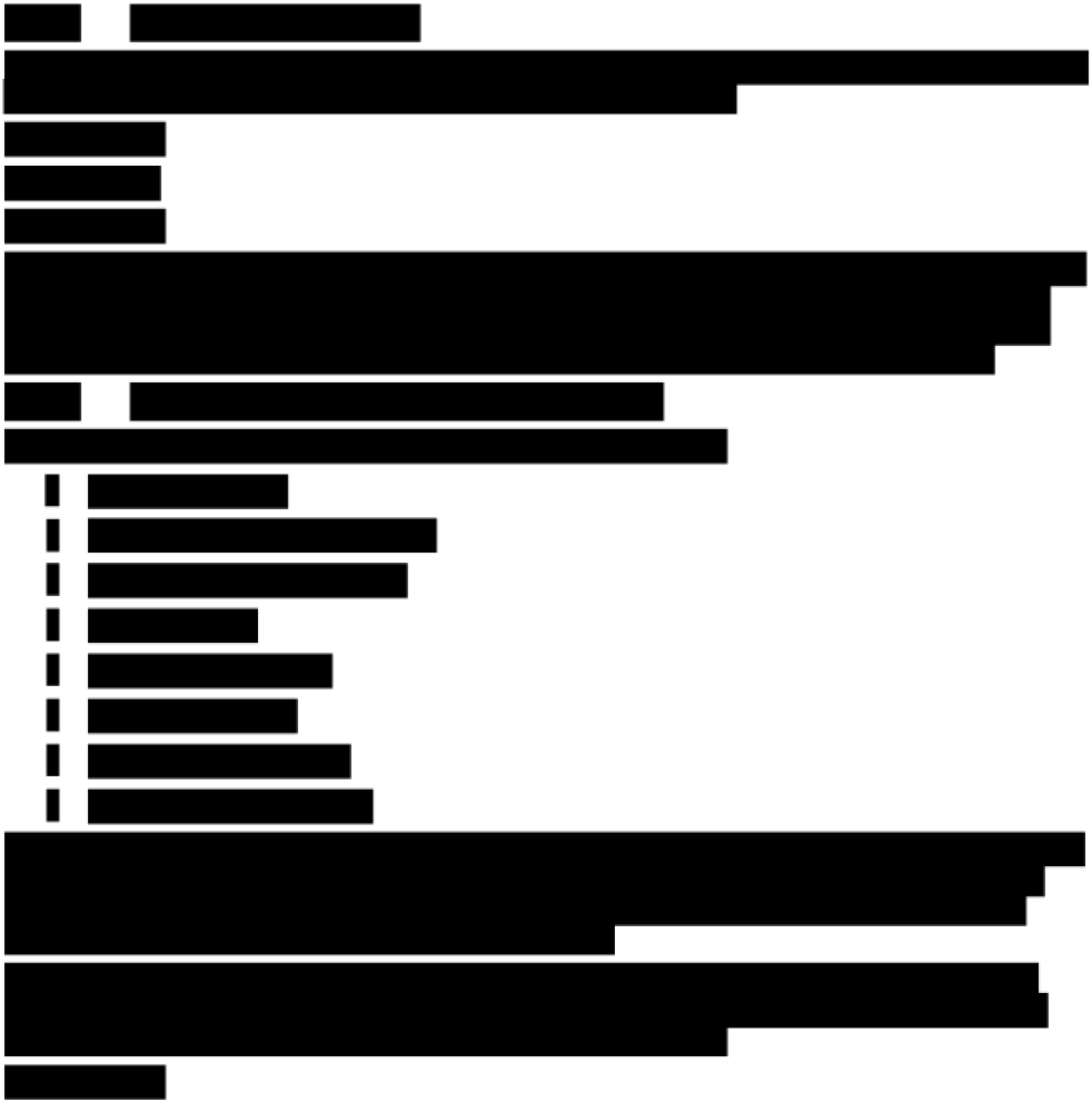
Part III total and individual scores will be summarized graphically over time by overall subjects. Additionally, Part III averaged total and individual scores will be summarized graphically over time for overall subjects.

