Official Title: A Phase 2, Two-Part Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in Subjects With Parkinson's Disease

NCT Number: NCT03000569

Document Date: SAP Version 1: 06-February-2017

9. DOCUMENTATION OF STATISTICAL METHODS

Statistical Analysis Plan v1.0 (dated 06Feb2017)

Sage Therapeutics, Inc.

Statistical Analysis Plan

Methods

Protocol Number SAGE-217-PRK-201

A PHASE 2, TWO-PART STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF SAGE-217 ORAL SOLUTION IN PATIENTS WITH PARKINSON'S DISEASE OF MODERATE SEVERITY RESPONDING TO IMMEDIATE-RELEASE ORAL LEVODOPA/CARBIDOPA AND WITHDRAWN FROM LEVODOPA/CARBIDOPA

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Version: Version 1.0

Version Date of SAP: 06 February 2017

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1 TABLE OF CONTENTS

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 statistical analyses plan (SAP) is for the interim analysis (IA) of Part A and final analysis of the study (Part A and Part B) and is based on the approved clinical study protocol, dated 24 OCT 2016, Version 3.0, incorporating Amendment 2.

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 unblinding of 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.

Wherever possible, listings will include data from both Part A and Part B. Separate 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 this study is to evaluate the safety and tolerability of SAGE-217 Oral Solution.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the effect of SAGE-217 Oral Solution on the severity of Parkinson's Disease (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.
- To compare the effect of SAGE-217 Oral Solution in combination with immediate-release oral Levodopa/Carbidopa to Levodopa/Carbidopa alone.

4.3 Other Objectives

Not applicable.

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

Not applicable.

5.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- Part A
  - Improvement in PD motor symptoms as assessed by changes in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) – Part III (Motor Examination) total score.
- Part B
  - Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS – Part III total score.
  - 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 this study 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) during both Part A and Part B.

The secondary safety endpoint of this study is sleepiness/sedation as assessed by the Stanford Sleepiness Scale (SSS) and Modified Observer's Assessment of Analgesia/Sedation (MOAA/S) scores.

5.3 Other Endpoints

Plasma concentrations of SAGE-217 and possibly SAGE-217 metabolites will be measured, and PK parameters such as C_{max}, t_{max}, λ_z, AUC_{0-t}, $AUC_{0-\infty}$, C_{ss}, and $t_{1/2}$, will be derived where appropriate and as data permit.

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 Oral Solution in up to 18 adult subjects with PD of moderate severity who respond to immediate-release oral Levodopa and are on a stable dose. Part A of the study is an open-label design with morning (AM) dosing of SAGE-217 for 4 days. Part B of the study is a double-blind, randomized, placebo-controlled, two-sequence crossover design. On Days 1 to 4 (Period 1 of crossover), subjects will receive open-label Levodopa plus blinded SAGE-217 or placebo. On Days 5 to 8 (Period 2 of crossover), all subjects will receive open-label SAGE-217 Oral Solution only. In Part B, subjects will receive their individually established tolerated dose of SAGE-217 Oral Solution from Part A. Subjects will be exposed to SAGE-217 for up to 12 days (4 days in Part A and up to 8 days in Part B) and will be followed for an additional 7 days in Part A and an additional 14 days in Part B after the administration of the last dose.

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:** Randomized, placebo-controlled, two-sequence crossover with AM dosing (up to 8 days). Part B will be initiated only after review of the Part A IA data.

  In order to qualify for Part B of the study, a subject must have tolerated a dose of at least 10 mg of SAGE-217 Oral Solution in Part A. Subjects who complete Part A through Day 14 will be re-admitted on Day -1 of Part B and they will receive their antiparkinsonian agent including immediate-release oral Levodopa. Subjects will be randomized the next day (Day 1) in a 1:1 manner to open-label Levodopa plus blinded SAGE-217 Oral Solution or placebo during Period 1 of the crossover. All doses of SAGE-217 Oral Solution (or placebo) will be administered in the morning with food as outlined in Section 9.1.2 of the protocol. Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and placebo oral solution in the AM for the first 4 days (Days 1 to 4). Subjects randomized to the combination arm of Levodopa and SAGE-217 Oral Solution will receive this combination in the AM for the first 4 days (Days 1 to 4). On Day 5, all subjects will crossover to Period 2 and will only receive open-label SAGE-217 Oral Solution for the remaining 4 days (Days 5 to 8). Subjects will receive their individually established tolerated dose of SAGE-217 Oral Solution (from Part A). All subjects will be able to resume Levodopa from Day 9 onwards.