MDS-UPDRS Parts I, II, IV, and overall total score will be listed only.

Part B Analysis

In Part B, observed values and change from baseline in the Parts I, II, III, and IV total and individual scores will be summarized by overall subjects in the Efficacy Population (Part B). The MDS-UPDRS overall total score (ie, sum of Parts I-IV) and change from baseline will be summarized by overall subjects.

9.3.3 Analysis of Exploratory Efficacy Variables



[redacted]

9.4 Safety Analysis

Safety is the primary objective of Part A and will be evaluated through frequency and severity of AEs and changes in vital signs, clinical laboratory measures, ECG parameters, suicidal ideation using the C-SSRS, SSS, and MOAA/S during both Part A.

Safety is a secondary objective of Part B and will be evaluated through frequency and severity of AEs and changes in vital signs, clinical laboratory measures, ECG parameters, and suicidal ideation using the C-SSRS.

All safety data will be presented in individual subject data listings. Safety analysis will be conducted for the Safety Population. Part A results for clinical laboratory, electrocardiogram, vital signs, AEs, medications, C-SSRS, SSS, and MOAA/S will be summarized by overall subjects. Part A AEs, concomitant medications, and rescue medications will also be summarized by day and dose (SAGE-217 only) on a given day. Part B results for clinical laboratory, ECG, vital signs, AEs, medications, and C-SSRS will be summarized by overall subjects. Part B AEs and concomitant medications will also be summarized by day and dose on a given day.

Safety Evaluation	Incidence	Observed Value	Change from Baseline	Abnormality/ Clinical Significance
AEs	X			
CMs	X			
Labs		X	X	X
ECG		X	X	*
Vital Signs		X	X	X
PE		*		*
C-SSRS		X	X	
SSS		X	X	
MOAA/S		X	X	

Safety Evaluation	Incidence	Observed Value	Change from Baseline	Abnormality/ Clinical Significance
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 during Part A and Part B is defined as an AE with onset after the start of open-label study drug in the respective study part, 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. In Part A, TEAEs will be assigned to treatment periods as follows:

- TEAEs that occurred or worsened on or after the first dose of Levodopa on Day 1 and within 24 hours after the last administration of L/C medication and before the first dose of SAGE-217 on Day 4 will be assigned to the L/C Day 1 to Day 3 period.
- TEAEs that occurred or worsened on or after the first dose of SAGE-217 on Day 4 and within 24 hours after the last administration of SAGE-217 on Day 7 will be assigned to the SAGE-217 Day 4 to Day 7 period.
- TEAEs that occurred or worsened more than 24 hours after the last dose of study drug will be assigned to the follow-up period.

In Part B, TEAEs will be assigned to treatment periods as follows:

- TEAEs that occurred or worsened on or after the first dose of study drug on Day 1 and within 24 hours after the last administration of study drug medication on Day 7 will be assigned to the SAGE-217 Day 1 to Day 7 period.
- TEAEs that occurred or worsened more than 24 hours after the last dose of study drug will be assigned to the follow-up period.

In Part A and Part B, AEs will be summarized by treatment period and by follow-up.

A summary of TEAEs will be provided. Frequencies and percents of the following will be included:

- Number of subjects with at least one TEAE
- Number of subjects with at least one TEAE leading to discontinuation
- Number of subjects with a TEAE leading to death
- Number of subjects with at least one serious adverse event (SAE)

In Part A and Part B, the incidence of TEAEs will be summarized by the following:

- SOC and PT
- PT
- Dose (SAGE-217 only), Day, and PT
- SOC, PT, and Maximum Severity

- SOC, PT, and Relationship to Study Drug

All SAEs, AEs leading to discontinuation, and AEs leading to death will be listed in a separate tables.