  Rescue treatment (at Investigator's discretion) will be allowed, if needed, on all days (Days 1 to 8).

Reductions in dose of SAGE-217 will be allowed during both parts of the study (Parts A and B). If at any time the 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 the next lowest dose and continued for the remainder of the dosing period (ie, subjects who are unable to tolerate the 30 mg dose will receive a dose of 20 mg, and subjects who are unable to tolerate 20 mg will receive a 10 mg dose on subsequent days). The dose received on Day 7 of the dosing period in Part A will be determined to be the tolerated dose for that subject, with this dose to be used as the starting dose for Part B for that subject. Subjects will be exposed to SAGE-217 Oral Solution for up to 12 days (4 days in Part A and up to 8 days in Part B) and will be followed for an additional 7 days in Part A and an additional 14 days in Part B 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 IA is planned after 10 subjects have completed Part A at least through Day 8 to inform the conduct of Part B. Twelve subjects are anticipated to be randomized in Part B. This number of subjects is thought to be sufficient to assess preliminary safety and tolerability as well as a signal of efficacy of SAGE-217 Oral Solution in subjects with PD.

6.3 Randomization

Not applicable for Part A of the study as it is open-label, single arm.

Part B is a randomized, placebo-controlled, two-sequence crossover study. Subjects will be randomly assigned in a 1:1 manner to one of two treatment sequences: AC or BC where A = Levodopa/Carbidopa + SAGE-217, B = Levodopa/Carbidopa + Placebo, and C = SAGE-217.

6.4 Blinding and Unblinding

For Part B, subjects, clinicians, and the study team will be blinded to treatment allocation in the first period. The pharmacist, who will prepare the oral solution according to the randomization schedule, will be unblinded.

During the study, the blind is to be broken only when the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. Unless a subject is at immediate risk, the Investigator must make diligent attempts to contact the Sponsor prior to unblinding the study treatment administered to a subject. Any request from the Investigator about the treatment administered to study subjects must be discussed with the Sponsor. If the unblinding occurs without the Sponsor's knowledge, the Investigator must notify the Sponsor as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented in the source records. Unless a subject is at immediate risk, any request for the unblinding of individual subjects must be made in writing to the Sponsor and approved by the appropriate Sponsor personnel, according to standard operating procedures.

The blinding of the study will be broken after the database has been locked. Electronic copies of the randomization code will be made available to the laboratory performing the bioanalytical analyses in order to allow for limited analysis of samples from subjects receiving placebo.

In all cases where the study drug allocation for a subject is unblinded, pertinent information 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.

7 MODIFICATIONS

7.1 Modifications to the Approved Clinical Study Protocol

The protocol stated that an interim analysis would be conducted after 10 subjects have completed Part A through Day 14. This text was updated in Section 6.2 to "An IA is planned after 10 subjects have completed Part A at least through Day 8 to inform the conduct of Part B".

There are no other modifications from the clinical study protocol (version 3.0, dated 24 OCT 2016) that impact statistical analysis.

7.2 Modifications to the Approved Statistical Analysis Plan

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

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. 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 for the treatment sequence.

The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the raw data. Measures of location (mean and median) will be reported to 1 degree of

precision more than the raw data and measures of spread (standard deviation) will be reported to two degrees of precision more than the raw 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 treatment sequence.

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 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.
    - 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.
    - 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 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, it will be imputed as "Severe"; any missing relationship to study drug of an AE will be imputed as "Probably Related." 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.

9.2 Background Characteristics

9.2.1 Subject Disposition

All subjects who provide informed consent will be accounted for in this study. The number of subjects screened and enrolled 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 Part A. Additionally, the number and percentage of subjects in each analysis population will be summarized overall. Percentages will be calculated using the number of enrolled subjects. For Part B, the number of subjects randomized will be summarized by overall subjects. The number and percentage of subjects completed, withdrawn, as well as reasons for withdrawal, and subjects will be summarized within treatment sequence for Period 1, Period 2, and Part B overall. The number of subjects in each analysis population will be summarized within treatment sequence. 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 in Part A), will be summarized by overall subjects in Part A and by treatment sequence in Part B.

Frequency and percentage of categorical summaries, such as gender, child-bearing potential, race, and ethnicity, will be summarized by overall subjects in Part A. In Part B, they will be summarized by treatment sequence. Continuous summaries, such as age, height, weight, BMI, and time since PD diagnosis, will be summarized using mean, standard deviation, median, minimum, and maximum. A demographic table 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 this study relate to safety and tolerability; there are no primary efficacy variables for this study.

The secondary efficacy variables for this study include:

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

The exploratory efficacy variables for this study (Part B only) include:

9.3.1 Analysis of Primary Efficacy Variable

Not applicable.

9.3.2 Analysis of Secondary Efficacy Variables

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 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. In Part A, raw values in the MDS-UPDRS – Part III total score 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. In Part B, the same method will be used to compare L/C + Placebo or L/C + SAGE-217 on Day 1 to Day 4 to SAGE-217 on Day 5 to Day 8 within each treatment sequence at the 2, 3, 4, 8, and 12 hour postdose time points for both the Part III individual and total scores.

Additionally in Part B, an MMRM model will be used to compare L/C + Placebo to L/C + SAGE-217 during the Day 1 to Day 4 period. The model will include the averaged Part III total score over time as the dependent variable and will have treatment sequence, time point, and treatment sequence by time point interaction as fixed effects, and subject as random effect. LS mean differences will be presented along with associated 95% CI and pairwise treatment p-values at each time point. The model will use an unstructured covariance matrix. In case of convergence issues, other covariance structures will be used including 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. The Kenward-Roger approximation will be used to estimate denominator degress of freedom.

In Part A, Part III averaged total and individual scores will be summarized graphically over time for overall subjects. In Part B, Part III averaged total and individual scores will be summarized graphically over time within treatment sequence. In Part B, overall scores will be summarized graphically over time within the randomized treatment period by treatment sequence. Part I, II, IV, and overall total score will be listed only for Part A. In Part B, MDS-UPDRS Part I, II, IV, and overall total score will be summarized and listed, but not included in the t-test or MMRM analysis.

9.3.3 Analysis of Exploratory Efficacy Variables

[redacted]

[redacted]

9.4 Safety Analysis

Safety is the primary objective of this study 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 and Part B.

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 wil be summarized by treatment sequence.

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Abnormality/ Clinical Significance
AEs	X			
CMs	X			
Labs		X	X	*
ECG		X	X	*
Vital Signs		X	X	
PE		*		*
C-SSRS		X	X	
SSS		X	X	
MOAA/S		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 18.1 or higher). The analysis of AEs will be based on the concept of treatment emergent AEs (TEAEs). A TEAE during 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. A TEAE during Part B is defined as an AE with onset after the start of randomized study drug, or any worsening of a pre-existing medical condition/AE with onset after the start of randomized 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 and before the first dose of SAGE-217 on Day 5 will be assigned to the L/C + SAGE-217 or L/C + Placebo Day 1 to Day 4 period.

- TEAEs that occurred or worsened on or after the first dose of SAGE-217 on Day 5 and within 24 hours after the last administration of SAGE-217 on Day 8 will be assigned to the SAGE-217 Day 5 to Day 8 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.

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

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, 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

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

- Treatment sequence, SOC, and PT
- Treatment sequence and PT
- Treatment sequence, SOC, PT, and Maximum Severity
- Treatment sequence, 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, 2015 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, a medication with a start date on or after the first dose of open-label study drug (even if end date is missing) but before the start of Part B 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. In Part B, a medication with a start date on or after the first dose of randomized study drug (even if end date is missing) will be considered concomitant. Medications with a start date before the first dose of randomized study drug that are ongoing or with a stop date on or after the first dose of randomized 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 antiparkinson agent at the Investigator's discretion taken on days 1 to 7 in Part A or days 1 to 8 in Part B that is not part of the planned study treatment will be considered rescue medication.

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. 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. 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, L/C + Placebo or L/C + SAGE-217 for Day 1 to Day 4, and follow-up. Medications that are concomitant to multiple periods will be summarized under each period. Part B summaries will be within treatment sequence.

The use of rescue medications 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 will be summarized by overall subjects in Part A. Raw values and mean changes from Baseline of Part B will be summarized by within randomized treatment sequence. 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.

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. Raw values, mean changes from Baseline, and investigator interpretation of Part A results will be summarized by overall subjects. Raw values, mean changes from Baseline, and investigator interpretation of Part B results will be summarized within treatment sequence.