9.4.2 Prior and Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD) (Version September 1, 2016 or later).

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

- Prior medication: medication taken prior to the date of the first dose of open-label study drug in Part A.
- Concomitant medication: In Part A and Part B, a medication with a start date on or after the first dose of open-label study drug within the study part (even if end date is missing) will be considered concomitant. 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.
- Rescue medication: any oral Levodopa or other antiparkinsonian agent at the Investigator's discretion taken on days 1 to 7 in Part A that is not part of the planned study treatment will be considered rescue medication. Rescue medications are not applicable to Part B.

Concomitant medications will be assigned to the study part in which they are being taken. 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. Details of prior and concomitant medications will be listed by study part, subject, start date, and verbatim term. Prior and concomitant medications will be summarized by Anatomic Therapeutic Chemical (ATC) class and preferred term (PT). In Part A, concomitant medications will be summarized under SAGE-217, Levodopa/Carbidopa for Day 1 to Day 3, and follow-up. The follow-up period begins 24 hours after the last dose of SAGE-217. Medications that are concomitant to both periods will be summarized under both treatments. Concomitant medications will also be summarized by dose, day, and PT during the SAGE-217 period. In Part B, concomitant medications will be summarized under SAGE-217 and follow-up. The follow-up period begins 24 hours after the last dose of SAGE-217. Concomitant medications will also be summarized by dose, day, and PT during the SAGE-217 period.

The use of rescue medications in Part A will be listed and summarized in the same manner as concomitant medications. Rescue medications will be summarized by PT only.

Medication summaries will be based on the Safety Population.

9.4.3 Clinical Laboratory

All statistical analyses of laboratory values will be performed using SI units. Continuous hematology, chemistry, and urinalysis results and changes from baseline of Part A and Part B will be summarized by overall subjects within each study part. All clinical laboratory results will be listed by subject and timing of collection. This listing will include data from scheduled and unscheduled time points. Clinically significant abnormal findings will be reported as AEs.

In Part B, the number of subjects with chemistry and hematology values below, within, or above the normal range by time point and in relation to baseline will be tabulated in a shift table within each parameter by overall subjects. The number of normal and abnormal urinalysis values by time point and in relation to baseline will be tabulated in a shift table within each parameter by overall subjects.

9.4.4 Electrocardiogram

The following 12-ECG parameters will be listed for each subject: heart rate, PR Interval, QRS Duration, QT Interval, and QTcF. Any clinically significant abnormalities or changes in ECGs should be listed as an AE. Observed values, mean changes from baseline, and investigator interpretation of Part A and Part B results will be summarized by overall subjects within each part.

9.4.5 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 mean changes from baseline at each time point of Part A and Part B will be summarized by overall subjects within each study part.

In Part B, the number of pulse oximetry values classified as normal, abnormal (not clinically significant), and abnormal (clinically significant) by time point and in relation to baseline will be tabulated in a shift table by overall subjects.

9.4.6 Physical Examination

Screening physical examination results for Part A and results for Part B that are clinically significant will be listed in the medical history listing. Post-screening physical examination results for Part A and post-screening results for Part B that are clinically significant will be presented in the AE listings.

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

Suicidality was monitored during the study using the C-SSRS. 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 behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS pre-treatment and post-baseline evaluations. Frequencies and percents for the subjects with at least one response of "Yes" on the Suicidal Ideation and Suicidal Behavior questions pre-treatment and post-baseline will be summarized. Part A and Part B results will be summarized by overall subjects within each study part. Results from all sections of the C-SSRS will be listed.

9.4.8 Stanford Sleepiness Scale

The SSS is a subject-rated scale designed to quickly assess how alert a subject is feeling. 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". A response of "X" indicates the subject is asleep. This response will be summarized categorically but will not be included in the numeric observed value and change from baseline tables.

Sedation data collected on the SSS will be listed for all subjects. Total score over time will be represented graphically by overall subjects in Part A. Observed values and change from baseline of Part A at each time point will be summarized overall subjects. Frequency tables by overall subjects in Part A will also be provided.