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. Raw values and mean changes from Baseline at each time point of Part A will be summarized by overall subjects. Raw values and mean changes from Baseline at each time point of Part B will be summarized within treatment sequence.

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 eximination results for Part A and results for Part B that are clinicially significant will be listed in the AE listing.

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 results will be summarized by overall subjects. Part B results will be summarized within treatment sequence. 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 raw 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 and by treatment sequence in Part B. Raw values and change from Baseline of Part A at each time point will be summarized overall subjects. Raw values and change from Baseline of Part B at each time point will be summarized within treatment sequence. Frequency tables by overall subjects in Part A and by treatment sequence in Part B will also be provided.

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 and by treatment sequence in Part B. Raw values and change from Baseline of Part A at each time point will be summarized by overall subjects. Raw values and change from Baseline of Part B at each time point will be summarized within treatment sequence. Frequency tables by overall subjects in Part A and by treatment sequence in part B 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.

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, summaries may be done by tolerated dose or by overall subjects only. In Part B, summaries may be done by tolerated dose or by overall subjects within treatment sequence. 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}, t_{max}, λ_z, AUC_{0-t}, $AUC_{0-\infty}$, C_{ss}, 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. 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 changes in MDS-UPDRS Part III total score and pharmacokinetic concentrations over time will be produced for overall subjects in the PK Population.

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 -14 to Day -1)	Admit (Day -1)	Period 1: Randomized, Blinded				Period 2: Open-label					Follow-up	End of Study
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15	Day 22
Inclusion/Exclusion	X	X											
Confined to Unit[a]		X	X	X	X	X	X	X	X	X	X		
Medical History	X												
Physical Examination	X	X	X		X	X	X		X	X	X	X	
Body Weight/Height	X												
CBC/Serum Chemistry[b]	X	X	X		X	X	X	X		X	X	X	
Pregnancy Test	X-serum	X-urine											
Urinalysis[c]	X	X				X				X		X	
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry[e]		X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
SSS[h]		X	X	X	X	X	X	X	X	X	X	X	X
MOAA/S[i]			X	X	X	X	X	X	X	X	X	X	X
MDS-UPDRS (complete)[j]	X	X									X	X	X
MDS-UPDRS (Part III only)[k]			X	X	X	X	X	X	X	X			
[redacted]													
Plasma PK Samples[q]			X	X	X	X	X	X	X	X	X	X	X
Administer Study Drug Combination[r]			X	X	X	X							
Administer SAGE-217 only[r]							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]; [redacted]; PK = pharmacokinetic; SSS = Stanford Sleepiness Scale

[a] Subjects will be discharged from the unit after completion of all Day 9 assessments.

[b] Screening and Safety Laboratory Tests: Screening and Day -1 [Admission]; predose for Day 1, Day 3, Day 4, Day 5, Day 6, and Day 8; and Day 9 and Day 15.

[c] Urinalysis: Screening and Admission (Day -1); Predose for Day 4 and Day 8; Day 15.

[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, 7, and 8; in AM of Day 9; and Days 15 and 22. 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, 7, and 8; in AM of Day 9; and Day 15. 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 and 1 (±10 minutes) and 12 (±15 minutes) hours postdose on Confinement Days 1, 2, 3, 4, 5, 6, 7, and 8; in AM of Day 9; and Days 15 and 22.

[g] C-SSRS: Screening and Admission (Day -1); 12 hours postdose on Day 1 through Day 8; Day 9, Day 15 and Day 22.

[h] Day -1 [Admission]; predose on Days 1 through Day 8; Day 9, and Day 15 and Day 22.

[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, 7, and 8; in AM of Day 9; and Days 15 and 22. 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 9 prior to resuming Levodopa, and Days 15 and 22.

[k] MDS-UPDRS (Part III only): 2 (±10 minutes), 3 (±10 minutes), 4 (±10 minutes), 8 (±15 minutes), and 12 (±15 minutes) hours postdose on Days 1, 2, 3, 4, 5, 6, 7, and 8. 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]

[q] Plasma PK sampling times: Days 1 to 4 predose 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 postdose on Day 7 and Day 8; in AM of Day 9; and Day 15 and Day 22. PK samples are to be collected within ±5 minutes of the scheduled sampling time.

[r] Study drug is to be administered in the morning

12.2 Appendix B: Details of Statistical Methodology

Not applicable.