This assessment is used in Part A only.

9.4.9 Modified Observer's Assessment of Alertness/Sedation (MOAA/S)

The MOAA/S allows exploration of deeper sedation states than the SSS. If a MOAA/S score of 3 or less was observed, the score was to be confirmed by waiting approximately 10 minutes and re-administering the MOAA/S assessment. The lowest score of 0 indicates the subject has "No response after painful trapezius squeeze" and the highest score of 5 indicates the subject "Responds readily to name spoken in normal tone".

Sedation data collected on the MOAA/S will be listed for all subjects. Total score over time will be represented graphically by overall subjects in Part A. Observed values and change from baseline of Part A at each time point will be summarized by overall subjects. Frequency tables by overall subjects in Part A will also be provided. If a re-assessment at a time point is required, only the first assessment will be summarized and both assessments will be listed.

This assessment is used in Part A 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 (n), mean, standard deviation, median, maximum, minimum, % coefficient of variation (CV) and geometric mean. For Part A and Part B, summaries may be done by tolerated dose or by overall subjects only within each study part. The final columns in the PK tables will depend on the final data and the judgement of the pharmacokineticist. Individual concentration plots and mean data graphs will be produced. 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 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, including C_{max}, λ_z, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{1/2}$, where appropriate and as data permit, will be summarized using descriptive statistics, including arithmetic and geometric means, SD, %CV, median, minimum, and maximum. Other parameters may be added at the discretion of the pharmacokineticist.

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

A graph comparing MDS-UPDRS Part III total score and pharmacokinetic concentrations over time will be produced for overall subjects in the PK Population in Part A and Part B.

A graph comparing MDS-UPDRS Part II/III tremor score and pharmacokinetic concentrations over time will be produced for overall subjects in the PK Population in Part B.

10 SUMMARY OF INTERIM ANALYSES

An interim analysis will be conducted upon the completion of 10 subjects in Part A to inform the conduct of Part B. All Part A tables, listings, and figures excluding any PK analysis will be generated for the interim analysis.

11 REFERENCES

Peto, V., Jenkinson, C., Fitzpatrick, R., & Greenhall, R. (1995). The Development of a Short Measure of Functioning and Well Being for Individuals with Parkinson's Disease. *Quality of Life Research, 4*(3), 241-248. Retrieved from http://www.jstor.org.

12 LIST OF APPENDICES

12.1 Appendix A: Schedule of Assessments

12.1.1 Part A

Visit Days	Screening (Day -28 to Day -1)	Admit (Day -1)	Part A: Open-Label								Follow-up
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 14 (±1)
Informed Consent	X										
Inclusion/Exclusion	X	X									
Confined to Unit[a]		X	X	X	X	X	X	X	X	X	
Demographics	X										
Medical History	X										
Physical Examination	X	X	X		X	X		X		X	
Body Weight/Height	X										
CBC/Serum Chemistry[b]	X	X				X		X		X	X
Pregnancy Test	X-serum	X-urine									
Urinalysis[c]	X	X				X			X		X
Hepatitis & HIV screen	X										
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry[e]		X	X	X	X	X	X	X	X	X	X
12-Lead ECG[f]	X	X	X		X	X	X	X	X	X	X
C-SSRS[g]	X	X	X	X	X	X	X	X	X	X	X
SSS[h]		X	X	X	X	X	X	X	X	X	X
MOAA/S[i]					X	X	X	X	X	X	X
MDS-UPDRS (complete)[j]	X	X								X	X
MDS-UPDRS (Part III only)[k]			X	X	X	X	X	X	X		
[redacted]											
Plasma PK Samples[p]						X	X	X	X	X	X
Administer Levodopa or Carbidopa-Levodopa[q]			X	X	X						
Administer SAGE-217[q]						X	X	X	X		
Adverse Events	X										
Prior/Concomitant Medications	X										

[redacted]; CBC = complete blood count; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; HIV = human immunodeficiency virus; MDS-UPDRS = Movement Disorder Society - Unified Parkinson's Disease Rating Scale; MOAA/S = Modified Observer's Assessment of Alertness/Sedation; [redacted]; PK = pharmacokinetic; SSS = Stanford Sleepiness Scale

[a] Subjects will be discharged from the unit after completion of all Day 8 assessments.

[b] Screening and Safety Laboratory Tests: Screening and Day -1 [Admission]; predose for Day 4, Day 6, and Day 8; Day 14.

[c] Urinalysis: Screening and Admission (Day -1); Predose for Day 4 and Day 7; Day 14.

[d] Vital Signs: Screening and Day -1 [Admission]; predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Confinement Days 1, 2, 3, 4, 5, 6, and 7; in AM of Day 8; and Day14. Vital signs assessments are to be performed within ±10 minutes of the scheduled times through the 4 hour time point and within ±15 minutes of the scheduled times thereafter.

[e] Pulse Oximetry: Admission (Day -1); predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Confinement Days 1, 2, 3, 4, 5, 6, and 7; in AM of Day 8; and Day 14. Pulse oximetry is to be performed within ±10 minutes of the scheduled times through the 4 hour time point and within ±15 minutes of the scheduled times thereafter.

[f] 12-Lead ECG: Screening and Admission (Day -1); predose on Day 1 and Day 3; predose and 1 (±10 minutes) and 12 (±15 minutes) hours postdose on Confinement Days 4, 5, 6, and 7; in AM of Day 8; and Day 14.

[g] C-SSRS: Screening and Admission (Day -1); 12 hours postdose on Day 1, Day 2, and Day 3; predose on Day 4, Day 5, Day 6, and Day 7 and Day 8 and Day 14.; Screening/Baseline version of C-SSRs should beused on day of screening and Since Last Visit version should be used on all subsequent time points.

[h] SSS: Admission (Day -1); predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Confinement Days 1, 2, 3, 4, 5, 6, and 7; in AM of Day 8; and Day 14. The SSS is to be performed within ±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times thereafter.

[i] MOAA/S: Predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Confinement Days 1, 2, 3, 4, 5, 6, and 7; in AM of Day 8; and Day 14. The MOAA/S is to be performed within ±10 minutes of the scheduled times through the 4 hour time point and within ±15 minutes of the scheduled times thereafter.

[j] MDS-UPDRS (complete): Screening, Admission (Day -1) (only if time between Screening and Admission is ≥7 days)], on Day 8 prior to resuming Levodopa, and Day 14.

[k] MDS-UPDRS (Part III only): 2 (±10 minutes), , 4 (±10 minutes), 8 (±15 minutes), and 12 (±15 minutes) hours postdose on Days 1, 2, 3, 4, 5, 6, and 7. If complete MDS-UPDRS is not completed on Admission due to it taking place <7 days after Screening, then the MDS-UPDRS Part III only should also take place on Admission (Day -1).

[redacted]

[p] Plasma PK sampling times (± 5 minutes): Days 4 prepose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose; predose on Day 5 and Day 6; predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours on Day 7; in AM of Day 8; and Day 14. PK samples are to be collected within ±5 minutes of the scheduled sampling time.

[q] Levodopa or Carbidopa-Levodopa and SAGE-217 are to be administered in the morning.

12.1.2 Part B

Visit Days	Screening (Day -28 to Day -2)	Admit (Day -1)	Part B: Open-Label								Follow-up
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 14 (±1)
Informed Consent	X										
Inclusion/Exclusion	X	X									
Confined to Unit		X	X	X	X	X	X	X	X	X	
Demographics	X										
Medical History	X										
Physical Examination	X	X	X		X	X		X		X	
Body Weight/Height	X	X									
CBC/Serum Chemistry	X	X				X		X		X	X
Pregnancy Test	X-serum	X-urine									X-urine
Urinalysis[d]	X	X				X		X		X	X
Hepatitis & HIV screen	X										
Vital Signs[e]	X	X	X	X	X	X	X	X	X	X[f]	X
Pulse Oximetry[g]		X	X	X	X	X	X	X	X	X[f]	X
12-Lead ECG[h]	X	X	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X
C-SSRS[i]	X	X	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X
MDS-UPDRS (complete)[j]	X	X	X[f]							X[f]	X
MDS-UPDRS (Part II only)[k]			X	X	X	X	X	X			
MDS-UPDRS (Part III only)[k]			X	X	X	X	X	X			
[redacted]											

Visit Days	Screening (Day -28 to Day -2)	Admit (Day -1)	Part B: Open-Label								Follow-up
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 14 (±1)
[redacted]											
Plasma PK Samples[f]			X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X
Administer SAGE-217[a]			X	X	X	X	X	X	X		
Adverse Events						X					
Prior/Concomitant Medications						X					

[redacted]; CBC = complete blood count; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; HIV = human immunodeficiency virus; MDS-UPDRS = Movement Disorder Society - Unified Parkinson's Disease Rating Scale; [redacted] PK = Pharmacokinetic

[a] Subjects will be discharged from the unit after completion of all Day 8 assessments.

[b] Screening and Safety Laboratory Tests: Screening and Admission (Day -1); predose (within 1 hour of dosing) on Days 4 and 6; and on Days 8 and 14.

[c] Two samples will be taken on Day-1: one sample will be sent to the central lab to be analyzed for reporting purposes and one sample to be analyzed locally for eligibility with regard to CBC/serum chemistry.

[d] Urinalysis: Screening and Admission (Day -1); predose on Days 4 and 6; and on Days 8 and 14.

[e] Vital Signs: Screening and Admission (Day -1); predose and 1, 2, and 12 hours postdose on Confinement Days 1, 2, 3, 4, 5, 6, and 7; and on Day 14. Assessments of vital signs are to be performed within ±10 minutes of the 1 and 2-hour time points and within ±15 minutes of the 12-hour time point.

[f] Morning assessment only (in the morning of Day 1 or 12 hours [or 13 hours for PK sampling] after the dose from the previous evening).

[g] Pulse Oximetry: Admission (Day -1); predose and 1, 2, and 12 hours postdose on Confinement Days 1, 2, 3, 4, 5, 6, and 7; and on Day 14. Pulse oximetry is to be performed within ±10 minutes of the 1 and 2-hour time points and within ±15 minutes of the 12-hour time point.

[h] 12-Lead ECG: Screening and Admission (Day -1); predose and 1 (±10 minutes) and 12 (±15 minutes) hours postdose on Confinement Days 1, 3, 5, and 7; and on Day 14.

[i] C-SSRS: Screening and Admission (Day -1); predose and 12 hours (±1 hour) postdose on Day 1; and 12 hours (±1 hour) postdose on Day 2, 3, 4, 5, 6, and 7. Screening/Baseline 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] MDS-UPDRS (complete, Parts I-IV): Screening, Admission (Day -1) (only if time between Screening and Admission is ≥7 days); at 8AM (±1 hour) on Day 1; 12 (±15 minutes) hours postdose on Day 7 (ie, 8AM on Day 8); and on Day 14. MDS-UPDRS should take place during the "on" period AND within 2 hours of dosing with antiparkinsonian agent(s).

[k] MDS-UPDRS (Part II/III only): 12 and 23 (±15 minutes) hours postdose on Confinement Days 1, 2, 3, 4, 5, and 6. MDS-UPDRS Part II/III should take place during the "on" period AND within 2 hours of dosing with antiparkinsonian agent(s).

[redacted]

[r] Plasma PK sampling times (±1 hour): predose and 13 hours postdose on Day 1; and 13 hours postdose on Days 2 through 7.
[s] SAGE-217 Capsules are to be administered in the evening (8PM ±30 minutes) with food.

12.2 Appendix B: Details of Statistical Methodology

Not applicable.